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Review Article

The association between complement factor H rs1061170 polymorphism and age-related macular degeneration: a comprehensive meta-analysis stratified by stage of disease and ethnicity

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ABSTRACT.

Purpose: **The strength of association between complement factor H (CFH) rs1061170 polymorphism and age-related macular degeneration (AMD) differs between AMD subtypes and ethnicities. The main aim was to provide a systematic review and an updated meta-analysis stratified by stage of disease and ethnicity.**

Methods: **A literature search in the PubMed-Medline, EMBASE and Web of Science databases was conducted to identify epidemiological studies, published before September 2017, that included at least twp comparison groups (a control group with no signs of AMD and a case group of AMD patients). Genotype distribution, phenotype of the cases, ethnicity, mean age and gender ratio were collected. Odds ratios (ORs) and 95%CIs were estimated under the allelic, homozygous and heterozygous models. Sensitivity and subgroup analyses, by AMD subtype and ethnicity, were performed.**

Results: **The meta-analysis included data of 27 418 AMD patients and 32 843 controls from 76 studies. In Caucasians, the rs1061170 showed a significant association with early AMD (OR: 1.44; 95%CI 1.27–1.63), dry AMD (OR: 2.90; 95%CI 1.89–4.47) and wet AMD (OR: 2.46; 95%CI 2.15–2.83), under an allelic model. In Asians, the rs1061170 showed a significant association with advanced AMD (OR: 2.09; 95%CI 1.67–2.60), especially wet AMD (OR: 2.24; 95%CI 1.81–2.77).**

Conclusion: **Our work provides a more comprehensive meta-analysis of studies investigating the effect of the CFH rs1061170 polymorphism on AMD risk. These findings not only improve the assessment of disease risk associated with the polymorphism, but also constitute a scientific background to be translated into clinical practice for AMD prevention.**

Key words: ageing – complement factor H – disease subtype – race – retinal degeneration – single nucleotide polymorphisms

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Introduction

Age-related macular degeneration (AMD) is the major degenerative disease of the retina that leads to progressive destruction of the neurosensory macular area, involving the retinal pigment epithelium (RPE), Bruch's membrane and choroid (Jager et al. 2008). It is the most common cause of blindness in the developed countries, with a prevalence, among elderly people, that ranges from 1.4% at 70 years of age to 20% at 90 years of age (Rudnicka et al. 2012).

The early stages of the disease are characterized by aberrant pigmentation of the RPE and accumulation of 'drusen', extracellular deposits of lipid, cellular debris and protein that may be extruded from the RPE cells and may be damaging to RPE function without compromising visual acuity (Sarks et al. 2007). The advanced stages may manifest as two subtypes of AMD, distinguishable by different clinical and pathological features. Non-exudative (dry) AMD is characterized by the geographic atrophy (GA) of RPE cell layer and thinning of the retina. Exudative (wet) AMD is characterized by the development of choroidal neovascularization (CNV) and subretinal neovascular fibrous tissue, resulting in the rapid deterioration in central vision (Ferris et al. 2005; Ding et al. 2009).

Although the pathogenesis of this complex disorder implicates sociodemographic (age and race) and environmental (cigarette smoking, light exposure and unhealthy diet) risk factors (Ferris et al. 2005), genetic variants confer at least the 60% of the attributable risk (Swaroop et al. 2009), with 34 genomic loci implicated in disease pathogenesis (Fritsche et al. 2013). Genetic variants associated with

the susceptibility to AMD are especially involved in complement system activity, lipid metabolism and angiogenesis (Fritsche et al. 2013, 2016; Barchitta & Maugeri 2016). More recently, the effect of additional polymorphisms, as well as the dysregulation of microRNAs, has been involved in both pathological CNV and functional response to treatment against neovascular AMD (Askou et al. 2018; Cobos et al. 2018).

Among the SNPs associated with the risk of developing AMD, the rs1061170 polymorphism in the complement factor H (*CFH*) gene has been extensively studied via genetic and molecular approaches, providing strong evidence for disease association in a plausible biological context (Ding et al. 2009). It leads to an amino acid change at position 402 of the factor H polypeptide (Y402H), which substitutes a tyrosine residue with histidine.

Prevalence of Y402H polymorphism varies between ethnicities and the strength of its association with the risk of developing AMD could differ within AMD subtypes. Therefore, we perform a comprehensive systematic review and an updated meta-analysis to assess the association between the rs1061170 polymorphism and AMD, stratifying for disease subtype and ethnicity.

Materials and Methods

Search strategy

A systematic literature search in the PubMed-Medline, EMBASE and Web of Science databases was conducted to identify relevant epidemiological studies, published before September 2017, investigating the association between rs1061170 polymorphism and AMD risk. The search strategy comprised the terms ('complement factor H' or 'CFH') and ('age-related macular degeneration' or 'AMD' or 'ARMD' or 'age-related macular disease' or 'age-related maculopathy' or 'ARM'); full details of the search strategy are available in the Appendix S1. The search was limited to human studies, and no language restrictions were imposed. Moreover, the reference lists from selected articles were checked to search for further relevant studies. After titles and abstracts were scanned to exclude irrelevant studies, the full texts of eligible articles were read to determine whether they provided relevant data on the topic of interest. The preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines were followed (Moher et al. 2015).

Inclusion/exclusion criteria and data extraction

Two of the investigators independently assessed the retrieved articles and extracted data from each included study. Any inconsistencies were resolved through discussion.

Studies were included in the meta-analysis only if they satisfied the following criteria: (1) they used a case–control design or provided baseline data from prospective analysis; (2) AMD was diagnosed using a validated method; (3) they evaluated the associations between rs1061170 polymorphism and AMD; (4) they contained at least two comparison groups (a control group with no signs of AMD and a case group that included AMD); and (5) they provided sufficient genotype data to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs). By contrast, exclusion criteria were as follows: (1) no case–control or cross-sectional design; (2) inadequate case or control group; and (3) insufficient or lacking data to estimate ORs and 95%Cis. If there were multiple publications from the same population, the article reporting the most comprehensive data was chosen for meta-analysis.

The two Authors independently reviewed all the eligible studies and abstracted the following information in a standard format: first Author's last name, year of publication, country where the study was performed, ethnicity, the mean age and gender ratio of the participants, phenotype of the cases evaluated, sample size of subjects with and without AMD, the methods for genotyping, the genotype distributions in cases and controls and p values for Hardy–Weinberg equilibrium (HWE) in controls. If additional data were needed, the Authors of retrieved articles were contacted.

Quality assessment

The quality of studies included in the meta-analysis was independently assessed by two of the Authors using the Newcastle-Ottawa scale (NOS) for case–control study (Stang 2010). In this scale, three perspectives were carefully checked and scored: selection (0–4 points), comparability (0–2 points) and exposure (0–3 points). Total scores ranged from 0 (worst) to 9 (best), and a study with a score ≥ 7 indicates good quality. Disagreements were adjudicated by a third Author.

Statistical analysis

The chi-square test was performed to determine whether the genotype distribution in the control groups of each study is deviated from the Hardy–Weinberg Equilibrium (HWE). The strength of the association between the rs1061170 polymorphism and AMD was estimated as ORs (95% CIs) under the allelic model (C vs. T), the homozygous model (CC vs. TT) and the heterozygous model (CT vs. TT). The significance of pooled OR was determined by the Z test. Heterogeneity across studies was measured using the Q-test, considering significant statistical heterogeneity as $p < 0.1$. As the Q-test only indicates the presence of heterogeneity and not its magnitude, we also reported the I^2 statistic, which estimates the percentage of outcome variability that can be attributed to heterogeneity across studies. An I^2 value of 0% denotes no observed heterogeneity, whereas, 25% is 'low', 50% is 'moderate' and 75% is 'high' heterogeneity (Higgins & Thompson 2002).

We also estimated the between-study variance using tau-squared (t) statistics (Higgins & Green 2008). According to heterogeneity across studies, we used the fixed-effects model (Mantel–Haenszel method) when heterogeneity was negligible or the random-effects models (DerSimonian-Laird method) when heterogeneity was significant. Furthermore, we conducted subgroup analyses by AMD subtypes and ethnicity.

To explore the source of heterogeneity and the effect of continuous variables on the estimate of effect size, we performed a meta-regression analysis, using mean age of the subjects and percentage of males as covariates (Thompson & Sharp 1999). To confirm the stability of findings, sensitivity analysis, removing each study one at a time, was performed.

The extent of publication bias was shown with a funnel plot and assessed by the Begg and Mazumdar rank

correlation test and the Egger's regression asymmetry test (Begg & Mazumdar 1994; Egger et al. 1997).

Except for the Q-test, $p < 0.05$ was considered statistically significant, and all tests were two-sided. All statistical analyses were performed using the comprehensive meta-analysis software (Version 2.0; Biostat Inc., Englewood, NJ, USA).

Results

Search findings and study characteristics

The detailed steps of the search strategy are given as a PRISMA flow diagram in Fig. 1. Briefly, a total of 7165 articles were retrieved from the databases and 3153 duplicates were excluded. Among the 4012 potentially eligible articles, 3842 were excluded after reading titles and/or abstracts. Thus, 170 articles were subjected to a full-text review, 75 of which met our inclusion criteria. Since the article by Rivera et al. (2005) investigated the association between rs1061170 polymorphism and AMD in two populations, the meta-analysis ultimately included data from 76 studies. Characteristics and genotype distribution from each individual study are listed in Table 1.

As required by the inclusion criteria, all studies had a case–control design or provided baseline data of prospective analysis. Overall, the meta-analysis included genotype data from 27 418 AMD patients and 32 843 controls; mean age ranged from 57.3 to 81.0 years and per cent of males ranged from 28.3% to 81.8%. Twenty-one studies grouped genotype data of cases in a group that included all AMD subtypes, whereas 55 studies reported data according to specific AMD subtypes. Among these, early and advanced AMD (wet and/or dry AMD) were investigated by 15 and 51 studies, respectively. According to advanced AMD subtypes, genotype data were provided by 38 studies from wet AMD patients and 14 studies from dry AMD patients. Thirty-nine studies were performed in participants of Caucasian ethnicity, 27 studies were conducted among Asians, three studies among Africans and seven studies have enrolled subjects of mixed ethnicity. All studies, except eight, observed HWE. The quality scores ranged from 4 to 9 and 50 studies were considered good quality.

Results of the meta-analysis

We initially performed a meta-analysis of the relationship between CFH rs1061170 variant and AMD, combining data of all AMD subtypes into the case group. The polymorphism showed a significant association with AMD under an allelic model (C vs. T; OR: 2.15; 95%CI 1.96–2.37). The Q-test and I^2 statistics indicated significant heterogeneity across the studies ($p < 0.001$; $I^2 = 90.47\%$,).

We also found a significant relationship under the heterozygous model (CT vs TT; OR: 2.12; 95% CI, 1.90–2.38) and under the homozygous model (CC vs TT; OR: 4.66; 95%CI, 3.81–5.69), with evidence of heterogeneity ($p < 0.001$; $I^2 = 83.07\%$ and $p < 0.001$; $I^2 = 88.15\%$, respectively).

To explore the source of heterogeneity, we performed an univariate meta-regression analysis based on the random-effects model (methods of moments). There was no statistically significant effect on the summary OR by mean age of study subjects ($p = 0.610$) and percentage of males ($p = 0.360$).

Subgroup analysis by AMD subtypes and ethnicity

In the subgroup analysis by AMD subtypes, the rs1061170 showed a significant association with early AMD (OR: 1.41; 95%CI 1.25–1.60) and advanced AMD (OR: 2.35; 95%CI 2.14–2.59), under an allelic model (Fig. 2). The Q-test and I^2 statistics indicated significant heterogeneity across studies ($p < 0.05$; $I^2 = 83.52\%$ and $p < 0.05$; $I^2 = 69.05\%$, respectively).

With regard to advanced AMD subtypes, the rs1061170 showed a significant association with dry AMD (OR: 2.52; 95%CI 1.78–3.57) and wet AMD (OR: 2.35; 95%CI 2.09–2.65), under an allelic model (Fig. 3). The Q-test and I^2 statistics indicated significant heterogeneity across studies ($p < 0.05$; $I^2 = 79.61\%$ and $p < 0.05$; $I^2 = 66.26\%$, respectively).

Then, we also performed a subgroup analysis by ethnicity. This analysis was limited to Caucasians and Asians because of the few studies available for Africans and the undetermined ethnicity of mixed populations.

In Caucasians, the rs1061170 showed a significant association with early AMD (OR: 1.44; 95%CI 1.27–1.63) and advanced AMD (OR: 2.47; 95%CI 2.24–2.72), under an allelic model. The Q-test and I^2 statistics indicated significant heterogeneity across studies ($p < 0.001$; $I^2 = 81.93\%$ and $p < 0.001$; $I^2 = 59.90\%$, respectively).

With regard to advanced AMD subtypes, the rs1061170 showed a significant association with dry AMD (OR: 2.90; 95%CI 1.89–4.47) and wet AMD (OR: 2.46; 95%CI 2.15–2.83), under an allelic model. The Q-test and I^2 statistics indicated significant heterogeneity across studies ($p < 0.001$; $I^2 = 74.63\%$ and $p = 0.003$; $I^2 = 56.34\%$, respectively).

In Asians, the rs1061170 showed a significant association with advanced AMD (OR: 2.09; 95%CI 1.67–2.60), but not with early AMD (p-value for Z test = 0.315), under an allelic model. The Q-test and I^2 statistics indicated significant heterogeneity across studies ($p < 0.001$; $I^2 = 73.32\%$ and $p = 0.001$; $I^2 = 81.909\%$, respectively).

With regard to advanced AMD subtypes, the rs1061170 showed a significant association with wet AMD (OR: 2.24; 95%CI 1.81–2.77), but not with dry AMD (p-value for Z test = 0.264), under an allelic model. The Q-test and I^2 statistics indicated significant heterogeneity across studies ($p < 0.001$; $I^2 = 69.64\%$ and $p < 0.001$; $I^2 = 92.30\%$, respectively).

For the sake of completeness, results of meta-analysis, subgroup analyses and heterogeneity across studies under homozygous and heterozygous models are summarized in Table S1.

Sensitivity analysis

To evaluate the robustness of the relationship between rs1061170 and AMD, a sensitivity analysis was performed by removing each study once at a time in every genetic model and recalculating the pooled OR. The summary OR remained stable under the allelic model, indicating that the association between rs1061170 and AMD subtypes was not driven by any single study. The sensitivity analysis also suggested that this finding was robust also under the heterozygous model and the homozygous model.

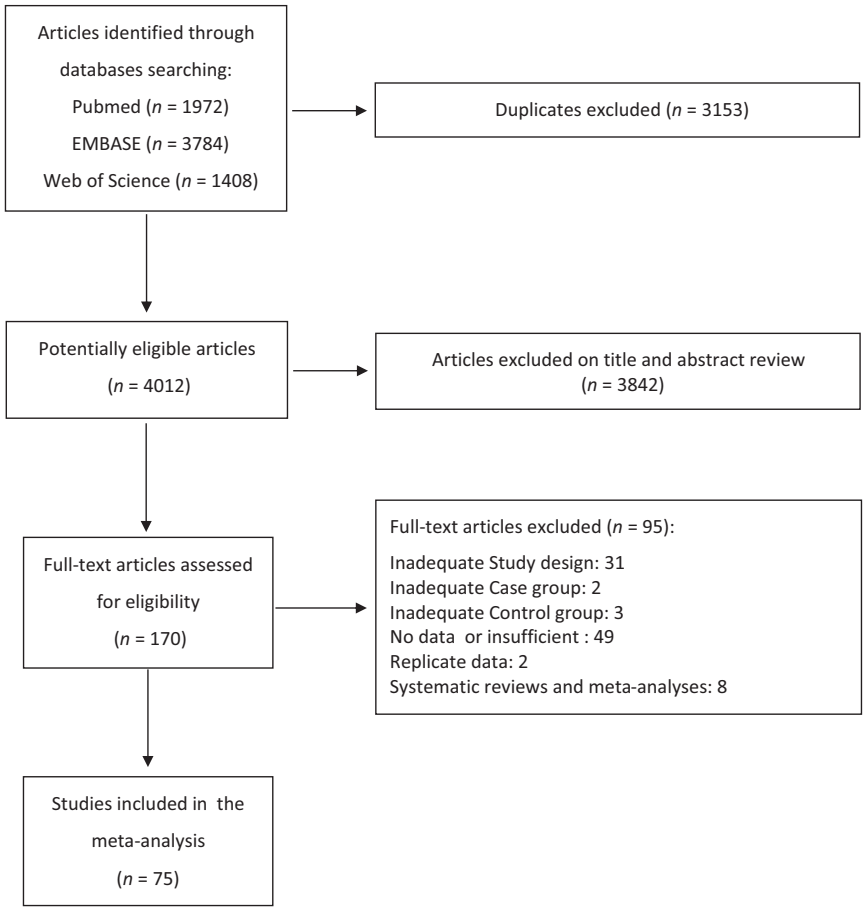

Fig. 1. Selection of studies included in the meta-analysis.

Publication bias

To determine the possible extent of publication bias, the symmetry of funnel plots was assessed by the Begg and Mazumdar rank correlation test and the Egger's regression asymmetry test. With regard to advanced AMD, symmetrical funnel plot was obtained under the allelic model (Fig. S1). Accordingly, neither the Begg and Mazumdar rank correlation test nor the Egger's test suggested publication bias for the association between rs1061170 polymorphisms and advanced AMD (p-value for Begg's test = 0.739; p-value for Egger's test = 0.524). Regarding to early AMD, the funnel plot indicated moderate asymmetry (Fig. S2), suggesting that publication bias cannot be completely excluded. Accordingly, the Egger's test but not the Begg and Mazumdar rank correlation test suggested publication bias for the association between rs1061170 polymorphisms and early AMD (p-value for Egger's test = 0.015; p-value for Begg's test = 0.656).

Discussion

The pathological features of AMD are mainly caused by the interaction of oxidative stress, impaired functions of the RPE, increased apoptosis and abnormal immune system activation (Seddon et al. 2006). Although smoking, low omega-3 diet and ageing represent the strongest non-genetic risk factors (Nozaki et al. 2006), genetic variants confer about the 60% of the attributable risk with 34 genomic loci implicated in disease pathogenesis (Swaroop et al. 2009). Genetic variants associated with the susceptibility to AMD are especially linked to complement system activity, lipid metabolism, extracellular matrix remodelling and angiogenesis (Swaroop et al. 2009; Fritsche et al. 2013).

The discovery of genetic variants in components of the complement system and findings that drusen are characterized by complement proteins and regulators (Hageman et al. 2001; Johnson et al. 2001; Mullins et al. 2001; Crabb et al. 2002) have aided the investigation of chronic local inflammation in the pathogenesis of AMD (Mullins et al. 2000). Although reduced complement system activity is frequently associated with decreased AMD risk, changes in its efficiency may be a hazardous compromise. In fact, some AMD-related genetic variants may also modulate the susceptibility to infections (Agbeko et al. 2010). Among these, the rs1061170 polymorphism in the *CFH* gene confers survival advantage against streptococcal infections in early life (Haapasalo et al. 2008). Accordingly, evidence that a combination of genetic variants may alter both systemic and local complement activation needs accurate investigations.

The rs1061170 polymorphism, located within a binding site for heparin and C-reactive protein, results in a malfunctioning CFH protein that is not able to inhibit the complement cascade. The relationship between this polymorphism and AMD has been well investigated, but the relatively small sample sizes in several studies have frequently hindered the assessment of the association. Moreover, these investigations show several differences with regard to population characteristics, disease subtypes and ethnic groups under examination.

It has been observed that the strength of the association between rs1061170 polymorphism and AMD seems to be lower when studies move from the West to the East, and the compelling association, observed in European cohorts, was not as relevant to the AMD risk in populations of Asian ancestry (Wu et al. 2016). Individual studies have been performed in Asian populations, but most of these reported a lack of association in Korean, Japanese and Chinese (Chen et al. 2006, 2013; Lau et al. 2006; Chu et al. 2008; Xu et al. 2008; Pei et al. 2009; Yang et al. 2010). To some extent, this controversy may be due to the low minor allele frequency in the Asian population. In European populations, there was strong evidence for association between the rs1061170 polymorphism and AMD; disease risk was increased by approximately 2.5-fold in individuals carrying at least 1 copy of the risk allele (Thakkinstian et al. 2006). More recently, several meta-analysis reported the evidence that the rs1061170 polymorphism is a

Table 1. Characteristics and genotype distribution of studies included in the meta-analysis.

First Author, year	Ethnicity	Genotyping method	Mean age	Male (%)	Type of AMD	Total cases	CC	TC	TT	Total controls	CC	TC	TT	HWE*	Quality score
Abbas & Azzazy 2013	African	RFLP	63.0	56.5	All	20	5	11	4	15	0	5	10	Yes	7
Almeida et al. 2013	Mixed	Real-time PCR-based (TaqMan)	75.0	53.9	All	161	54	74	33	290	71	66	153	No	7
Babanejad et al. 2016	Asian	RFLP	NA	60.0	All	100	32	58	10	100	9	40	51	Yes	7
Baird et al. 2006	Caucasian	Direct sequencing	67.8	29.5	All	236	91	109	36	144	14	79	51	No	7
					Early	117	39	56	22						
					Advanced	119	52	53	14						
					Wet	93	38	45	10						
					Dry	26	14	8	4						
Bonyadi et al. 2016	Asian	RFLP	74.3	59.2	Advanced	254	80	133	41	164	34	68	62	Yes	7
					Wet	175	52	102	21						
					Dry	79	28	31	20						
Brantley et al. 2007	Caucasian	Direct sequencing	74.7	62.0	Advanced	188	57	93	38	189	18	93	78	Yes	7
					Wet	155	50	76	29						
Buentello-Volante et al. 2012	Mixed	Direct sequencing	75.2	30.5	Advanced	159	18	57	84	152	3	24	125	Yes	5
Chakravarthy et al. 2013	Caucasian	Competitive alle-specific PCR SNP genotyping	73.2	45.0	All	2275	386	1056	833	2058	244	977	837	Yes	8
					Early	2136	347	983	806						
					Advanced	139	39	73	27						
Chen et al. 2006	Asian	Real-time PCR-based (TaqMan)	74.3	49.6	Wet	163	1	17	145	244	0	19	225	Yes	7
Chen et al. 2013	Asian	Real-time PCR-based (TaqMan)	61.6	28.3	Early	158	146	12	0	157	144	13	0	Yes	7
Chowers et al. 2008	Mixed	MALDI-TOF MS	75.7	NA	Wet	240	58	127	55	118	15	54	49	Yes	7
Chu et al. 2008	Asian	RFLP	67.2	54.8	Wet	144	1	34	109	126	1	11	114	Yes	7
Conley et al. 2005	Caucasian	RFLP	73.1	41.7	All	168	65	81	22	108	14	40	54	Yes	6
Delcourt et al. 2011	Caucasian	Real-time PCR-based (TaqMan)	80.0	36.6	All	273	40	123	110	523	51	222	250	Yes	8
					Early	228	33	101	94						
					Advanced	45	7	22	16						
					Wet	24	5	15	4						
					Dry	21	2	7	12						
Despriet et al. 2006	Caucasian	Real-time PCR-based (TaqMan)	68.7	40.5	All	2062	364	910	788	3619	417	1644	1558	Yes	9
					Early	1984	333	875	776						
					Advanced	78	31	35	12						
Dong et al. 2011	Asian	RFLP	70.4	59.1	Wet	136	4	56	76	140	2	21	117	Yes	7
Droz et al. 2008	Caucasian	PCR followed denaturing high-performance liquid chromatography (DHPLC) analysis and denaturing high-performance liquid chromatography (DHPLC) analysis	75.6	36.3	All	420	139	210	71	50	4	27	19	Yes	9
					Early	156	47	83	26						
					Advanced	264	92	127	45						
					Wet	208	70	100	38						
					Dry	56	22	27	7						
Edwards et al. 2005	Caucasian	Real-time PCR-based (TaqMan)	72.7	54.2	All	395	124	186	85	190	26	83	81	Yes	5
Fisher et al. 2007	Caucasian	Direct sequencing	72.6	27.7	All	155	38	69	48	150	24	59	67	Yes	6

Table 1. (Continued)

First Author, year	Ethnicity	Genotyping method	Mean age	Male (%)	Type of AMD	Total cases	CC	TC	TT	Total controls	CC	TC	TT	HWE*	Quality score
Fourgeux, 2012	Caucasian	RFLP	76.1	34.8	Advanced	1388	389	708	291	487	65	234	188	Yes	7
Fuse et al. 2006	Asian	Direct sequencing	70.0	57.9	Dry	80	0	7	73	192	2	24	166	Yes	5
Gangnon et al. 2012	Caucasian	NA	65.0	43.3	All	2901	446	1465	990	8474	1089	3903	3482	Yes	8
					Early	2607	375	1285	947						
					Advanced	294	71	180	43						
García et al. 2015	Caucasian	Real-time PCR-based (TaqMan)	75.8	41.6	Advanced	130	41	66	23	96	11	44	41	Yes	5
Goverdhan et al. 2008	Caucasian	Real-time PCR-based (TaqMan)	73.8	42.4	All	557	167	258	132	551	75	261	215	Yes	7
Gu et al. 2009	Caucasian	Direct sequencing	NA	NA	All	788	244	384	160	381	48	172	161	Yes	8
					Early	262	75	123	64						
					Advanced	526	169	261	96						
Haas et al. 2009	Caucasian	Direct sequencing	76.8	48.0	Advanced	75	18	40	17	75	10	29	36	Yes	7
					Wet	66	17	35	14						
					Dry	9	1	5	3						
Habibi et al. 2013	African	Direct sequencing	70.9	53.4	All	127	51	64	12	135	10	60	65	Yes	8
					Advanced	117	48	59	10						
					Wet	105	45	51	9						
					Fibro vascular	10	3	5	2						
					Dry	12	3	8	1						
Hageman et al. 2005	Caucasian	Direct sequencing	73.9	NA	All	952	306	454	192	403	53	169	181	Yes	8
Hao et al. 2015	Asian	RFLP	61.7	59.5	All	109	1	20	88	165	1	16	148	Yes	6
Hautamäki et al. 2015	Caucasian	Direct sequencing	NA	34.8	Advanced	329	129	162	38	41	13	59	41	Yes	6
					Wet	301	109	154	38						
					Dry	28	20	8	0						
Hayashi et al. 2010	Asian	Real-time PCR-based (TaqMan)	57.3	57.7	Wet	401	7	75	319	1342	8	160	1174	Yes	8
Huang et al. 2014	Asian	MALDI-TOF MS	68.0	52.0	Wet	312	8	52	252	461	1	57	403	Yes	7
Nazari Khanamiri et al. 2014	Asian	Direct sequencing	71.2	48.7	All	70	24	33	13	86	15	36	35	Yes	7
Kim et al. 2008	Asian	Direct sequencing	67.4	46.8	Wet	114	1	22	91	187	1	22	164	Yes	6
Kim et al. 2013	Asian	RFLP	NA	NA	Wet	114	0	26	88	240	2	34	204	Yes	6
Klein et al. 2005	Caucasian	Microarray	80.0	47.4	Advanced	95	42	39	14	48	6	25	17	Yes	5
Lau et al. 2006	Asian	RFLP	76.1	81.8	Wet	163	6	25	132	232	0	13	219	Yes	6
Lin et al. 2008	Asian	Real-time PCR-based (Melting curve analysis)	70.5	54.3	Early	133	8	19	106	180	0	16	164	Yes	7
Losonczy et al. 2011	Caucasian	RFLP	76.1	52.5	All	105	38	38	29	95	7	49	39	Yes	7
					Early	48	15	16	17						
					Advanced	57	23	22	12						
Magnusson et al. 2005	Caucasian	Real-time PCR-based (TaqMan)	NA	NA	All	1330	422	644	264	1265	182	613	470	Yes	6
Marioli et al. 2009	Caucasian	Direct sequencing	77.7	37.0	All	100	36	49	15	115	23	39	53	No	6
					Early	40	10	23	7						
					Advanced	60	26	26	8						
Mori et al. 2007	Asian		69.6	65.7	All	188	3	27	158	139	0	15	124	Yes	7

Table 1. (Continued)

First Author, year	Ethnicity	Genotyping method	Mean age	Male (%)	Type of AMD	Total cases	CC	TC	TT	Total controls	CC	TC	TT	HWE*	Quality score
		Real-time PCR-based (TaqMan)													
Narayanan et al. 2007	Caucasian	Direct sequencing	76.0	NA	Advanced	66	21	34	11	58	7	22	29	Yes	5
					Wet	51	13	29	9						
					Dry	15	8	5	2						
Ng et al. 2008	Asian	Direct sequencing	74.3	50.3	Wet	163	1	17	145	155	0	9	146	Yes	7
Okur et al. 2015	Mixed	Direct sequencing	67.6	52.7	Advanced	87	25	44	18	80	12	37	31	Yes	7
					Wet	45	11	25	9						
					Dry	42	14	19	9						
Pei et al. 2009	Asian	Direct sequencing	69.9	53.0	Wet	123	2	28	93	130	0	12	118	Yes	5
Pulido et al. 2007	Caucasian	RFLP	NA	NA	Wet	89	32	31	26	230	25	104	101	Yes	4
Reynolds et al. 2009	Caucasian	MALDI-TOF MS	81.0	50.0	Advanced	103	40	43	20	56	10	18	28	No	9
					Wet	51	21	22	8						
					Dry	52	19	21	12						
Ricci et al. 2009	Caucasian	Real-time PCR-based (TaqMan)	71.3	44.7	Wet	101	27	55	19	100	5	48	47	Yes	6
Rivera et al. 2005 (population A)	Caucasian	MALDI-TOF MS and sequencing	76.3	36.2	All	793	288	368	137	611	70	327	214	No	5
Rivera et al. 2005 (population B)	Caucasian	MALDI-TOF and sequencing	71.8	37.3	All	373	149	162	62	335	46	148	141	Yes	5
Schaumberg et al. 2006	Caucasian	Real-time PCR-based (TaqMan)	NA	NA	All	111	25	49	37	401	55	166	180	Yes	7
Schaumberg et al. 2007	Caucasian	Real-time PCR-based (TaqMan)	60.2	35.8	All	437	130	208	99	1015	131	462	422	Yes	8
Seddon et al. 2006	Caucasian	MALDI-TOF MS	68.4	46.3	Advanced	574	228	250	96	280	41	126	113	Yes	8
					Wet	429	166	190	73						
					Dry	145	62	60	23						
Seddon et al. 2010	Caucasian	MALDI-TOF MS	NA	NA	All	244	74	115	55	209	30	89	90	Yes	8
					Advanced	69	32	30	7						
Sharma et al. 2013	Asian	Real-time PCR-based (TaqMan)	63.4	65.3	Advanced	109	44	45	20	59	6	8	45	No	7
					Wet	80	31	33	16						
					Dry	29	13	12	4						
Simonelli et al. 2006	Caucasian	Real-time PCR-based (TaqMan)	72.4	45.96	All	104	39	41	24	131	21	61	49	Yes	7
Soheilian et al. 2016	Asian	RFLP	73.3	61.3	Wet	137	44	90	3	92	6	37	49	Yes	6
Souied et al. 2005	Caucasian	Direct sequencing	74.4	40.0	Wet	141	48	63	30	91	11	33	47	Yes	8
Soysal et al. 2012	Mixed	RFLP	68.2	54.0	All	147	44	71	32	105	15	45	45	Yes	6
Sundaresan et al. 2012	Asian	Real-time PCR-based (TaqMan)	NA	49.1	All	1634	164	663	807	1862	187	804	871	Yes	8
					Early	1594	158	642	794						
					Advanced	40	6	21	13						
Tanimoto et al. 2007	Asian	Real-time PCR-based (TaqMan)	73.5	70.1	Wet	95	3	20	72	99	2	13	84	Yes	7
Tedeschi-Blok et al. 2007	Caucasian	RFLP	58.3	NA	Early	285	12	93	180	570	14	165	391	Yes	9
Teixeira et al. 2010	Mixed	Direct sequencing	72.4	37.1	All	119	44	46	29	152	20	71	61	Yes	7

Table 1. (Continued)

First Author, year	Ethnicity	Genotyping method	Mean age	Male (%)	Type of AMD	Total cases	CC	TC	TT	Total controls	CC	TC	TT	HWE*	Quality score
Teper et al. 2012	Caucasian	Direct sequencing	NA	NA	Wet	90	28	47	15	40	22	3	15	No	5
Tian et al. 2012	Asian	MALDI-TOF MS	66.6	53.8	All	489	9	89	391	445	1	49	395	Yes	7
					Early	62	1	6	55						
					Advanced	427	8	83	336						
					Wet	420	8	81	331						
Uka et al. 2006	Asian	Real-time PCR-based (TaqMan)	72.4	58.5	Wet	67	3	13	51	107	3	18	86	Yes	7
Velissari et al. 2015	Caucasian	Real-time PCR-based (Melting curve analysis)	77.5	55.6	Wet	120	39	54	27	103	16	51	36	Yes	7
Wang et al. 2015	Asian	RFLP	66.0	36.2	All	119	0	33	86	99	0	10	89	Yes	6
Wegscheider et al. 2007	Caucasian	RFLP	77.6	39.9	Wet	179	63	92	24	163	14	68	81	Yes	6
Xu et al. 2008	Asian	RFLP	66.1	54.9	Wet	121	1	23	97	132	0	21	111	Yes	7
Yang et al. 2010	Asian	RFLP	64.8	46.7	Wet	110	2	22	86	150	2	22	126	Yes	7
Yücel et al. 2012	Mixed	RFLP and sequencing	69.4	56.6	Advanced	95	0	67	28	87	0	47	40	No	7
					Wet	26	0	20	6						
					Dry	69	0	47	22						
Zareparsi et al. 2005	Caucasian	Direct sequencing	77.8	37.8	All	616	219	311	86	275	25	136	114	Yes	7
Zerbib et al. 2011	Caucasian	Real-time PCR-based (TaqMan)	76.1	34.8	Wet	1093	309	553	231	396	54	188	154	Yes	7
Ziskind et al. 2008	African	RFLP	NA	NA	Early	16	5	7	4	98	13	56	29	Yes	5

AMD = age-related macular degeneration; DHPLC = denaturing high-performance liquid chromatography; MALDI-TOF MS = matrix-assisted laser desorption ionization–time-of-flight mass spectrometry; NA = not available; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; SNP = single nucleotide polymorphism.
* Hardy–Weinberg equilibrium in control group.

risk factor for AMD in Asian populations (Kondo et al. 2011; Quan et al. 2012; Wu et al. 2016).

The high variability in the strength of association, reported by different studies, may be due to an increased genetic effect with age, but it may also represent a variation between early and advanced AMD. Previous individual studies have reported that the rs1061170 polymorphism was associated to AMD with similar risk estimates within AMD subtypes (Magnusson et al. 2006), whereas others have showed a stronger association with neovascular AMD (Haines et al. 2005). In Asians, the meta-analysis by Wu et al. suggested that the effect might be more relevant for the CNV, thought the related mechanism still remained uncertain (Wu et al. 2016).

Our study reported results of a more comprehensive meta-analysis and provides subgroup analyses to evaluate the effect of the rs1061170 polymorphism on different AMD subtypes and ethnicities. Overall, we combined genotype data from 76 case–control studies, including 27 418 AMD patients and 32 843 controls.

Consistently with the previous meta-analyses (Thakkinstian et al. 2006; Kondo et al. 2011; Quan et al. 2012; Wu et al. 2016), our results showed a significant association between the rs1061170 polymorphism and the risk of all AMD subtypes, with a summary allele OR of 2.15. However, our analysis indicated significant between-study heterogeneity, with an I^2 measure that ranged from 81.2% to 92.4% in any genetic model. To explore the source of heterogeneity, we initially performed an univariate meta-regression analysis, which revealed no statistically significant effect of demographics variables (mean age and percentage of males) on the summary ORs.

Moreover, we performed subgroup analyses by AMD subtypes and ethnicity. In Caucasians, the risk was lower for early AMD (OR of 1.44 under the allelic model) compared to advanced AMD (OR of 2.47). Particularly, the mutant allele conferred a 2.9-fold increased risk of dry AMD and a 2.5-fold increased risk of wet AMD. In Asians, the rs1061170 polymorphism was significantly associated with advanced AMD, but not with early AMD. It is worth of note that the mutant allele conferred a 2.2-fold

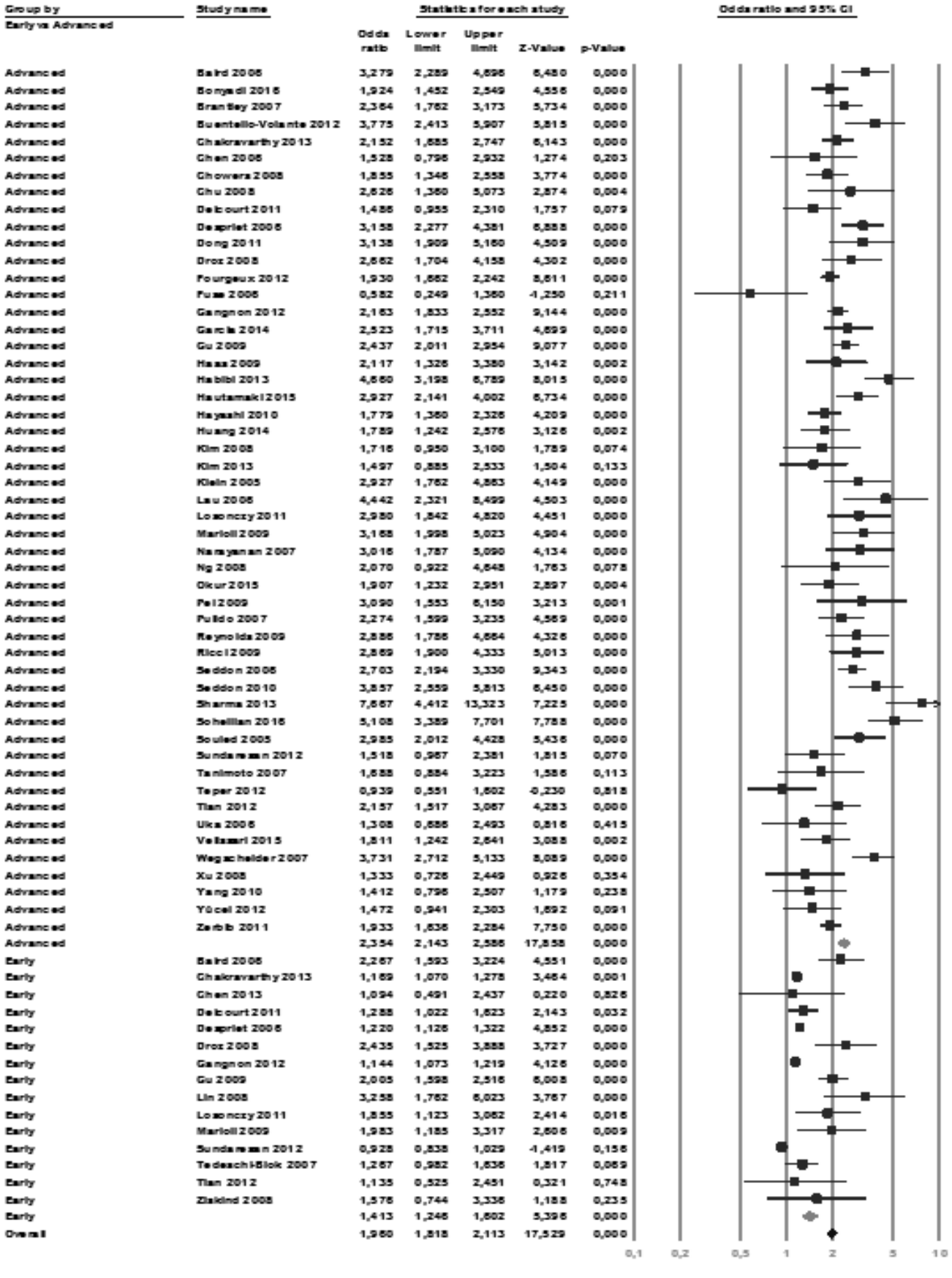

Fig. 2. Association between rs1061170 and age-related macular degeneration under an allelic model/Subgroup analysis by age-related macular degeneration subtypes based on the random effects model.

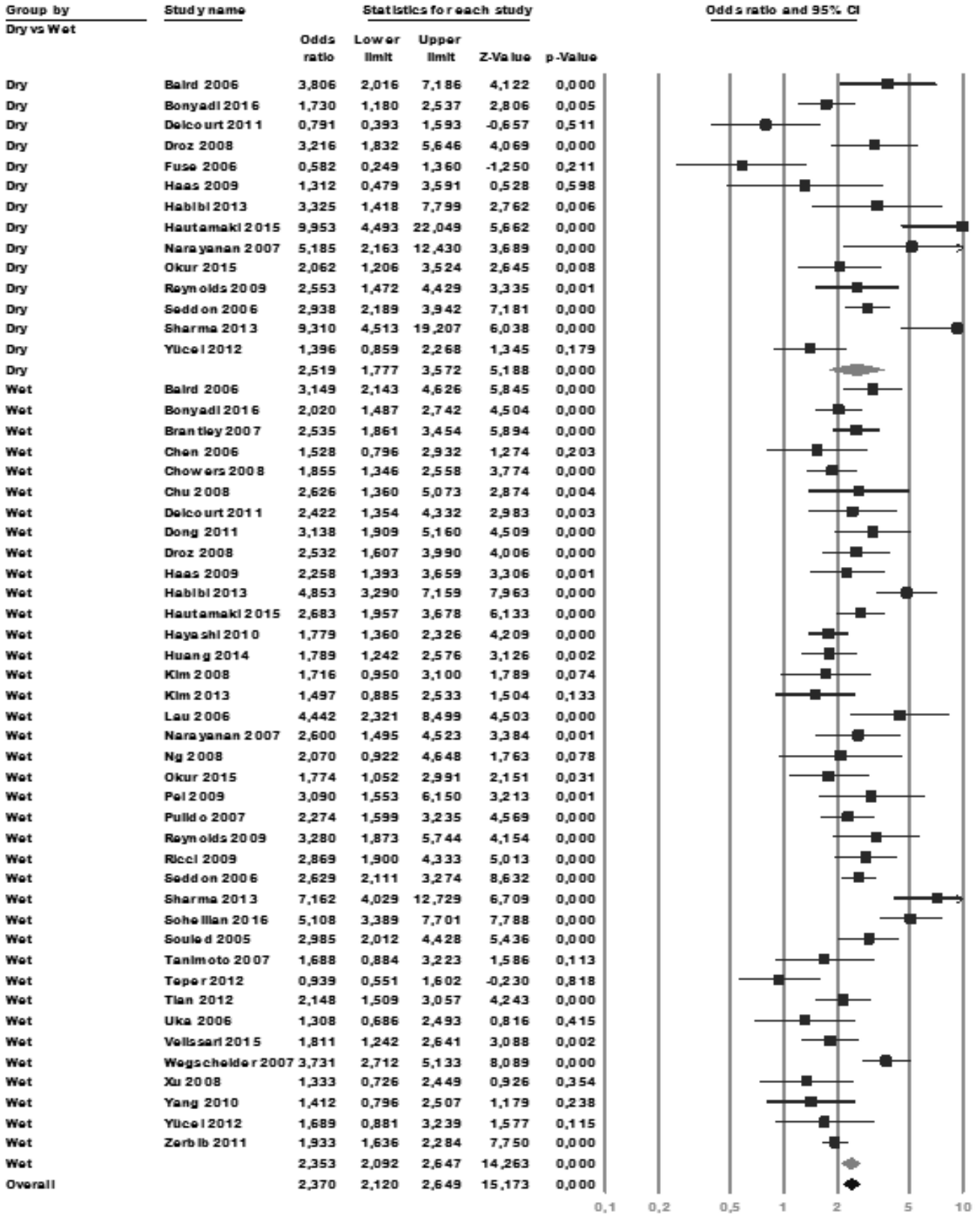

Fig. 3. Association between rs1061170 and advanced age-related macular degeneration (AMD) under an allelic model/subgroup analysis by AMD subtypes based on the random effects model.

increased risk of wet AMD, but it was not associated with the risk of dry AMD.

As mentioned previously, the controversy between Caucasian and Asian populations may be due to the low minor allele frequency in the Asians. However, it is well-known the suggestion that the genetic effects of disease-

associated variants are usually similar across ethnicities, regardless of divergent allelic frequency between different populations (Ioannidis et al. 2004). Thus, controversial results raise the need for the reliable assessment of the association between rs1061170 polymorphism and AMD, particularly in the Asian populations.

The main limitation of this meta-analysis is the high heterogeneity across studies. To take into account this issue, data of individual studies were combined through a random effects model; consequently, the pooled ORs should be interpreted with caution. Moreover, to explore the source of heterogeneity, a meta-regression was conducted and the pooled ORs were calculated in more homogeneous subsets of studies through a subgroups analysis. In addition, the possible existence of a publication bias was considered and the symmetry of funnel plots was assessed by the Begg's test and Egger's regression asymmetry test. No publication bias was detected under any genetic model. Finally, AMD is a complex disorder with sociodemographic, environmental and genetic risk factors. Although potential confounding factors and gene-environment interactions should be considered, not all included studies provided adjusted ORs. Thus, the present meta-analysis combined crude ORs from each study and hence the effect of confounders cannot be completely excluded. To partially overcome this weakness, we performed a meta-regression, adjusting for age and gender, and then we stratified our analysis by ethnicity.

Conclusions

Our work provides the most comprehensive meta-analysis of studies investigating the role of the rs1061170 polymorphism on AMD risk. These findings not only improve the comprehension of AMD pathogenesis, but also constitute a scientific background to be translated into clinical practice for AMD prevention (Gorin 2012). Because of the genetic discoveries in AMD, several prediction models, able to predict AMD risk, are now widely available. However, findings from the evaluation of these models are not encouraging, because the same subject can receive controversial results (Simone et al. 2013; Kalf et al. 2014). To overcome this issue, genetic tests for AMD should be based on a more accurate assessment of disease risk. Although convincing evidence shows that the rs1061170 polymorphism is a risk factor for all AMD subtypes in Caucasians, well-designed studies with larger sample and more ethnic groups size are required. In Asians, in fact, the polymorphism seems to be closely associated with neo-vascular AMD. Thus, given the above-mentioned limitations, further investigations are needed to better clarify the effect of genetic susceptibility in the development of AMD and its perspectives for disease prevention.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Search strategy to identify studies.
Figure S1. Funnel plot of random-effect meta-analysis of the association between rs1061170 and early age-related macular degeneration under an allelic model.
Figure S2. Funnel plot of random-effect meta-analysis of the association between rs1061170 and advanced age-related macular degeneration under an allelic model.
Table S1. Results of meta-analyses and subgroup analyses under the allelic model, the homozygous and the heterozygous models.