Int Ophthalmol (2019) 39:949–956
https://doi.org/10.1007/s10792-018-0853-y

REVIEW

Comparison of ARMS2/LOC387715 A69S and CFH Y402H risk effect in wet-type age-related macular degeneration: a meta-analysis

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Received: 6 October 2017 / Accepted: 1 February 2018 / Published online: 8 February 2018

Abstract
Purpose We designed this meta-analysis to pool studies which have analyzed both CFH (Y402H or I62V) and ARMS2 A69S in the same samples to compare the effect of CFH and ARMS2 in neovascular AMD.
Methods Relevant studies identified and reviewed separately in order to select those for inclusion. Included studies had genotype data of studied groups for both ARMS2 A69S and CFH. To modify the heterogeneity in the variables, we used random effects model. Meta-analysis was performed using STATA. Funnel plot and Egger's regression test used for evaluation of the possible publication bias.
Results Overall, we included 6676 neovascular AMD cases and 7668 controls. Pooled overall odds ratios (ORs) (95% CI) for neovascular AMD/control were ARMS2 A69S: OR = 2.35 (2.01–2.75) for GT versus GG; OR = 8.57 (6.91–10.64) for TT versus GG; CFH Y402H: OR = 1.94 (1.73–2.18) for CT versus TT; OR = 4.89 (3.96–6.05) for CC versus TT. ARMS2 A69S genotype OR/CFH Y402H genotype OR (homogeneous genotypes): Asia = 2.14, Europe: 1.87, America: 1.82, Middle East: 3.56, pooled: 1.75. ARMS2 A69S genotype OR/CFH Y402H genotype OR (heterogeneous genotypes): Asia = 0.93, Europe: 1.39, America: 2.06, Middle East: 1.20, pooled: 1.21. ARMS2 A69S risk genotypes have stronger predisposing effect on neovascular AMD compared to CFH Y402H risk genotypes.
Conclusion Our inclusion criteria to select those studies which have analyzed the effect of these two loci in the same case-control samples showed much stronger effect of ARMS2 A69S in neovascular AMD compared to the CFH Y402H.

Keywords ARMS2/LOC387715 A69S · CFH Y402H · Wet-type age-related macular degeneration · Meta-analysis

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Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialized countries [1]. Choroidal neovascularization, the hallmark of wet-type AMD, is responsible for the majority of cases with severe vision loss in AMD [2]. Predisposing

genetic factors, most importantly CFH Y402H mapped on chromosome 1q31 and ARMS2 A69S mapped on chromosome 10q26, are well-established risk factors for AMD [3, 4].

In a recent survey, we have shown that there may be a common pathway for the effect of ARMS2 A69S and CFH Y402H risk genotypes in AMD [5]. Previous meta-analyses have shown that these two genetic factors may have a roughly equal risk effect in AMD (ARMS2 TT and GT OR = 7.51 and 2.35; CFH Y402H CC and CT OR = 6.32 and 2.50, respectively) [6, 7]. Although these studies have shown roughly equal risk effect, the major limitation of these studies is that none of them has exclusively included studies evaluating the effect of both of these two genes in the same population. It seems that the pooled data of these two genes each in different samples and population could not reflect precisely the difference in risk effect of these two genetic loci. We designed this meta-analysis to gather studies that have investigated both CFH (Y402H or I62V) and ARMS2 A69S genotypes in the same samples to compare the risk effect of CFH and ARMS2 in neovascular AMD.

Methods

To understand the significance of the observed associations of ARMS2/LOC387715 (rs10490924), CFH Y402H, and CFH I62V genotypes in neovascular AMD versus control group in different studies, we designed a meta-analysis with calculation of the estimated odds ratios (ORs). For each locus genotype, OR was calculated compared to the non-risk genotype (such as CC vs. TT CFH Y402H). The included studies were based on a literature search in the PubMed in September 2016 using the phrase "AMD or age-related macular degeneration or age related macular degeneration and rs1061170 or Y402H or I62V or complement factor H or CFH or rs10490924 or ARMS2 or age-related maculopathy susceptibility 2 or age related maculopathy susceptibility 2 or LOC387715" in the title or abstract.

Data extraction

Two retina specialists (MHJB, HN) identified relevant studies and reviewed the full-text manuscripts of the 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 neovascular AMD, there were at least two comparison groups (neovascular AMD vs. control with available data of genotype distributions), there were sufficient results for extraction of data, and the study contained genotype data (not allele) of both ARMS2 A69S and CFH (Y402H or I62V) single nucleotide polymorphisms (SNPs). For the duplicated data, the largest one was included. Summary data were extracted independently and in duplicate by two of the authors (MHJB, HN) using a standardized data extraction form, and covariates were also extracted where possible. Any disagreements between these authors were resolved through consensus. The articles were restricted to the English language. Figure 1 illustrates summary of study search and selection in this meta-analysis.

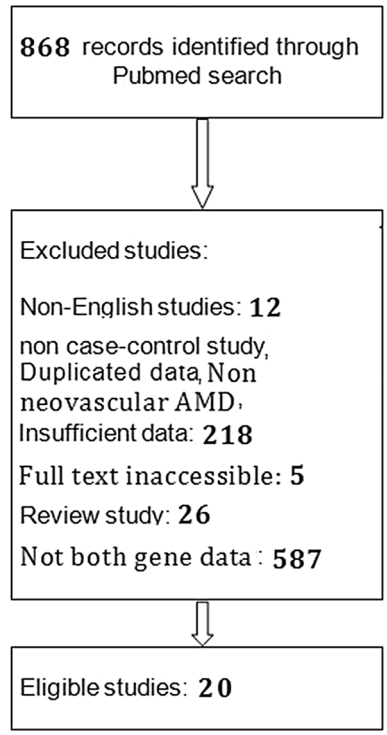

Fig. 1 Summary of study search and selection in this meta-analysis

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 studies.

We used forest plots to obtain 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 Q-test and I-square index, and $P < 0.05$ considered as the standard for heterogeneity. To modify the heterogeneity in the variables, we used the 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 evaluation of possible publication bias. To modify heterogeneity among studies, the results were pooled using random effects analysis.

Results

Of the screened articles, twenty studies were identified to be eligible by our search strategy for inclusion in the present meta-analysis [8–27]. Overall, we included 6676 neovascular AMD cases and 7668 controls in the present meta-analysis. Characteristics of the included studies have been described in Table 1.

Publication bias was assessed by Egger's test as follows: Neovascular AMD versus control group, ARMS2 TG/GG: coefficient = − 0.15, $P = 0.88$; ARMS2 TT/GG: coefficient = 1.41, $P = 0.10$; CFH Y402H CT/TT: coefficient = 0.67, $P = 0.36$ and CFH Y402H CC/TT: coefficient = − 0.206, $P = 0.767$. CFH I62V GA/AA: coefficient = − 2.01, $P = 0.284$; and CFH I62V GG/AA: coefficient = − 1.76, $P = 0.363$.

Pooled overall ORs (95% CI) for neovascular AMD/control were as follows: **ARMS2 A69S:** OR = 2.35 (2.01–2.75) for GT versus GG; OR = 8.57 (6.91–10.64) for TT versus GG; **CFH Y402H**: OR = 1.94 (1.73–2.18) for CT versus TT; OR = 4.89 (3.96–6.05) for CC versus TT; **CFH I62V:** OR = 1.31 (0.58–2.94) for GA versus AA; OR = 2.57 (1.09–6.04) for GG versus AA (Figs. 2, 3, 4).

ARMS2 A69S risk genotypes have stronger predisposing effect on neovascular AMD compared to CFH Y402H risk genotypes. Calculating ARMS2 A69S genotype OR/CFH Y402H genotype OR shows that for different geographic regions ARMS2 A69S risk genotypes have stronger risk effect toward neovascular AMD: Ratio of ARMS2 A69S genotype OR to CFH Y402H genotype OR (homogeneous genotypes) was: Asia = 2.14, Europe: 1.87, America: 1.82, Middle East: 3.56, and pooled: 1.75. Ratio of ARMS2 A69S genotype OR to CFH Y402H genotype OR (heterogeneous genotypes) was: Asia = 0.93, Europe: 1.39, America: 2.06, Middle East: 1.20, and pooled: 1.21.

Ratio of ARMS2 A69S genotype OR to CFH I62V genotype OR (homogeneous genotypes) was: Asia = 2.55, Europe: 2.83, and pooled: 2.57. Ratio of ARMS2 A69S genotype OR to CFH I62V genotype OR (heterogeneous genotypes) was: Asia = 1.33, Europe: 1.22, and pooled: 1.31.

Discussion

Previous meta-analyses have shown that ARMS2 A69S and CFH Y402H have roughly equal risk effect for AMD (ARMS2 A69S TT and GT, OR = 7.51 and 2.35; CFH Y402H CC and CT OR = 6.32 and 2.50, respectively) [6, 7]. The major limitation of previous meta-analyses was that they have studied the effect of these two genes in different case-control samples. In the present meta-analysis, we selected only those neovascular AMD studies which have analyzed the effect of these two genes in the same case-control samples. One of the included studies (Bonyadi et al ref. No. 20) had only CFH Y402H results, but because we had access to the ARMS2 A69S genotypes data in that case-control study (unpublished data), it was entered in the meta-analysis. Our database search phrase also covered those studies which have evaluated CFH I62V polymorphism in neovascular AMD. All pooled studies had ARMS2 A69S and CFH Y402H data except three, which had ARMS2 A69S and CFH I62V data.

In an earlier study, we have shown that ARMS2 and CFH Y402H have unequal risk effects in different AMD subtypes. We have shown that compared to CFH Y402H, ARMS2 A69S has a stronger predisposing effect in cases with retinal angiomatous

Table 1 General Characteristics of Studies Included in the Meta-Analysis

	Country	Case/control	ARMS2/LOC387715 (rs10490924) A69S			CFH Y402H (rs1061170)			CFH I62V (rs800292)			HWE ARMS2/ CFH Y402H/CFH I62V
			TT	GT Case/ control	GG (ref) Case/ control	CC Case/ control	CT Case/ control	TT (ref) Case/ control	CC Case/ control	CT Case/ control	TT (ref) Case/ control	
Yoneyama	Japan	157/205	73/26	60/87	24/92	–	–	–	85/74	57/89	15/42	+/…/+
Rivera	Germany	417/946	78/43	186/288	131/591	137/116	197/475	82/355	–	–	–	+/−/…
Yu	AREDS USA	817/217	171/5	395/65	251/147	322/27	368/106	125/83	–	–	–	+/+/..
Hayashi	Japan	405/1342	183/196	155/638	67/502	7/8	75/160	319/1174	228/456	148/649	24/233	+/+/+
Tian	China	460/467	228/97	166/223	66/147	8/1	81/49	331/395	219/158	176/221	47/76	+/+/+
Merle	France	290/144	76/5	133/46	81/93	20/93	134/68	63/56	–	–	–	+/−/…
Pulido	USA	89/230	19/13	38/60	30/159	32/25	31/104	26/101	–	–	–	−/+/…
Losoncz	Hungary	210/106	71/5	95/50	45/49	80/11	89/51	35/42	–	–	–	+/+/…
Tanaka	Japan	253/277	126/36	81/142	46/99	–	–	–	147/100	93/141	13/36	−/…/−
Kim	South Korea	114/240	58%/10%	29.5/55%	12.5/35%	0/0.8%	22.4/14.2%	77.6/85%	50.3/31.5%	38/51.7%	11.7/16.8%	−/−/−
Schick	Germany, Netherlands	893/1673	221/92	390/606	269/961	308/214	400/796	171/646	–	–	–	+/+/..
Bonyadi	Iran	200/217	61/13	91/71	48/133	80/34	133/68	41/62	–	–	–	+/+/..
Goto	Japan	100/189	52/20	30/84	18/85	–	–	–	47/60	46/92	3/36	+/./+
Hautama ki	Finnish	301/119	63/2	157/42	78/70	109/13	154/59	38/41	–	–	–	+/+/…
Recalde	Spain	120/151	30/7	57/51	33/91	30/9	54/68	36/74	–	–	–	+/+/…
Tanimoto	Japan	95/99	39/10	34/50	22/39	3/2	20/13	72/84	–	–	–	+/+/…
Xu	China	121/132	54/22	49/70	18/40	1/0	23/21	97/111	–	–	–	+/+/..
Zerbib	France	1080/406	234/15	507/129	339/253	299/54	551/192	229/160	–	–	–	+/+/..
Fang	China	464/468	228/97	166/223	66/147	8/1	81/49	331/395	219/158	176/221	47/76	+/+/+
Teper	Poland	90/40	26/14	33/2	31/24	28/22	47/3	15/15	–	–	–	−/−/…

+ indicates Hardy–Weinberg equilibrium for desired genotype

− means no HWE

.. and … means that HWE could not be calculated

HWE Hardy–Weinberg equilibrium in neovascular AMD/control

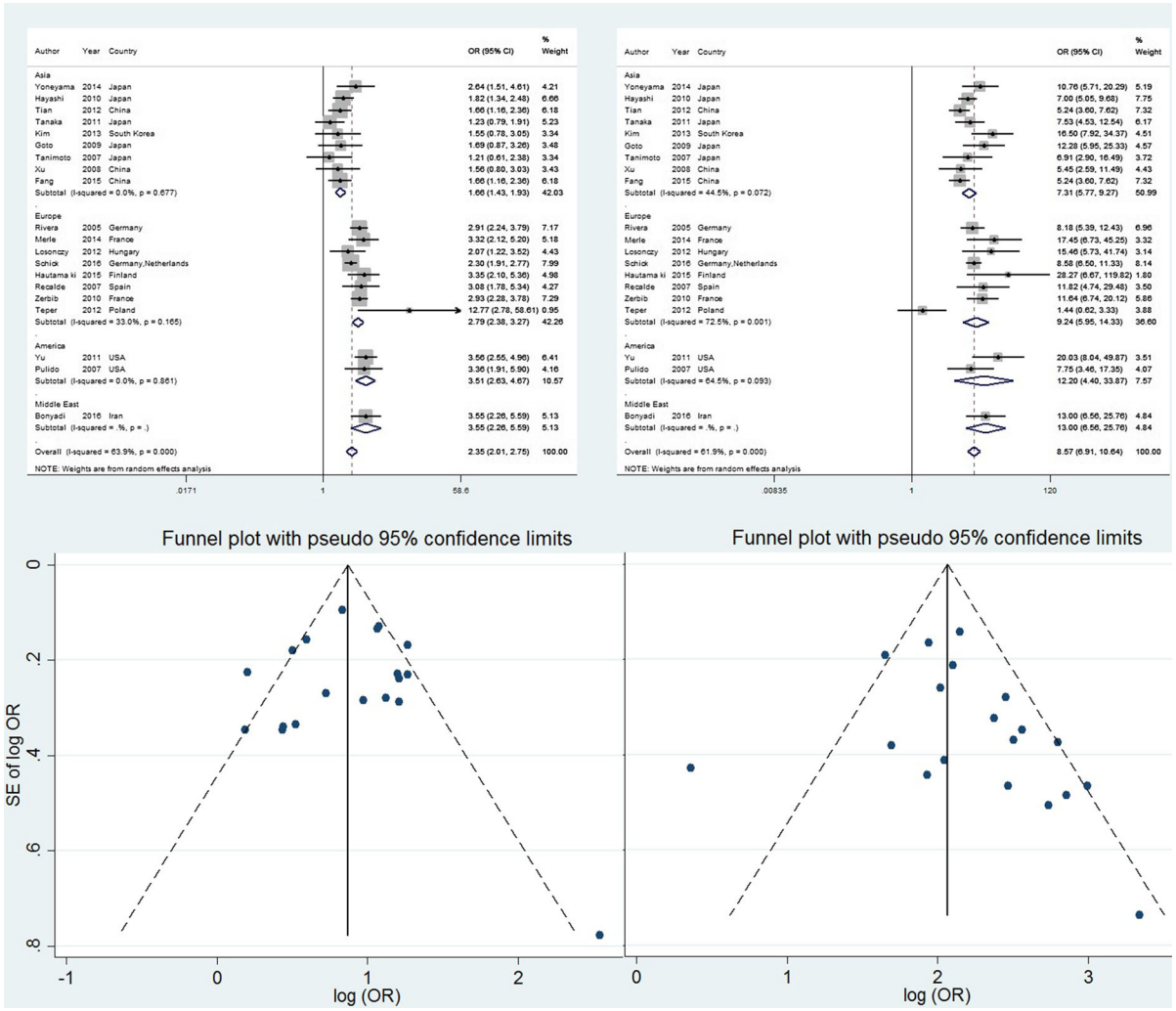

Fig. 2 Upper side: forest plots for the effect of ARMS2/LOC387715 A69S (rs10490924) in neovascular AMD versus control [Individual and pooled odds ratio estimates for GT versus GG (left), TT versus GG (right)]. The pooled odds ratio is indicated by the diamond using random effect model for analysis. CI: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

proliferation compared to neovascular AMD [28] and also in AMD with reticular pseudodrusen compared to those without [29].

Interestingly present analysis has shown that in neovascular AMD cases, homogeneous and heterogeneous ARMS2 A69S risk genotypes have 1.75 and 1.21 times stronger risk than CFH Y402H risk genotypes, respectively.

Because of shortage of studies from Middle East region (only one study) in our meta-analysis, we could not have comprehensive judgment for this region. Although it has been thought that the risk effect magnitude of CFH Y402H in AMD becomes lower in Asian populations, Wu et al. [30] in their recent meta-analysis showed that the CFH Y402H variant is also a strong risk factor for AMD in Asian populations. Their pooled data showed OR of 1.88 and 3.89 in neovascular AMD for hetero and homogeneous CFH Y402H genotypes, respectively; these numbers are similar to our pooled CFH Y402H OR data from this region. For all geographic regions in our analysis and for all types of genotypes (hetero or homogeneous state), we could

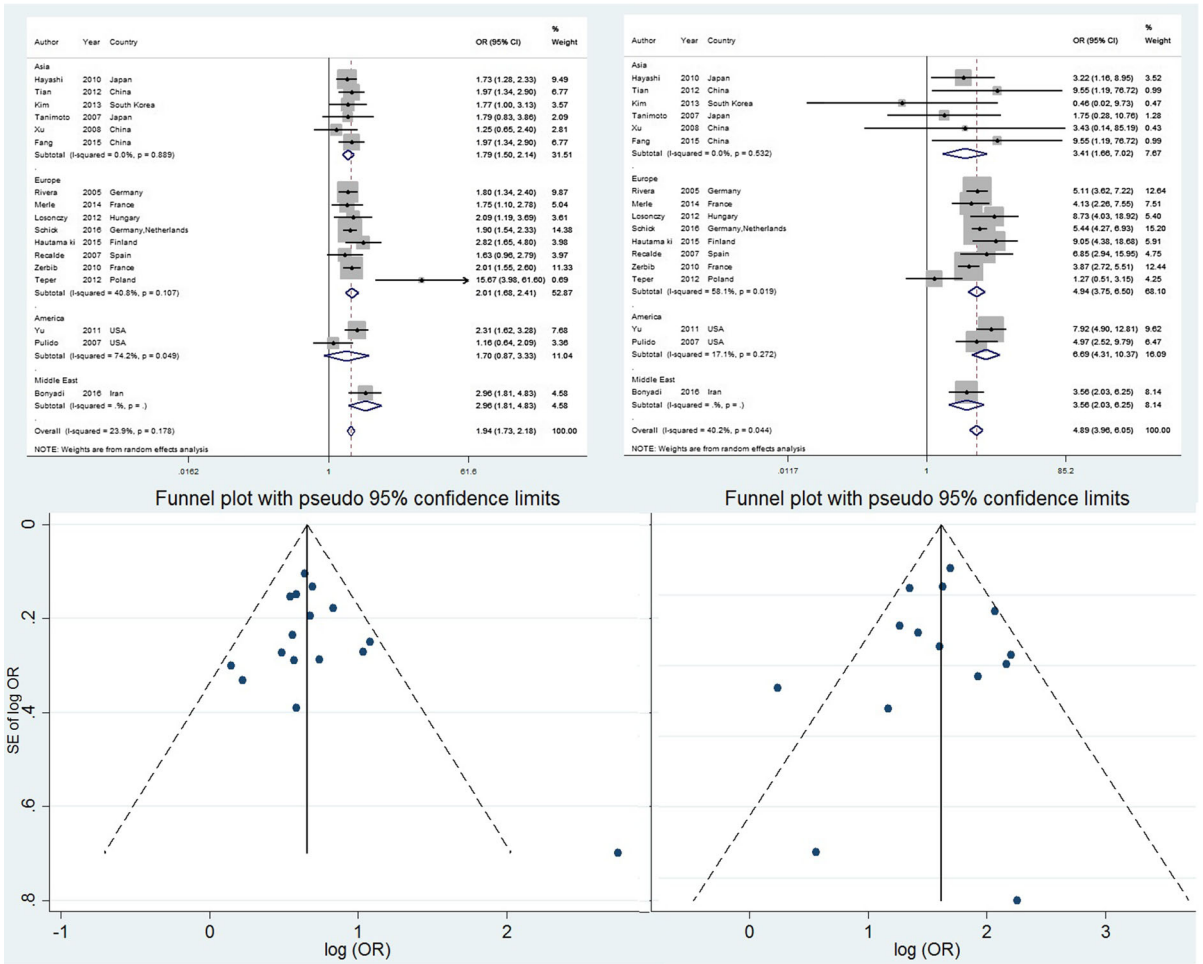

Fig. 3 Upper side: forest plots for the effect of CFH Y402H in neovascular AMD versus control [individual and pooled odds ratio estimates for CT versus TT (left), CC versus TT (right)]. The pooled odds ratio is indicated by the diamond using random effect model for analysis. CI: confidence interval (horizontal Lines). Diamond: the pooled estimate of the odds ratios. I^2: index for heterogeneity of studies. Lower side: funnel plots for the effect of CFH Y402H in neovascular AMD versus control (Left part: CT versus TT, Right part: CC versus TT). These plots indicate that most studies are in the non-significant bias area (the area between the 2 lines)

see that ARMS2 A69S genotypes have stronger effect than CFH Y402H genotypes except for Asia region and for heterogeneous genotype (ARMS2 A69S OR/CFH Y402H OR = 0.93). On the other hand, it is visible that among the mentioned regions (Middle East was not considered) ARMS2 A69S OR/CFH Y402H is highest in Asia for homogeneous genotypes and is lowest for heterogeneous genotypes in the same region.

We supposed that our search protocol to select studies which had analyzed the effect of these two genes in the same case-control samples could yield a precise comparison of these two genetic loci in neovascular AMD. Although the precise mechanism of ARMS2 A69S has not been elucidated yet, it has been shown to have a common pathway of effect with CFH Y402H in AMD susceptibility [5]. In conclusion, current study highlighted much stronger effect of ARMS2 A69S in neovascular AMD compared to CFH Y402H, while considering only studies that extracted data for both genotypes. The precise role of this locus in neovascular AMD and its subtypes needs to be clarified through further trials and may help find effective therapeutic modalities in the future.

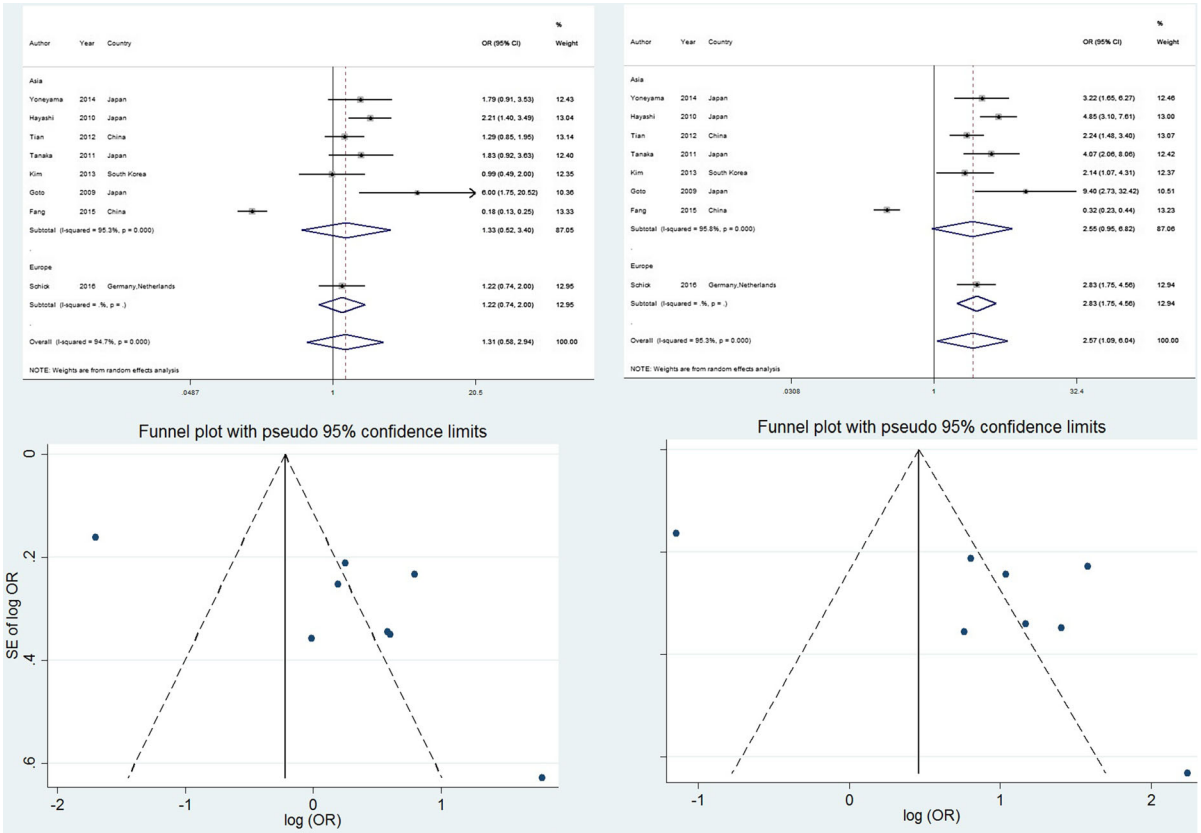

Fig. 4 Upper side: forest plots for the effect of CFH I62V rs800292 in neovascular AMD versus control [individual and pooled odds ratio estimates for GA versus AA (left), GG versus AA (right)]. The pooled odds ratio is indicated by the diamond using random effect model for analysis. CI: confidence interval (horizontal Lines). Diamond: the pooled estimate of the odds ratios. I^2: index for heterogeneity of studies. Lower side: funnel plots for the effect of CFH I62V rs800292 in neovascular AMD versus control (Left part: GA versus AA, Right part: GG versus AA). These plots indicate that most studies are in the non-significant bias area (the area between the 2 lines)

Funding Center of Excellence for Biodiversity sponsored this study. The sponsor had no role in the design or conduct of this research.

Compliance with ethical standards

Conflict of interest There is no conflict of interest. No conflicting relationship exists for any author.

Ethical approval This study adhered to the tenets of the declaration of Helsinki and is approved by the ethics committee of the Shahid Beheshti Medical University.

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