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ORIGINAL ARTICLE

The *FCGR3A* polymorphism predicts the response to rituximab-based therapy in patients with non-Hodgkin lymphoma: a meta-analysis

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Abstract Epidemiological studies have assessed the association between *Fc gamma receptor IIIA* (*FCGR3A*) 158 V/F and the response to rituximab-based therapy in patients with non-Hodgkin lymphoma (NHL), but the findings have been inconsistent. We performed this meta-analysis to obtain a better assessment of this relationship. Electronic database searches were conducted for relevant studies. A pooled odds ratio (OR) with a 95 % confidence interval (95 % CI) was used to assess the strength of the association. Analyses of the subgroup and publication bias were conducted. A total of 10 studies involving 1050 patients were analyzed. In all the genetic models, no clear relationship was found between the *FCGR3A* 158 V/F polymorphism and the response to rituximab-based therapy in NHL patients. When categorized by ethnicity, Asian individuals with the *FCGR3A* 158 V/V allele (OR = 4.37; 95 % CI = 1.07–17.73; $P = 0.039$) or the non-F/(FV + VV) (OR = 2.50; 95 % CI = 1.04–5.98; $P = 0.040$) allele have a significantly higher complete response rate (CR) compared to FF individuals. No obvious heterogeneities were observed. In addition, no statistical evidence for a publication bias was found. Our study suggested that the *FCGR3A* 158 V/F polymorphism can predict the treatment response to rituximab-based chemotherapy in NHL patients, especially for Asian individuals.

Keywords Non-Hodgkin's lymphoma · *FCGR3A* · Polymorphism · Rituximab · Meta-analysis

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Introduction

Rituximab has been successfully used for the treatment of patients with non-Hodgkin's lymphoma (NHL) [1, 2]. Rituximab is a chimeric Ab that was engineered by grafting the murine anti-human CD20 variable regions onto human *FCG*. Human FCG targets CD20+ B cells and depletes subpopulations of peripheral B cells via several putative mechanisms, including Ab-dependent cell cytotoxicity (ADCC) via NK cells, complement dependent lysis (CDL), and apoptosis via cross-linking membrane CD20 [3]. The Fc gamma receptors (FCGRs) play an important role in the recognition of immune complexes (ICs) [4]. The *FCGR3A* 158 V/F (rs396991) polymorphism exhibits biologic functions that differ among the different FCGR genotypes [5].

Given the crucial role played by the *FCGR3A* polymorphism in the pathogenesis of NHL, a number of studies have examined the potential contributions of the *FCGR3A* 158 V/F polymorphism on non-responsiveness to rituximab [6–15]. However, results remain inconsistent. This could be due to the possibility of small effects or relatively small sample sizes in the early publications. Therefore, the aim of the present study was to use a meta-analysis approach to investigate whether the functional *FCGR3A* 158 V/F polymorphism is associated with non-responsiveness to rituximab therapy in NHL patients.

Materials and methods

Literature search strategy

MEDLINE, EMBASE, and Cochrane Library searches were conducted using the following search terms: "*FCγR*" or "*FCGR*" and "polymorphism" and "Rituximab" (the last search update was on 30 July 2015). All identified studies were obtained and their reference lists were also checked for other relevant studies.

Inclusion and exclusion criteria

Studies published in languages other than English were excluded. Related articles, and also potentially relevant articles, were screened. Studies had to meet the following criteria to be eligible for the analysis: (1) involved patients with NHL that were treated with rituximab-based chemotherapy, (2) investigated the association between the *FCGR3A* 158 V/F polymorphism and the treatment response, i.e., overall response rate (ORR) (complete responders (CR) and partial responders (PR)) and non-responders (stable disease (SD) or progressive disease (PD)), and (3) was a published study with full text available.

Data extraction

The characteristics of selected studies were extracted using a standardized protocol conducted by two investigators independently (Duo Liu and Yuyang Tian). The following information was extracted: the surname of the first author, the year of publication, and the ethnicity, diagnosis, sample size, age group, gender, stages, chemotherapy, outcomes, and number of cases for each genotype of the *FCGR3A* 158 V/F polymorphism. For studies including subjects of different ethnic groups, data were extracted separately for each ethnic group whenever possible.

Statistical analysis and publication bias

The treatment response (TR) was used to measure chemotherapy efficacy. To summarize this information, patients were divided into responders (CR or PR) and non-responders (SD or PD) according to the WHO criteria [16] or the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [17]. For *FCGR3A* 158 V/F, four genetic comparison models were analyzed (A: dominant model, FV + VV vs FF; B: heterozygote model, FV vs FF; C: homozygote model, VV vs FF; D: recessive model, VV vs FV + FF). The pooled odds ratio (OR) and the 95 % confidence interval (CI) were calculated for CR vs SD + PD, PR vs SD + PD, and ORR vs SD + PD. Because this study is a systematic review and meta-analysis, each eligible study had already been approved by local institutional review boards, and each local institution has obtained matching informed consent from their patients.

Heterogeneity was checked using the chi-square test based on the Cochran's Q test, and a P value >0.1 indicated a lack of heterogeneity. The pooled OR estimation of each study was calculated with a random-effect model using the Der Simonian and Laird method or with a fixed-effect model using the Mantel-Haenszel method. The inter-study variance (I^2) was used to quantify the amount of heterogeneity between studies, and the percentage of I^2 was used to express the extent of explained heterogeneity of the characteristics [18]. The publication bias was checked with Begg's test and Egger's asymmetry test, and with visual inspection of the funnel plots, in which the standard error was plotted against the Log (OR) to produce a simple scatter plot. All of the statistical analyses were performed using STATA version 11.0 (Stata Corporation, College Station, TX). The P values were in relation to two-sided tests, and $P > 0.05$ was considered to be statistically significant.

Results

Characteristics of the studies

A total of 76 studies on relationship between the *FCGR* polymorphism and the response to rituximab-based chemotherapy were identified and screened for data retrieval. As shown in Fig. 1, 19 papers that did not involve NHL, 15 studies that did not involve SNP, and 7 studies relating to other *FCGR* polymorphisms were excluded. Fifteen studies [19–33] were also discarded because they lacked the clinical outcome data, and another three studies were discarded because they only reported rituximab-induced toxicity [34–36]. Furthermore, five articles were reviews [37–41], and two were not in English [42, 43], so these were also excluded. Each group was considered to be a separate study for the analysis.

Response to rituximab-based chemotherapy

There were 10 articles identified that match the criteria chosen for this analysis (Table 1). Three studies were conducted on Asian patients [6, 11, 13], and seven studies were conducted on European patients [7–10, 12, 14, 15]. The data sets that were included in this meta-analysis had a total sample size of 1050 patients. Table 2 shows the genotype frequency of the *FCGR3A* 158 V/F polymorphism with the response to rituximab-based chemotherapy. Furthermore, Table 3 summarizes the pooled OR estimates and the corresponding 95 % CI of this meta-analysis. When the data were analyzed altogether, no significant associations with the CR, PR

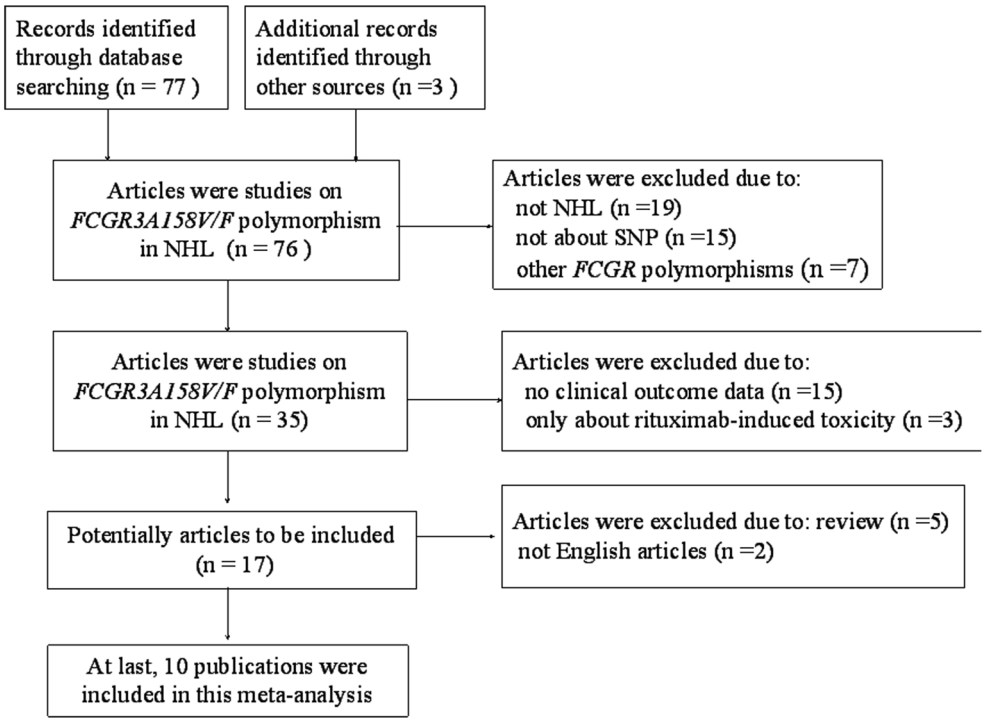

Fig. 1 A flow diagram for selection of studies and specific reasons for exclusion in this meta-analysis

rate, or ORR were found for the FF allele compared using all the genetic models.

Considering the potential impact of confounding factors, such as genetic variation in different ethnic groups, we conducted further subgroup analyses based on ethnicity. The data showed that Asian individuals with the *FCGR3A* 158 V/V (OR = 4.37; 95 % CI = 1.07–17.73; $P = 0.039$) (Fig. 2) and the non-F/(FV + VV) (OR = 2.50; 95 % CI =1.04–5.98; $P = 0.040$) (Fig. 3) allele have a significantly higher CR rate compared with the FF allele (Table 3).

Heterogeneity and publication bias

Heterogeneity analysis suggested that there were differences between the meta-analysis results and the actual results. As shown in Table 3, no obvious heterogeneities were found in the overall analysis of the data using all of the genetic models. However, when subgroup analyses based on ethnicity were conducted, we found heterogeneities in the Asian group with the homozygote comparison ($P_{\text{heterogeneity}} = 0.039$, $I^2 = 69.2$ %).

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Country	Diagnosis	Sample size	Median age year (range)	Gender (male/female)	Stages 3, 4 (%)	Genotyping method
Liu F [6]	2014	China (Asia)	DLBCL	129	53 (15–90)	NA	89 (69)	PCR sequencing
Váróczy L [7]	2012	Hungary (Europe)	DLBCL	51	53.1 (19–86)	19/32	NA	PCR sequencing
Ghesquières H [8]	2012	France (Europe)	FL	455	NA	NA	419 (91)	Taqman SNP assay
Cornec D [9]	2012	France (Europe)	FL, MZ	50	61 (25–86)	24/26	25 (50)	PCR
Fabisiewicz A [10]	2011	Poland (Europe)	DLBCL	87	57 (25–81)	41/46	64 (74)	Taqman SNP assay
Zhang W [11]	2010	China (Asia)	DLBCL	34	42 (19–73)	NA	18(53)	PCR
Mitroviç Z [12]	2007	Croatia (Europe)	DLBCL	58	NR (18–84)	37/21	34 (59)	PCR-RFLP
Kim DH [13]	2006	Korea (Asia)	DLBCL	113	60 (18–84)	64/49	45 (40)	PCR-RFLP
Galimberti S [14]	2007	Italy (Europe)	MCL	24	60 (27–72)	17/7	19 (79)	Real-time PCR
Cartron G [15]	2001	France (Europe)	NHL (B)	49	NA	25/24	34 (69)	PCR

NA not available, *NHL* non-Hodgkin lymphomas, *DLBCL* diffuse large B cell lymphoma, *MCL* mantle cell lymphoma, *FL* follicular lymphoma, *MZ* marginal zone lymphoma, *PCR-RFLP* polymerase chain reaction–restriction fragment length polymorphism

Table 2 Genotype frequency of *FCGR3A* 158 V/F polymorphism with response to rituximab-based chemotherapy

Reference	Total				CR				PR				SD + PD			
	FF	FV	VV	FF + FV	FV + VV	FF	FV	VV	FF + FV	FV + VV	FF	FV	VV	FF + FV	FV + VV
Liu F [6]	70	50	9	120	59	42	31	7	73	38	18	14	1	32	15	10	5	1	15	6
Váróczy L [7]	10	29	12	39	41	7	10	20	17	30	1	0	5	1	5	2	2	4	4	6
Ghesquières H [8]	174	213	68	387	281	118	144	44	262	188	46	61	21	107	82	10	8	3	18	11
Cornec D [9]	23	21	6	44	27	10	12	6	22	18	10	7	0	17	7	3	2	0	5	2
Fabisiewicz A [10]	37	35	15	72	50	27	23	11	50	34	10	8	3	18	11	0	4	1	4	5
Zhang W [11]	5	18	11	23	29	2	12	6	14	18	1	3	3	4	6	2	3	2	5	5
Mitroviç Z [12]	10	32	16	42	48	8	26	10	34	36	1	1	2	2	3	1	5	4	6	9
Kim DH [13]	6	53	51	59	104	3	42	45	45	87	0	6	5	6	11	3	5	1	8	6
Galimberti S [14]	4	16	4	20	20	1	3	2	4	5	3	11	2	14	13	0	2	0	2	2
Cartron G [15]	17	22	10	39	32	6	7	7	13	14	4	3	2	7	5	7	12	1	19	13

CR complete responders, *PR* partial responders, *SD* stable disease, *PD* progressive disease

Table 3 Stratified analyses of the *FCGR3A* 158 V/F polymorphism in the pooled sample

Contrast group	Pooled OR of 158 V/F		Heterogeneity	
	P value	OR (95 % CI)	I^2 (%)	Ph
CR vs. SD + PD				
Heterozygote model: FV vs FF				
Asian	0.062	2.40 (0.96–6.02)	23.4	0.271
European	0.836	0.94 (0.51–1.72)	0	0.641
Total	0.370	1.26 (0.76–2.07)	6.1	0.385
Homozygote model: VV vs FF				
Asian	*0.039*	*4.37 (1.07–17.73)*	*50.5*	*0.133*
European	0.465	1.33 (0.62–2.86)	17.8	0.299
Total	0.077	1.81 (0.94–3.49)	38.2	0.114
Dominant model: FV + VV vs FF				
Asian	*0.040*	*2.50 (1.04–5.98)*	*56.3*	*0.102*
European	0.777	1.09 (0.62–1.91)	0	0.654
Total	0.165	1.39 (0.87–2.22)	21.4	0.246
Recessive model: VV vs FV + FF				
Asian	0.098	2.59 (0.84–8.01)	9.2	0.332
European	0.360	1.36 (0.71–2.61)	5.9	0.382
Total	0.090	1.63 (0.93–2.86)	4.6	0.398
PR vs. SD + PD				
Heterozygote model: FV vs FF				
Asian	0.175	2.09 (0.72–6.10)	0	0.629
European	0.518	0.80 (0.40–1.58)	0	0.502
Total	0.824	1.07 (0.61–1.87)	0	0.565
Homozygote model: VV vs FF				
Asian	0.163	3.09 (0.63–15.04)	28.5	0.247
European	0.638	1.26 (0.48–3.28)	0	0.540
Total	0.250	1.61 (0.71–3.64)	0	0.493
Dominant model: FV + VV vs FF				
Asian	0.141	2.12 (0.78–5.78)	0	0.427
European	0.862	0.94 (0.50–1.79)	0	0.643
Total	0.497	1.20 (0.71–2.05)	0	0.657
Recessive model: VV vs FV + FF				
Asian	0.242	2.22 (0.58–8.40)	0	0.371
European	0.287	1.60 (0.67–3.82)	0	0.783
Total	0.127	1.76 (0.85–3.65)	0	0.804
CR + PR vs. SD + PD				
Heterozygote model: FV vs FF				
Asian	0.058	2.38 (0.97–5.85)	31.3	0.233
European	0.412	0.78 (0.43–1.41)	4.0	0.396
Total	0.691	1.10 (0.68–1.79)	32.7	0.147
Homozygote model: VV vs FF				
Asian	0.338	3.49 (0.27–44.96)	69.2	0.039
European	0.928	1.04 (0.42–2.58)	9.1	0.358
Total	0.460	1.46 (0.54–3.95)	42.0	0.087
Dominant model: FV + VV vs FF				
Asian	0.056	2.29 (0.98–5.36)	61.7	0.073
European	0.760	0.92 (0.53–1.59)	0	0.586
Total	0.422	1.20 (0.77–1.89)	33.0	0.144
Recessive model: VV vs FV + FF				
Asian	0.258	1.89 (0.63–5.71)	59.0	0.087
European	0.448	1.29 (0.67–2.49)	0	0.546
Total	0.209	1.44 (0.82–2.52)	9.9	0.352

Italic refers to the association between *FCGR3A* 158 V/F and treatment outcome is significant especially in Asian population when stratified by ethnicity

OR odds ratios, *95%CI* 95 % confidence interval, *Ph* P value of heterogeneity test

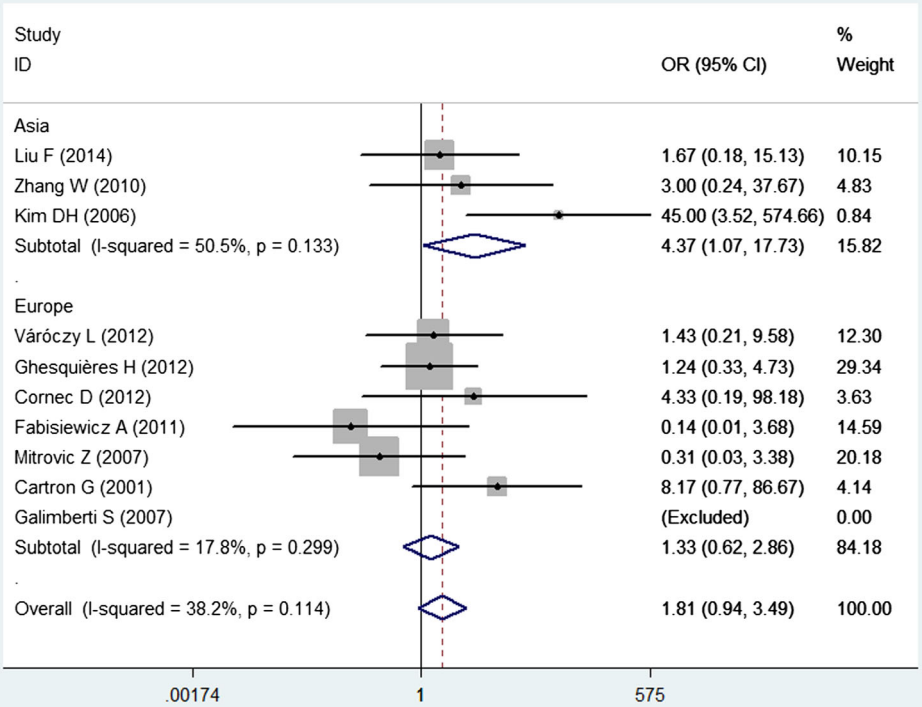

Fig. 2 Association of the *FCGR3A* 158 V/F polymorphism with the CR rate to rituximab-based chemotherapy in non-Hodgkin lymphoma patients under the heterozygous model (VV vs FF)

Begg's funnel plots were created and Egger's tests were performed to appraise the publication bias among the studies selected for the meta-analysis. The shape of the funnel plots appeared symmetrical, and Egger's regression tests showed no

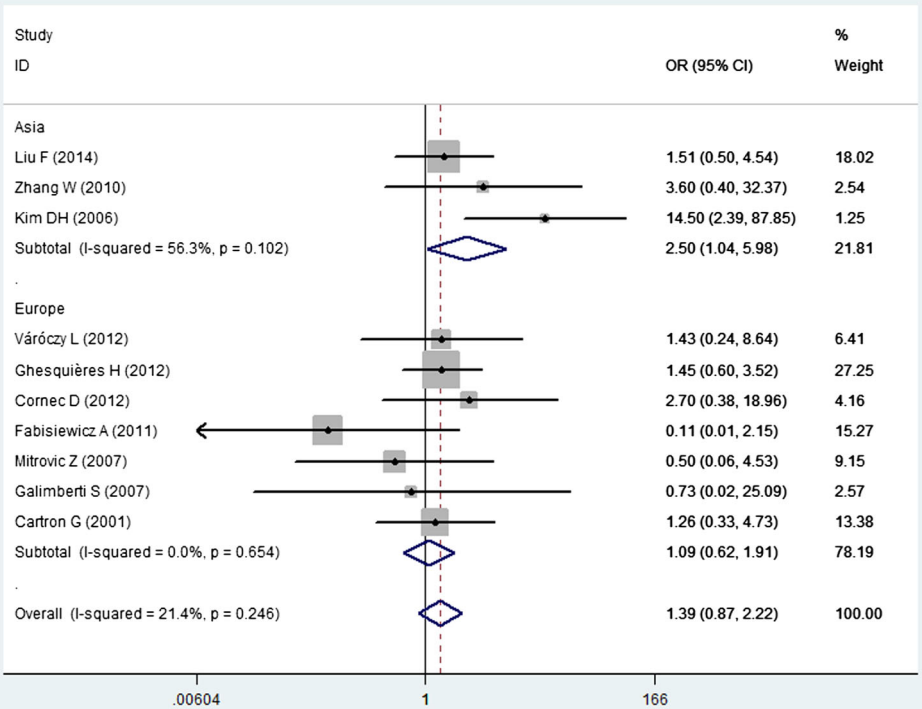

Fig. 3 Association of the *FCGR3A* 158 V/F polymorphism with the CR rate to rituximab-based chemotherapy in non-Hodgkin lymphoma patients under the dominant mode (FV + VV vs FF)

evidence of publication bias ($P = 0.427$ for VV vs FF) in the meta-analysis (Fig. 4).

Discussion

In this meta-analysis, we provided evidence that the *FCGR3A* FF genotype could be a low-penetrant risk factor in NHL patients. Furthermore, in subgroup analyses based on ethnicity, a significantly higher CR rate was observed for Asian populations under the homozygote comparison and the dominant model. To our knowledge, the present meta-analysis is the first to analyze the relationship between the *FCGR3A* 158 V/F polymorphism and the response to rituximab-based chemotherapy for NHL patients and uses meta-analysis to analyze data from ten published studies to be able to state a powerful conclusion.

Kim et al. [13] observed a significantly higher CR and ORR rate in the *FCGR3A* V/V allele, when compared with the *FCGR3A* V/F or F/F alleles, for Korean individuals. However, Liu et al. [6] suggested that the *FCGR3A* 158 V/F polymorphism did not affect the CR rate and the ORR of R-CHOP therapy, but there was no subgroup analysis conducted. Furthermore, Table 4 of Liu's study [6] has little deviation from the included studies, and we have confirmed our findings by checking the data carefully. Another study that also used rituximab with CHOP had a much higher efficacy in patients with the V/V and V/F genotypes [11]. The study by Ahlgrimm et al. [32] did not include the response data, and therefore, it was not included in our study. Based on these studies, we added four additional articles [8, 9, 14, 15] to our analysis. Two French studies [9, 15] found an association between the *FCGR3A* polymorphism and the clinical and molecular responses to rituximab.

Cartron et al. found a disappearance of the *BCL2-JH* gene rearrangement in both peripheral blood and marrow was observed at 1 year (12 months) in 5 of 6 of *FCGR3A* 158VV genotype patients compared with 5 of 17 of *FCGR3A* 158FF carriers [15]. However, two other reports [8, 14] did not show that the *FCGR3A* polymorphism influences the response rate and outcome when rituximab is combined with chemotherapy or used as a maintenance treatment.

This meta-analysis also has some limitations that could influence the results slightly. First, in our study, no obvious heterogeneities were observed for the overall analysis, but heterogeneities were found in the analysis of the ethnicity subgroups. These heterogeneities could be due to differences in the frequency of genetic variations between the different groups. In the studies by Liu et al. [6] and Mitroviç et al. [13], the SD or PD rates for the carriers with the FF allele were 14.3 % (10/70) and 10 % (1/10), respectively. However, Zhang et al. [11] found that patients with the FF genotype had a 40 % (2/5) SD or PD rate, which was much higher than the percentage reported by the other two studies. When the number of studies is small, the power to be able to detect bias is low. Therefore, an increase in the number of studies included could improve the validity of the meta-analysis. Second, we only included studies published in English for the analysis, and some relevant reports have been published in other languages and in other electronic databases that we may have missed. However, we did not detect publication bias in our study. Third, our results were based on unadjusted estimates and were also not adjusted for potential confounds such as age, gender, smoking status, and other lifestyle risk factors, as information on potential confounding variables was unavailable.

In summary, the results of this systematic review and meta-analysis suggest that, in patients with non-Hodgkin

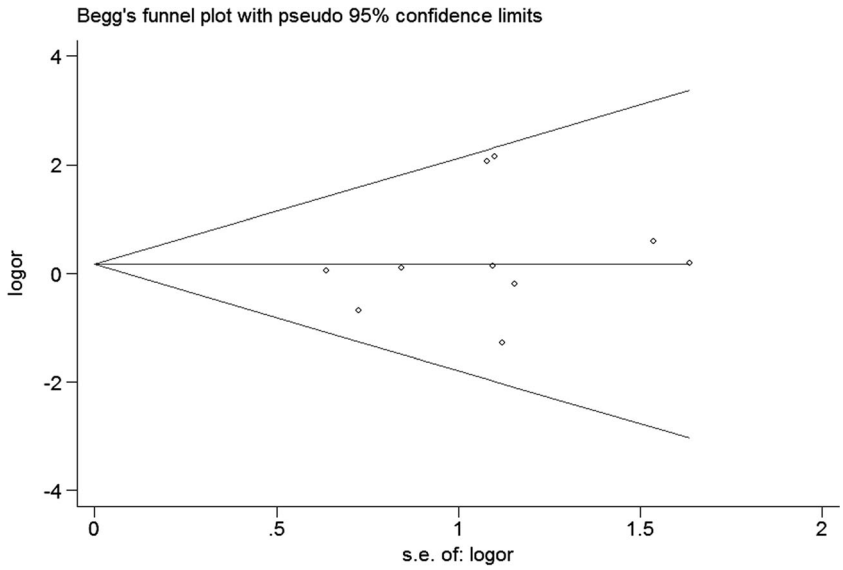

Fig. 4 Begg's funnel plot for publication bias test (VV allele vs FF allele). Each point represents a separate study for the indicated association. *Horizontal line* means effect size. Log OR natural logarithm of OR

lymphoma, there is an association in Asian individuals between carrying the *FCGR3A* 158 FF allele and a poor response to rituximab-based chemotherapy. However, future studies with larger sample sizes and suitable designs are needed to confirm these findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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