

Association of ARMS2/LOC387715 A69S, CFH Y402H, and CFH I62V polymorphisms with retinal angiomatous proliferation compared with typical age-related macular degeneration: a meta-analysis

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Abstract

Purpose To compare the published results of studies on the genotype association of ARMS2/LOC387715 A69S, CFH Y402H, and CFH I62V in cases diagnosed as retinal angiomatous proliferation (RAP) versus neovascular age-related macular degeneration (AMD) or healthy controls.

Methods Heterogeneity of studies was evaluated using Cochran's *Q* test and *I*-square index. To modify the heterogeneity in the variables, we used random effects model. Meta-analysis was performed using STATA.

Results Four studies were included with 1076 neovascular AMD patients, 222 RAP cases, and 2276 control subjects. Pooled overall odds ratios for RAP/AMD were 1.15 (95% CI 0.60–2.18) for GT versus GG, 3.52 (95% CI 1.25–9.91) for TT versus GG ARMS2, 0.98 (95% CI 0.22–4.29) for GA versus AA, 1.00 (95% CI 0.25–4.02) for GG versus AA CFHI62V,

0.57 (95% CI 0.35–0.93) for CT versus TT CFH Y402H, and 0.40 (95% CI 0.22–0.74) for CC versus TT CFH Y402H. Regression analysis showed that ARMS2 TT genotype has a statistically significant effect on RAP versus AMD compared to CFH genotypes ($P < 0.001$).

Conclusion This meta-analysis disclosed a stronger effect of ARMS2 genotypes in RAP cases compared with CFH Y402H and I62V genotypes.

Keywords Meta-analysis · ARMS2/LOC387715 A69S · CFH Y402H · CFH I62V · Age-related macular degeneration (AMD) · Retinal angiomatous proliferation (RAP) · Mechanism of pathogenesis

Introduction

Age-related macular degeneration (AMD) is the primary cause of irreversible central visual loss in the geriatric population with deleterious global effect on the quality of life [1]. Retinal angiomatous proliferation (RAP) is a rare variant of neovascular AMD which is characterized by intraretinal neovascularization and retinal–retinal and retinal–choroidal anastomosis [2, 3]. The exact developmental mechanism of RAP remains unclear and its natural history is characterized by a rapid loss of vision and resistance to various treatments [4, 5]. Two major genetic loci which have been described in association with an increased risk of

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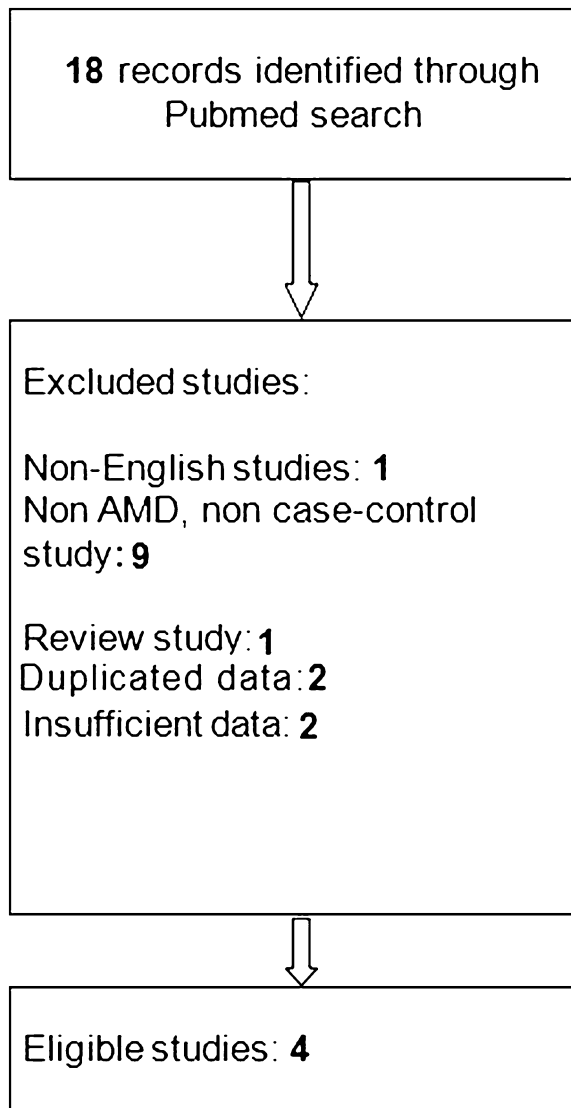


Fig. 1 Summary of study search and selection in this meta-analysis. There is one non-English review article

AMD are the age-related maculopathy susceptibility 2 (ARMS2)/LOC387715 locus mapped on chromosome 10q26 and the complement factor H (CFH) gene mapped on chromosome 1q31 [6–8].

Thinner subfoveal choroidal thickness with resultant compromised choroidal perfusion has highlighted the role of sub-retinal pigment epithelium (RPE) tissues in the development of RAP [9]. Some authors have suggested that, with regard to the location of neovascular lesions, the effect of the CFH polymorphism is weaker for RAP than for typical neovascular AMD, while the risk genotypes of the ARMS2 may

have stronger effect [10, 11]. They theorized that the location of characteristic neovascularization corresponds to the location of susceptible gene expression in each subtype of AMD, while CFH may play a major role beneath the RPE (primarily in the RPE, drusen, and choroidal capillaries) [7], and ARMS2 would have a major role above the RPE (shown by some authors to be expressed in the ellipsoid region of the photoreceptor cells) [10, 12]. In accordance with Yannuzzi et al. [2] who proposed that the origin of RAP neovascularization is the neural retina, the above-mentioned authors also postulated the major role of ARMS2 gene compared to CFH gene in the pathogenesis of RAP. According to this theory, increased systemic complement activation has been shown in neovascular AMD but not in RAP cases [13]. Common pathway of mechanism between ARMS2 and CFH genes in AMD pathogenesis through complement system [14], development of choroidal neovascularization in the course of RAP [3], and Gass et al.'s [15] theory which suggested the choroidal origin of these vessels further complicate the clarifying role of sub- or supra-RPE tissues in this disease.

One of the major limitations of the studies on RAP is its rarity and limited genotype information, though in this study we decided to perform a meta-analysis to pool the published results of studies on ARMS2/LOC387715 A69S, CFH Y402H, and CFH I62V genotypes in RAP versus neovascular AMD or healthy controls to evaluate the magnitude of the effect of each gene in RAP pathogenesis.

Materials and methods

Search strategy

To understand the significance of the observed associations across the ARMS2/LOC387715 (rs10490924), CFH Y402H, and CFH I62V (rs800292) genotypes in RAP versus neovascular AMD or healthy controls in different studies, we designed a meta-analysis with the calculation of the estimated odds ratios (OR). The included studies were based on a literature search in PubMed in February 2016 with the phrases (RAP or retinal angiomatous proliferation) and (ARMS or age-related maculopathy susceptibility or age related maculopathy susceptibility or LOC387715 or CFH or complement factor H) in title or abstract.

Table 1 General characteristics of studies included in the meta-analysis

References	Age (nAMD/RAP/control)	Number (nAMD/RAP/control)	Male (nAMD/RAP/control) (%)	Smoking (nAMD/RAP/control)(%)	Type of case	Type of control	HWE
Yoneyama et al. [16]	75.6 ± 8.4/82.7 ± 7.9/72.4 ± 8.8	157/27/205	72.6/37.0/50.7	–	nAMD: Classic/occult CNV in FA without polypoidal lesions in ICGA RAP: based on OCT and angiography including FA and ICGA	No retinal or choroidal vascular pathology	+
Caramoy et al. [17]	76.7 ± 7.8/79.2 ± 7.1/72.7 ± 7.8	258/108/443	35.3/30.6/43.1	59.7/56.6/59.5	RAP: based on ICGA nAMD: occult or classic CNV no enrollment of patients with retinal scars, if no sufficient history of RAP or CNV was present	Healthy controls	+
Tanaka et al. [18]	73.7 ± 7.5/80.1 ± 6.8/72.9 ± 8.7	253/51/277	74.3/37.2/40.1	34.8/15.7/17.7	Based on fundus photography, fluorescein angiography, and indocyanine green angiography	No AMD	–
Hayashi et al. [19]	77.7 ± 8.4/83.8 ± 7.0/51.2 ± 16.3	408/36/1351	71.8/52.7/53.4	–	nAMD: classic CNV, occult CNV, or both RAP: based on fundus biomicroscopy, fluorescein angiography, ICGA, and OCT	Healthy controls	–
Pooled number nAMD: 1076, RAP: 222, controls: 2276							

HWE Hardy–Weinberg equilibrium, (+) indicates Hardy–Weinberg equilibrium in all groups (controls, AMD and RAP patients) for all genotypes, nAMD neovascular age-related macular degeneration, RAP retinal angiomatous proliferation, CNV choroidal neovascularization, ICGA indocyanine green angiography, OCT optical coherence tomography

Data extraction

Two retina specialists (MHJB and MS) identified relevant studies and reviewed all titles/abstracts and full-text manuscripts of the identified studies separately in order to select those for inclusion. Any human-based association study, regardless of ethnicity or sample size, was included if it met the following criteria: the main outcome of interest or one of the study outcomes was RAP; there were at least 2 comparison groups (RAP vs. control group or neovascular AMD or both); and there were sufficient results for the extraction of data. Summary data were extracted independently and in duplicate by two of the authors (MHJB and MS) using a standardized data extraction form. Other data such as mean age, gender, and proportion of smokers were also extracted for analysis. Any disagreements between these authors were resolved by consensus. The articles were restricted to the English language. Figure 1 illustrates the summary of study search and selection in this meta-analysis.

Statistical analysis

To present data, we used mean, standard deviation, range, frequency, and percent. In order to determine whether SNP was in the Hardy–Weinberg equilibrium (HWE), a Chi square test was performed in all groups of studies.

We used forest plots for the estimation of the effect of each study and pooled effect of all studies with their confidence interval (CI) to provide a visual summary of the data. Heterogeneity of studies was evaluated using Cochran's Q test and I -square index, and $P < 0.05$ was considered as heterogeneity. To modify the heterogeneity in the variables, we used random effects model. Meta-analysis was performed using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Funnel plot (qualitative method) and Egger's regression test (quantitative method) were used for the evaluation of possible publication bias. Using an interaction term in a random effect logistic regression, we evaluated the difference in the effects of ARMS2 and CFH on the odds ratios of RAP versus neovascular AMD.

Results

Of the 18 screened articles, four studies [16–19] were identified to be eligible using our search strategy for inclusion in the meta-analysis. Characteristics of the included studies are described in Table 1.

Publication bias was assessed using Egger's test as follows:

RAP versus control group coefficient = 0.19, 95% CI –3.81 to 4.20, $P = 0.85$ for ARMS2 TG/GG; coefficient = 2.28, 95% CI 0.46–4.1, $P = 0.03$ for ARMS2 TT/GG; coefficient = 2.97, 95% CI –9.77 to 15.72, $P = 0.21$ for CFH I62V GA/AA; and coefficient = 2.57, 95% CI –4.59 to 9.74, $P = 0.14$ for CFHI62V GG/AA.

RAP versus neovascular AMD group coefficient = 1.12, 95% CI –2.85 to 5.09, $P = 0.35$ for ARMS2 TG/GG; coefficient = 2.77, 95% CI –0.29 to 5.83, $P = 0.06$ for ARMS2 TT/GG; coefficient = 3.31, 95% CI –12.49 to 19.13, $P = 0.23$ for CFHI62V GA/AA; and coefficient = 3.12, 95% CI –5.54 to 11.79, $P = 0.14$ for CFHI62V GG/AA.

We had two studies containing CFH Y402H data though Egger's test for publication bias was not possible for its genotypes.

Accumulation of data from these studies provided a total sample size of 3574 cases and controls; among them, RAP group sample size was 222 versus 1076 in the neovascular AMD group and 2276 in the control group. To modify the heterogeneity between studies, the results were pooled using a random effects analysis.

Pooled overall ORs for RAP versus control 2.96 (95% CI 1.90–4.62) for GT versus GG ARMS2; 28.54 (95% CI 13.83–58.93) for TT versus GG ARMS2; 1.82 (95% CI 0.49–6.70) for GA versus AA CFHI62V; and 3.79 (95% CI 1.26–11.38) for GG versus AA CFHI62V (Figs. 2, 3).

Pooled overall ORs for RAP versus AMD 1.15 (95% CI 0.60–2.18) for GT versus GG ARMS2; 3.52 (95% CI 1.25–9.91) for TT versus GG ARMS2; 0.98 (95% CI 0.22–4.29) for GA versus AA CFH I62V; and 1.00 (95% CI 0.25–4.02) for GG versus AA CFH I62V (Figs. 4, 5).

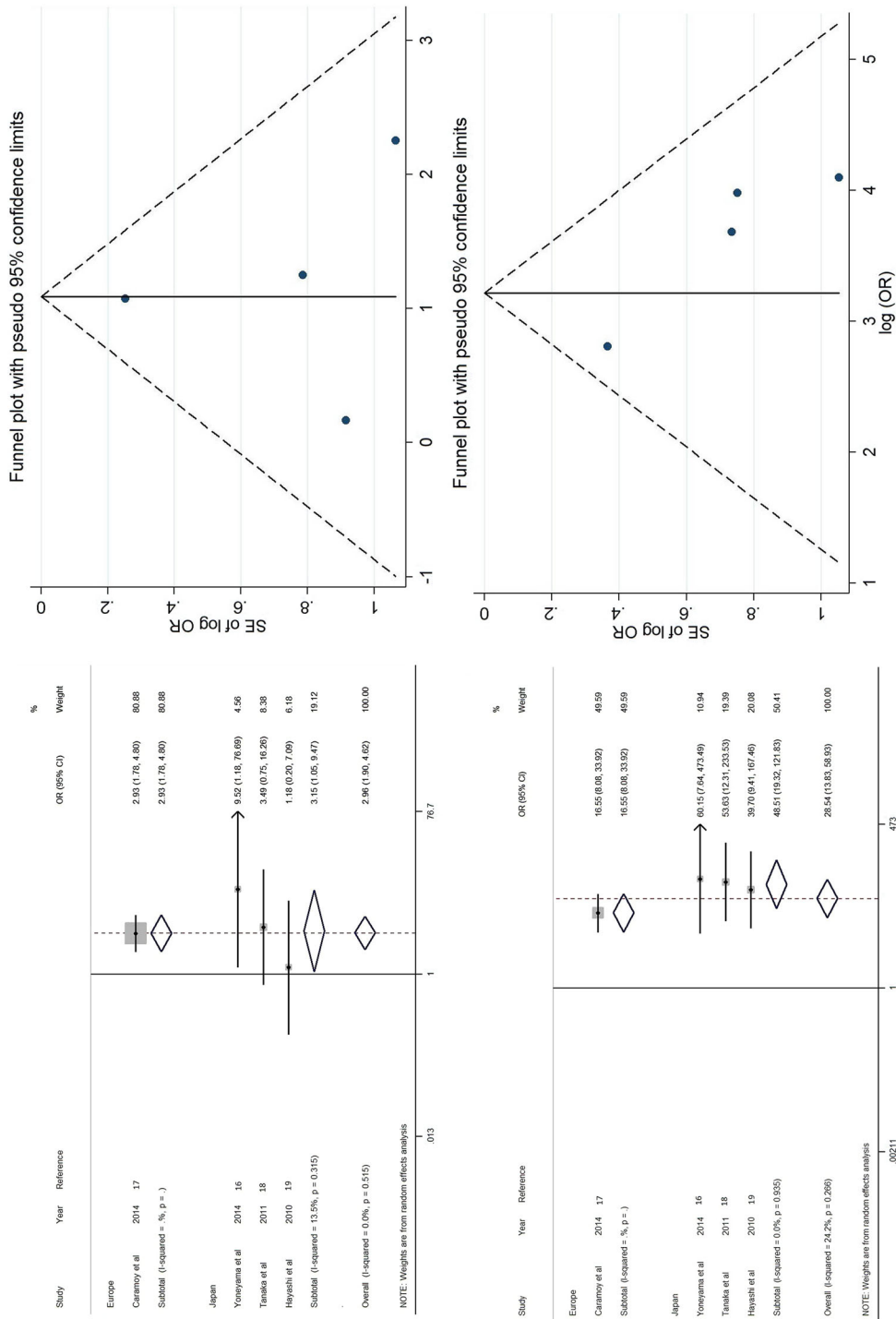


Fig. 2 Right side funnel plots for the effect of ARMS2/LOC387715 A69S (rs10490924) in RAP versus control (upper part GT vs. GG, lower part TT vs. GG). These plots indicate that most studies are in the non-significant bias area (the area between the two lines). Left side forest plots for the effect of ARMS2/LOC387715 A69S (rs10490924) in RAP versus control [individual and pooled odds ratio estimates for GT vs. GG (upper part) and TT vs. GG (lower part)]. The pooled odds ratio is indicated by diamond using a random effect model for analysis. CI confidence interval (horizontal lines). Diamond the pooled estimate of the odds ratios. I²: index for heterogeneity of studies

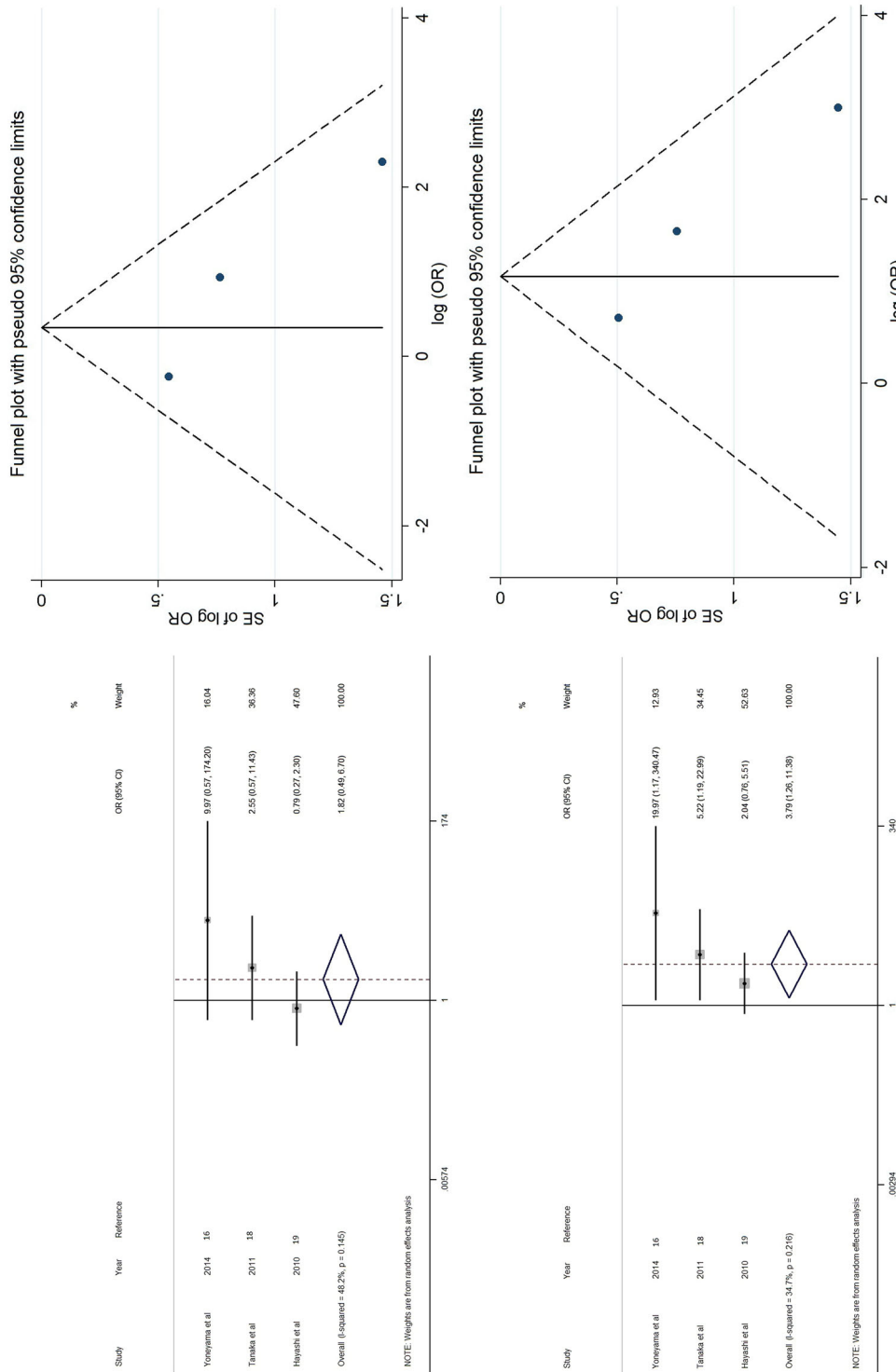


Fig. 3 Right side funnel plots for the effect of CFH I62V rs800292 in RAP versus control (upper part GG vs. AA, lower part GG vs. AA). These plots indicate that most studies are in the non-significant bias area (the area between the two lines). Left side forest plots for the effect of CFH I62V rs800292 in RAP versus control [individual and pooled odds ratio estimates for GA vs. AA (upper part) and GG vs. AA (lower part)]. The pooled odds ratio is indicated by diamond using a random effect model for analysis. CI confidence interval (horizontal lines). Diamond the pooled estimate of the odds ratios. I^2 : index for heterogeneity of studies

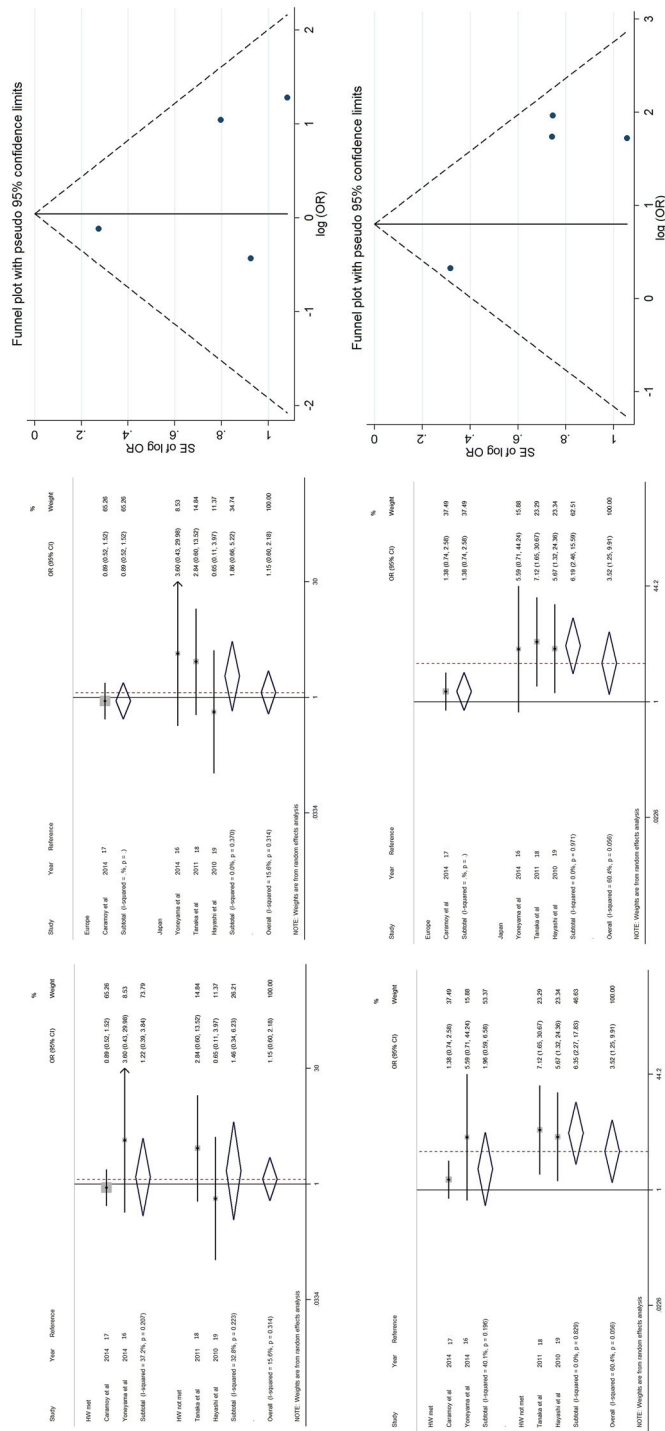


Fig. 4 Right side funnel plots for the effect of ARMS2/LOC387715 A69S (rs10490924) in RAP versus neovascular AMD (upper part GT vs. GG, lower part TT vs. GG). These plots indicate that most studies are in the non-significant bias area (the area between the two lines). Middle and left side forest plots for the effect of ARMS2/LOC387715 A69S (rs10490924) in RAP versus neovascular AMD [individual and pooled odds ratio estimates for GT vs. GG (upper part) and TT vs. GG (lower part)]. Separated and pooled data based on region (Europe or Japan; middle figure) and based on equilibrium or disequilibrium or Hardy–Weinberg rule in studies (left side). The pooled odds ratio is indicated by diamond using a random effect model for analysis. CI confidence interval (horizontal lines). Diamond the pooled estimate of the odds ratios. I²: index for heterogeneity of studies

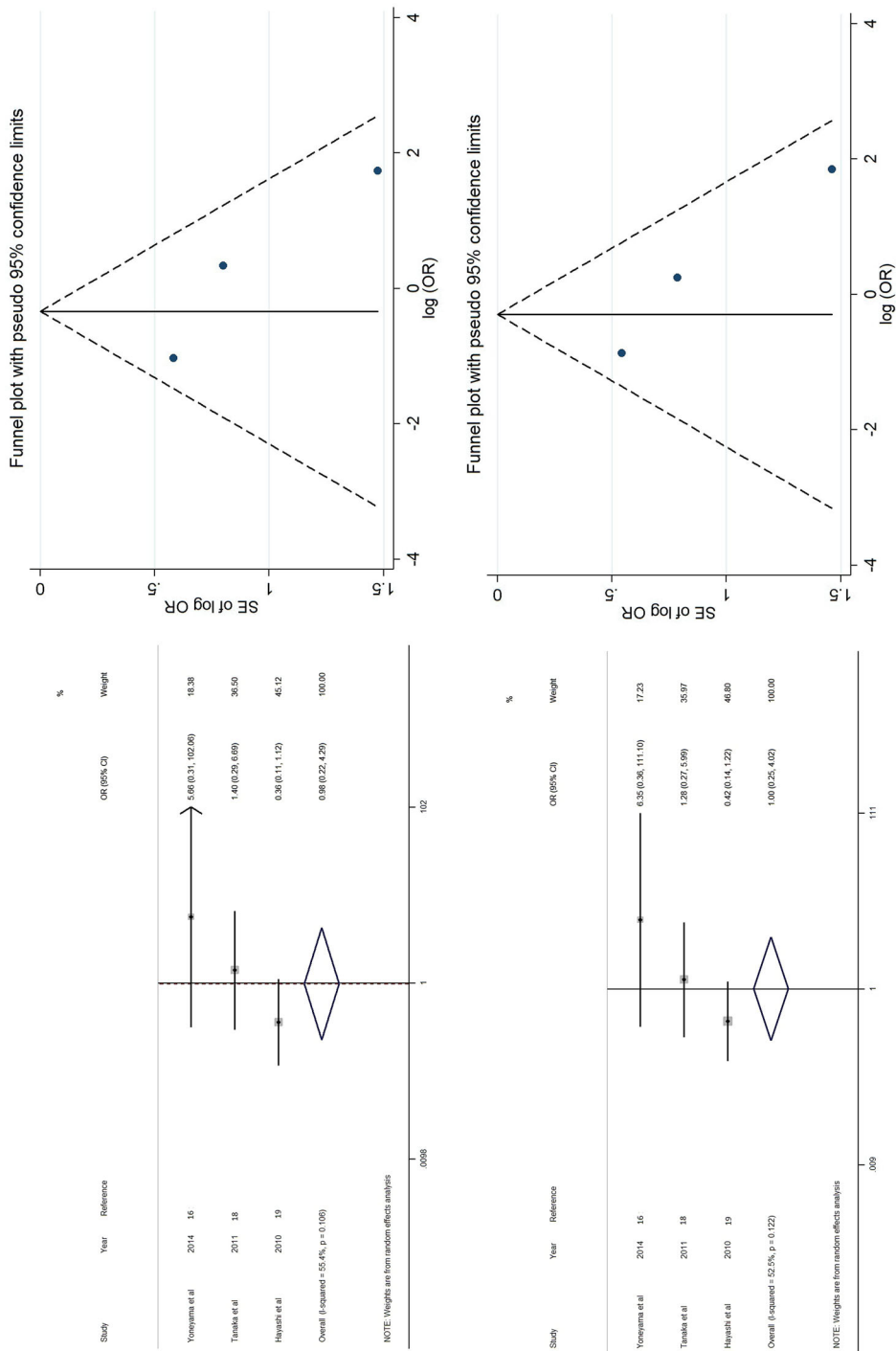


Fig. 5 *Right side* funnel plots for the effect of CFH I62V rs800292 in RAP versus neovascular AMD (*upper part* GA vs. AA, *lower part* GG vs. AA). These plots indicate that most studies are in the non-significant bias area (the area between the two lines). *Left side* forest plots for the effect of CFH I62V rs800292 in RAP versus neovascular AMD [individual and pooled odds ratio estimates for GA vs. AA (*upper part*) and GG vs. AA (*lower part*)]. The pooled odds ratio is indicated by *diamond* using a random effect model for analysis. *CI* confidence interval (*horizontal lines*). *Diamond* the pooled estimate of the odds ratios. *I²*: index for heterogeneity of studies

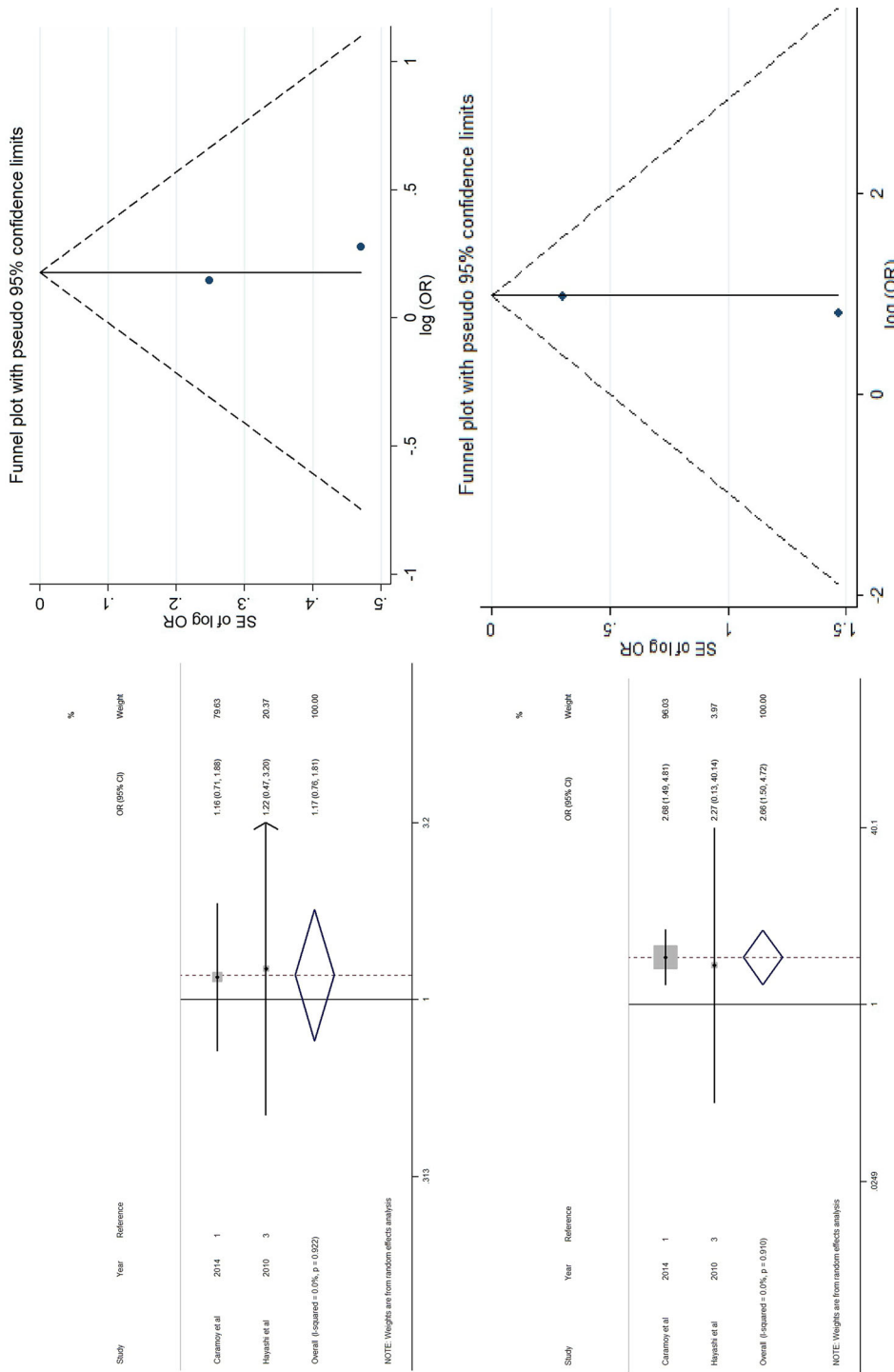


Fig. 6 Right side funnel plots for the effect of CFH Y402H RAP versus control group (upper part CT vs. TT, lower part CC vs. TT). These plots indicate that most studies are in the non-significant bias area (the area between the two lines). Left side forest plots for the effect of CFH Y402H RAP versus control group [individual and pooled odds ratio estimates for CT vs. TT (upper part) and CC vs. TT (lower part)]. The pooled odds ratio is indicated by diamond using a random effect model for analysis. CI confidence interval (horizontal lines). Diamond the pooled estimate of the odds ratios. I²: index for heterogeneity of studies

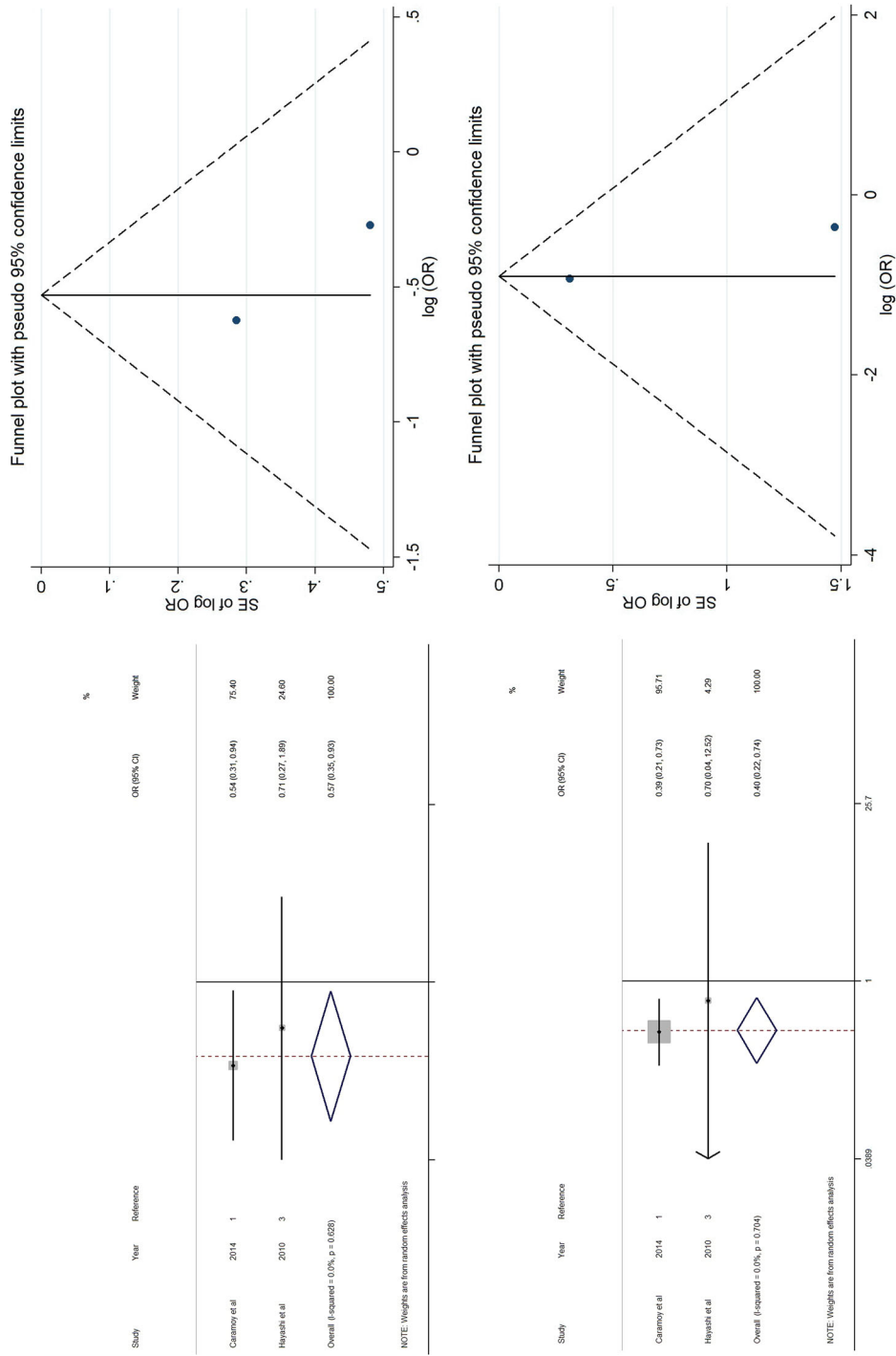


Fig. 7 Right side funnel plots for the effect of CFH Y402H in RAP versus neovascular AMD (upper part CT vs. TT, lower part CC vs. TT). These plots indicate that most studies are in the non-significant bias area (the area between the two lines). Left side forest plots for the effect of CFH Y402H in RAP versus neovascular AMD [individual and pooled odds ratio estimates for CT vs. TT (upper part) and CC vs. TT (lower part)]. The pooled odds ratio is indicated by diamond using a random effect model for analysis. CI confidence interval (horizontal lines). Diamond the pooled estimate of the odds ratios. I²: index for heterogeneity of studies

Pooled overall ORs for RAP versus control 1.17 (95% CI 0.76–1.81) for CT versus TT CFH Y402H and 2.66 (95% CI 1.50–4.72) for CC versus TT CFH Y402H.

Pooled overall ORs for RAP versus AMD 0.57 (95% CI 0.35–0.93) for CT versus TT CFH Y402H and 0.40 (95% CI 0.22–0.74) for CC versus TT CFH Y402H (Figs. 6, 7).

Regression analysis showed that ARMS2 TT genotype has a statistically significant effect on RAP versus AMD compared to CFH genotypes ($P < 0.001$). On the other hand, ARMS2 GT genotype has no statistically significant effect on RAP versus AMD compared to CFH genotypes ($P = 0.103$).

Discussion

Our knowledge of the genetic factors involved in the pathogenesis of AMD has expanded substantially in recent years, while data on the major genetic factors in RAP and its development are very limited. The present meta-analysis revealed that the ARMS2 A69S risk variants confer a significantly greater risk of RAP compared with neovascular AMD. The phenotypic diversity of AMD is supposed to be related to differences in genetic backgrounds [11, 16–21]. The genetic association of RAP has not been evaluated sufficiently because of its rarity. While its natural history is characterized by a rapid visual loss and treatment resistance [4, 5], its exact developmental mechanism remains controversial. Pooling published data for the association of these genetic loci with RAP versus neovascular AMD and control groups may further help clarify the pathogenesis of RAP.

In this meta-analysis, we pooled the results of available association studies between ARMS2/LOC387715 A69S, CFHY402H, and CFH I62V genotypes with RAP versus neovascular AMD cases or healthy controls to evaluate the magnitude of the effect of these factors. Our meta-analysis showed the stronger effect of ARMS2 in RAP compared with CFH genotypes. Previous studies have demonstrated the prevalence of RAP in newly diagnosed neovascular AMD to be lower in Asians (15.1% in whites and 4.5% in Asians) [22–24]. Despite this lower prevalence of RAP in Asians, the majority of studies included in our meta-analysis were from Asian population. We

suppose that it is because of the higher prevalence of polypoidal choroidal vasculopathy (PCV) subtype of AMD in these regions. In fact, the main purpose of genetic analysis of AMD subtypes in these regions may be revealing the genetic nature of PCV rather than RAP.

In contrast to the hypothesis of Yannuzzi [2], Gass [15] believes that choroidal neovascularization is the initiating event of RAP lesion rather than retinal neovascularization, and some authors prefer to refer to this entity as ‘retinal anastomosis to the lesion’ or RAL rather than RAP [25]. Different retinal sites and subcellular organelles such as mitochondria, extracellular matrix, and cytosol (RPE and ellipsoid region) have been shown as ARMS2 expression sites in retina [12, 28–30]. On the other hand, RPE has been identified as the main local source of CFH expression in the eye [7, 31]. Regarding these findings, it seems that ARMS2 has at least some expression site superior to RPE, while CFH is confined to RPE and sub-RPE layers. In previous meta-analyses [32, 33], ARMS2 and CFH Y402H had roughly equal risk effect in typical AMD (ARMS2 TT and GT: OR = 7.51 and 2.35; CFH Y402H CC and CT: OR = 6.32 and 2.50), while our study has shown that there is a difference in the effects of these two genes on RAP.

Because of the distinctive expression site of these two genes (ARMS2/LOC387715: RPE and above RPE; CFH: RPE and below RPE), it seems that the distinctive genetic nature of RAP could help clarify the pathway of disease pathogenesis. ARMS2/LOC387715 mechanism has common pathway with CFH in AMD susceptibility [14, 26]. While these two genes have been shown to have a common pathway possibly through complement activation in AMD pathogenesis, a previous study has shown a lower level of complement activation in RAP versus neovascular AMD [13]. These two genetic loci have a common pathway of effect toward typical AMD cases and their different effect in RAP subtype of AMD can be explained by the different pathogenetic pathway of RAP compared with neovascular AMD, by the possible effect of other genetic/non-genetic risk factors and/or by the existence of other pathogenetic pathway of ARMS2 in RAP. This meta-analysis summarizes the evidence of a stronger effect of ARMS2 in RAP compared with CFH Y402H and I62V genotypes. Our findings are in accordance with those of Maguire et al. [27], which showed that

ARMS2 is associated specifically with retinal angiomatous proliferation lesions among patients with neovascular AMD. Understanding the relationships between these genetic loci and disease subtypes will provide important insights, elucidating the biologic architecture of this heterogeneous disorder. These two genetic loci have roughly equal risk effect in typical AMD susceptibility but ARMS2 is a significantly stronger risk for RAP compared with CFH. This difference may be a result of wider extension of ARMS2 expression in retinal layers.

Future studies with a large sample size especially from Caucasians considering the possible interactional role of other proposed genes and factors such as complement system are needed to clarify the pathogenesis of RAP.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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