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Original Article

FCGR2A and FCGR3A polymorphisms predict prognosis in metastatic colorectal cancer patients treated with cetuximab-based therapies: a systematic review and meta-analysis

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Abstract: A meta-analysis of the FCGR2A H131R and FCGR3A V158F polymorphisms in patients with metastatic colorectal cancer was performed to assess the association between these genetic polymorphisms and the clinical efficacy and prognostic value of cetuximab-based therapies. A search of the PubMed and EMBASE databases identified 11 published studies including 907 patients treated with cetuximab-based regimens. The clinical response, disease control rate (DCR), and prognosis were evaluated using a fixed or random effects model. Patients carrying the FCGR2A 131R allele (HR and RR genotypes) had a better clinical response than those with the FCGR2A 131HH genotype in the overall pooled analysis (HR+RR vs. HH; overall response rate (ORR) = 1.54; 95% confidence interval (CI) = 1.31-2.09; *P* = 0.01) and in subgroup analysis of patients who received cetuximab as a single agent (HR+RR vs. HH; ORR = 1.77; 95% CI = 0.95-3.28; *P* = 0.07). No significant association between the FCGR2A 131H/R polymorphism and DCR or prognostic factors was observed. Patients harboring the FCGR3A 158F allele had better DCR than those with the FCGR3 158VV genotype (VF+FF vs. VV; DCR = 1.45; 95% CI = 1.04-2.05; *P* = 0.03), whereas no significant differences between the two groups were observed in the clinical response rate or prognostic factors. Pooled analysis showed that FCGR3A V allele carriers had a better clinical response (VV+VF vs. FF; ORR = 0.59; 95% CI = 0.35-0.99; *P* = 0.05) and longer overall survival than those with the FCGR3A FF genotype (VV+VF vs. FF; HR = 0.79; 95% CI = 0.64-0.97; *P* = 0.03). This meta-analysis showed that the FCGR polymorphism is associated with treatment efficacy and the prognosis of patients with metastatic colorectal cancer treated with cetuximab.

Keywords: FCGR, polymorphism, mCRC

Introduction

The mortality rates of colorectal cancer (CRC) have decreased in the last decade because of the introduction of new targeted therapies such as cetuximab; however, CRC remains the second leading cause of cancer-related death worldwide [1]. Furthermore, the clinical prognosis of patients with metastatic CRC (mCRC) is unsatisfactory.

Cetuximab, a chimeric immunoglobulin 1 (IgG1) monoclonal antibody (moAb) that targets the epidermal growth factor receptor (EGFR), exerts its antitumor effects through the RAS-RAF-mitogen-activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase-AKT pathway [2-4], and its use is restricted to Kras wild-type mCRC patients [5, 6]. However, the presence of wild-type Kras type is not sufficient to predict the tumor response to cetuximab. Therefore, the identification of novel predictive markers of the response to cetuximab is necessary.

Recent studies showed that the interaction of the Fc gamma receptor (FCGR) expressed on immune effector cells (i.e., macrophages and natural killer cells) with the fragment crystallizable (FC) region of the IgG1 MoAb has antitumor effects mediated by antibody-dependent cellular cytotoxicity (ADCC) [7, 8]. In addition, the

FCGR2A and FCGR3A polymorphisms are associated with tumor response and ADCC in follicular lymphoma patients treated with rituximab [9-11]. However, despite extensive research, no consensus has been reached regarding the relationship between FCGR polymorphisms and the efficacy of cetuximab. Therefore, whether FCGR polymorphisms modulate ADCC induced by cetuximab, and whether these polymorphisms are associated with tumor response and prognosis in mCRC patients treated with cetuximab-based therapies remains unclear.

To the best of our knowledge, the present meta-analysis is the first to assess the value of FCGR polymorphisms as molecular markers to predict the efficacy of cetuximab-based therapies with the purpose of defining the subpopulation of patients who might benefit from cetuximab treatment.

Material and methods

Search strategy

To identify relevant studies assessing FCGR2A and FCGR3A polymorphisms and cetuximab-based therapies in mCRC patients published before December 2014, a search of the English literature was performed using the PubMed and EMBASE databases with the following terms: "colorectal cancer", "colon cancer", "rectal cancer", "cetuximab", "gene variation", "genetic variation" and "polymorphism". The reference lists of the retrieved articles and reviews were further screened manually to identify relevant studies.

Eligibility criteria

The studies were considered eligible and included in our meta-analysis when they met the following inclusion criteria: (1) patients were diagnosed with mCRC; (2) therapeutic regimens contained cetuximab; (3) the associations between FCGR polymorphisms and prognosis and tumor response were evaluated; (4) the outcomes of interest were directly reported or could be indirectly calculated from the available information. In cases in which studies were duplicated, the most informative study was included.

Studies were excluded if (1) the studies did not involve any interest polymorphism, (2) the outcomes of interest were not reported and it was impossible to calculate outcomes from the originally published data, (3) repeated studies were based on the same database or patients.

Data extraction and quality assessment

Data extraction and quality assessment of the included studies were performed independently by two authors (Xiaowan Chen and Jingxu Sun), and disagreements were resolved through discussion. The following information was extracted: first author, year and country of publication, sample size and age of patients, type of genetic variant, and evaluation criteria of tumor response, Kras status, chemotherapy regimens, and effect estimates with the corresponding 95% confidence intervals (CIs). The quality of the studies was determined using a descriptive and qualitative approach, rather than a quantitative one, with regard to the following aspects, which were largely consistent with REMARK (Reporting recommendations for tumor marker prognostic studies) guidelines [12], patient characteristics, treatment details, genotyping method, clinical endpoints, sample size, measurement methods, and analysis methods.

Statistical analysis

The odds ratio (OR) and corresponding 95% CIs were calculated to assess the relationship between overall response rate (ORR, defined as the rate of complete response and partial response rate) and FCGR polymorphisms in mCRC patients treated with cetuximab. The hazard ratio (HR) and corresponding 95% CIs were calculated to assess the relationship between prognosis (progression-free survival [PFS] and overall survival [OS]) and FCGR polymorphisms in mCRC treated with cetuximab. When these statistical variables were not given explicitly in studies, they were estimated from available data using the methods reported by Tierney et al. [13]. The overall analysis was performed by including all the relevant studies. Additional subgroup analysis was performed according to the chemotherapy regimens (single-agent cetuximab and combined cetuximab) and Kras status (wild type).

Heterogeneity among studies was assessed using the χ^2-based Q statistic and I^2 statistic [14]. Heterogeneity was considered statistically significant when p for heterogeneity < 0.05

and/or I^2 > 50%. If heterogeneity existed, data were analyzed using a random-effects model; otherwise, a fixed-effects model was used [15]. Sources of heterogeneity were appraised by subgroup analysis. Potential publication bias was evaluated using Begg's and Egger's tests [16, 17].

All statistical analyses were performed using RevMan 5.2 (Copenhagen: The Nordic Cochrane Centre; The Cochrane Collaboration, 2012) and STATA 12.0 analysis software (Stata Corporation, College Station, TX, USA). The two-sided *P* value for statistical significance was set at 0.05 for all statistical tests.

Results

Summary of eligible studies

A total of 125 studies were initially identified. Of these, 77 were duplicates and 48 were further evaluated by full-text review. Thirty-seven studies were excluded because they did not include polymorphisms of interest or did not assess pharmacogenetic or prognostic outcomes of interest. Finally, 11 studies met the inclusion criteria and were included in the meta-analysis (**Figure 1**).

The 11 studies analyzed were published between 2007 and 2012 and were conducted in the US, France, Spain, Netherlands, and Korea. Ten studies assessed the prognostic significance of FCGR2A and FCGR3A polymorphisms in mCRC patients treated with cetuximab-based therapies. One study only assessed the prognostic significance of FCGR3A polymorphisms. Four studies evaluated cetuximab as a single agent and seven studies evaluated combined cetuximab regimens. The present study included 907 mCRC patients (median sample size, 76 [range, 35-127]). The baseline characteristics of eligible studies were listed in **Table 1A** and **1B** [18-33].

Quality assessment of eligible studies

All included studies provided a detailed description of patient characteristics and treatments received as well as the methods used for genotyping and outcome assessment. Clinical endpoints were clearly defined in four studies. Three of the eligible studies portrayed simple on statistical analysis. In terms of sample size, four studies included less than 50 patients, five studies included 50-100 patients, and seven studies included more than 100 patients.

Predictive value of FCGR2A H131R polymorphism

The association between the FCGR2A H131R polymorphism and tumor response to cetuximab-based treatment was evaluated in six trials including 571 individuals [19, 22, 23, 25, 29, 31, 32]. The pooled results showed a significant association between the FCGR2A H131R polymorphism and clinical response rate (HR+RR vs. HH; ORR = 1.54; 95% CI = 1.31-2.09; *P* = 0.01), without significant heterogeneity (I^2 = 25.4%). In the subgroup analysis, the FCGR2A R allele was associated with a better tumor response to single-agent cetuximab therapy (HR+RR vs. HH; ORR = 1.77; 95% CI = 0.95-3.28; *P* = 0.07), although statistical significance was not reached. By contrast, the FCGR2A R allele was not associated with a better tumor response to combined cetuximab therapy (HR+RR vs. HH; ORR = 0.72; 95% CI = 0.11-4.67; *P* = 0.73) (**Table 2**). The results of the analysis indicated that the FCGR2A H131R polymorphism does not predict the response to treatment regardless of the chemotherapy regimens.

Four studies provided OS data [19, 22, 23]. There was no significant association between the FCGR2A polymorphism and prolonged survival in mCRC patients (HR+RR vs. HH; HR = 1.02; 95% CI = 0.94-1.10; *P* = 0.66) (**Table 3**), and a similar result was observed in patients treated with single-agent cetuximab therapy (HR+RR vs. HH; HR = 1.01; 95% CI = 0.94-1.09; *P* = 0.77). Six studies provided PFS data [19, 22, 23, 25, 26, 31], and the result showed no significant association between the FCGR2A polymorphism and PFS in mCRC patients treated with cetuximab (HR+RR vs. HH; HR = 1.06; 95% CI = 0.85-1.33; *P* = 0.58) (**Table 3**). In the subgroup analysis according to chemotherapy regimens, no significant association between the FCGR2A polymorphism and PFS was observed in patients treated with single-agent cetuximab therapy (HR+RR vs. HH; HR = 0.87; 95% CI = 0.66-1.15; *P* = 0.32) (**Table 3**).

Predictive value of FCGR3A V158F polymorphism

Seven studies assessed the relationship between the FCGR3A polymorphism and tumor

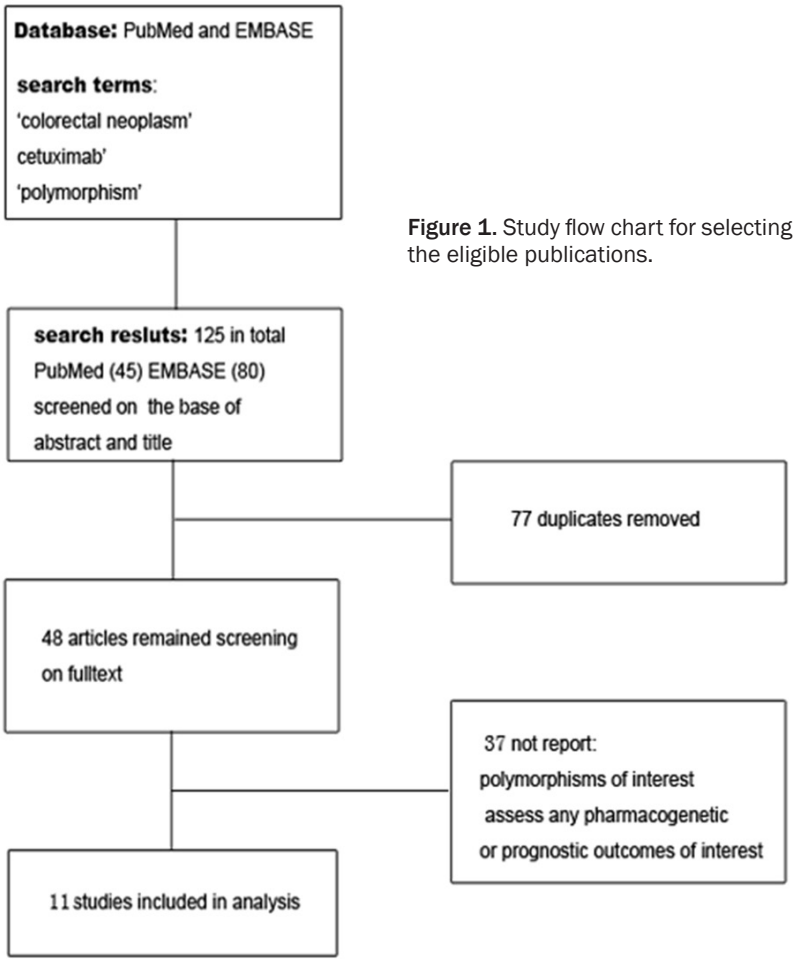

Figure 1. Study flow chart for selecting the eligible publications.

response by comparing the F allele to VV homozygotes [19, 22, 23, 25, 27, 29, 31], and no significant association was found (VF+FF vs. VV; ORR = 0.98; 95% CI = 0.68-1.42; *P* = 0.93) (**Table 4**). In the subgroup analysis according to chemotherapy regimen, no significant association between the FCGR3A polymorphism and tumor response was observed in the single-agent subgroup (VF+FF vs. VV; ORR = 1.03; 95% CI = 0.51-2.09; *P* = 0.93) or the combined subgroup (VF+FF vs. VV; ORR = 0.97; 95% CI = 0.63-1.48; P = 0.88) (**Table 4**). The FCGR3A F allele was associated with better disease control (VF+FF vs. VV; DCR = 1.45; 95% CI = 1.04-2.05; *P* = 0.03). A similar result was obtained in patients treated with single-agent cetuximab therapy. The effect of the F allele and VV homozygotes on OS and PFS was assessed in four and four studies, respectively. The pooled results showed no association between the F allele and OS (FF+VF vs. VV; HR = 0.88; 95% CI = 0.56-1.39; *P* = 0.59) or between the F allele and PFS (VF+FF vs. VV; HR = 0.85; 95% CI = 0.58-1.27; *P* = 0.43). In the subgroup analysis according to chemotherapy regimens, the FCGR3A F allele was not a predictor of survival in patients treated with single-agent cetuximab or combined cetuximab therapy (**Table 5**).

Seven studies assessed the relationship between the FCGR3A polymorphism and cetuximab response by comparing the V allele with FF homozygotes [19, 22, 23, 25, 27, 29, 31-33]. The pooled analysis showed an association that was not statistically significant (VV+VF vs. FF; ORR = 0.68; 95% CI = 0.42-1.09; *P* = 0.11) (**Table 6**); however, a significant relationship was found between FF homozygotes and better tumor response to single-agent cetuximab therapy (VV+VF vs. FF; ORR = 0.59; 95% CI = 0.35-0.99; *P* = 0.05) (**Table 6**). There was no significant association between the FCGR3A V allele and FF homozygotes among patients treated with combined cetuximab therapy (VV+VF vs. FF; ORR = 1.26; 95% CI = 0.41-3.93) (**Table 6**). In terms of disease control, no significant association was observed in the comparison between the FCGR3A V allele and FF homozygotes (VV+VF vs. FF; DCR = 1.16; 95% CI = 0.74-1.82). In the subgroup analysis according to chemotherapy regimens, the FCGR3A V allele and FF homozygotes did not predict disease control in single-agent cetuximab therapy. The FCGR3A V allele was associated with better disease control in combined cetuximab therapy (VV+VF vs. FF; DCR = 2.06; 95% CI = 0.92-4.61) in a limited number of studies (only two eligible studies), although statistical significance was not reached. Five studies compared the effect of the V allele and FF homozygotes on OS. The pooled results showed a significant association between the V allele and better OS (VV+VF vs. FF; HR = 0.79;

Table 1A. Characteristics of eligible studies and baseline patients

Author-Year	Country	Genetic variant	Total number	Evaluation criteria	Methods	Kras status	Median age	Study type
Zhang-2007	USA	FCGR2A	35	RECIST	PCR-RFLP	NS	64	phase II
		FCGR3A	35		PCR-RFLP			
Lurje-2008	USA	FCGR2A	100	WHO	PCR-RFLP	Both	NS	phase II
		FCGR3A	127		PCR-RFLP			
Bibeau-2009	France	FCGR2A	61	RECIST	PCR-sequence	separated	60	NS
		FCGR3A	68		PCR-sequence			
Paez-2010	Spain	FCGR2A	104	RECIST	Taq-PCR	separated	64	phase II
		FCGR3A	104		Taq-PCR			
Pander-2010	Netherlands	FCGR2A	126	RECIST	Taq-PCR	WT	NS	phaseIII
		FCGR3A	122		Taq-PCR			
Zhang-2010	USA	FCGR3A	65	NS	PCR-RFLP	NS	NS	phase II
Dahan-2011	France	FCGR2A	56	RECIST	PCR-RFLP	Both	60.2	NS
		FCGR3A	56		PCR-RFLP			
Hu-2011	European cancer centers	FCGR2A	123	Dworak	PCR-RFLP	Both	61	NS
		FCGR3A	101		PCR-RFLP			
Park-2012	Korea	FCGR2A	107	RECIST	Taq-PCR	separated	56	NS
		FCGR3A	107		Taq-PCR			
Rodriguez-2012	Spain	FCGR2A	44	RECIST	Taq-PCR	Both	59.5	NS
		FCGR3A	44		Taq-PCR			
Etienne-2012	France	FCGR2A	52	RECIST	PCR-RFLP	Both	63.3	NS
		FCGR3A	52		Taq-PCR	Both		

95% CI = 0.64-0.97; *P* = 0.03) (**Table 7**) Similar tendencies were observed in the subgroup analysis based on chemotherapy regimens (single-agent cetuximab therapy: HR = 0.82; 95% CI = 0.64-1.05, *P* = 0.12; combined cetuximab therapy: HR = 0.70; 95% CI = 0.46-1.05, *P* = 0.09). Four studies compared the effect of the V allele and FF homozygotes on PFS, and pooled analysis indicated no association between FF homozygotes and PFS (VV+VF vs. FF; HR = 0.88; 95% CI = 0.70-1.12; *P* = 0.97) (**Table 7**).

Publication bias

Begg's and Egger's tests showed no evidence of significant publication bias in our meta-analysis. The plot charts of publication bias analysis were showed in **Figure 2**.

Discussion

Targeted therapies, including the anti-EGFR antibody cetuximab, have shown efficacy in the treatment of mCRC. The anti-tumor effect of cetuximab, an IgG1 mAb, may be mediated by the ADCC mechanism. Binding of fragment C of the mAb to the Fc receptors (FcR) on the surface of immune cells, such as macrophages and natural killer cells, could trigger tumor cell lysis. In vivo and in vitro experiments have shown that FCGR2A and FCGR3A polymorphisms, in particular the H/R polymorphism at position 131 of FCGR2A and the V/F polymorphism at position 158 of FCGR3A, affect the affinity for human IgG. Moreover, these polymorphisms influence the efficacy of therapeutic IgG moAbs, as confirmed in studies of follicular lymphoma patients and breast cancer patients treated with rituximab. Although the role of FCGR polymorphisms in the response of mCRC to cetuximab therapy were investigated previously, studies have shown inconsistent results. The present meta-analysis was performed to examine the results of these studies.

The present meta-analysis showed that patients carrying the FCGR2A 131R allele (HR and RR genotype) had a better clinical response than patients with the FCGR2A 131HH genotype in both overall pooled analysis and in subgroup analysis in patients who received cetuximab as single agent. No significant association was observed between the FCGR2A 131H/R polymorphism and DCR or prognostic factors.

Table 1B. Characteristics of eligible studies and baseline patients (continued)

Author-Year	Previous chemotherapy	Therapeutic method	Originial
Zhang-2007	Two prior chemotherapy regimens/adjuvant therapy plus one chemotherapy regimen for metastatic disease	Cetuximab	(IMC 0144)
Lurje-2008	Two prior chemotherapy regimens/adjuvant therapy plus one chemotherapy regimen for metastatic disease	Cetuximab	(IMC 0144)
Bibeau-2009	capecitabine/oxaliplatin+bevacizumab/the same regimen plus cetuximab	Cetuximab+Irinotecan	NS
Paez-2010	at least one prior chemotherapy regimen	Cetuximab/Panitumumab	(EORTC)
Pander-2010	untreated	capecitabine, oxaliplatin, bevacizumab, Cetuximab	DCCG
Zhang-2010	at least one irinotecan-containing regimen for metastatic disease	Cetuximab+Bevacizumab+Irinotecan/-	BOND-2 study
Dahan-2011	untreated	Cetuximab+Irinotecan/FOLFIRI/FOLFOX	NS
Hu-2011	untreated	Cetuximab+Radiation+5-FU/Capecitabine/Oxaliplatin	4 centers
Park-2012	at least one course of irinotecan-based chemotherapy	Cetuximab	NS
Rodriguez-2012	untreated	Cetuximab+Irinotecan/Oxaliplatin	NS
Etienne-2012	untreated	Cetuximab+Irinotecan+UFT	NS

Abbreviations: WHO, World Health Organization; RECIST, Response Evaluation Criteria in Solid Tumors; PCR-RFLP, PCR-restriction fragment length polymorphism; WT, wild-type; Both, both include mutation KRAS and wild-type KRAS; separated, wild-type KRAS and mutation KRAS were separated; NS, not state.

Table 2. FCGR2A polymorphism (HR+RR vs. HH) and cetuximab based treatment efficacy

	Response rate			DCR		
	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)
All	1.54 (1.31-2.09)	0.006	25.4	0.97 (0.72-1.29)	0.825	23.8
single-C225	1.77 (0.95-3.28)	0.072	0.0	1.43 (0.63-2.07)	0.659	12.7
combined-C225	0.72 (0.11-4.67)	0.731	84.0	0.92 (0.66-1.28)	0.62	47.7
wt-Kras	1.44 (0.75-2.77)	0.273	25.9	1.61 (0.65-3.98)	0.30	12.8
mut-Kras	—	—	—	0.57 (0.22-1.49)	0.26	34.8
Irinotecan	—	—	—	0.50 (0.13-1.87)	0.30	53.5
Non- Irinotecan	1.68 (1.22-2.31)	0.001	0.0	1.05 (0.77-1.42)	0.78	0.0
Oxaliplatin	—	—	—	—	—	—
Non-Oxaliplatin	1.54 (1.31-2.09)	0.006	25.4	1.04 (0.77-1.40)	0.81	0.0

Table 3. FCGR2A polymorphism (HR+RR vs. HH) and prognostic value of mCRC patients with cetuximab based treatment

	OS			PFS		
	HR (95% CI)	P	I^2 (%)	HR (95% CI)	P	I^2 (%)
All	1.02 (0.94-1.10)	0.663	34.4	1.06 (0.85-1.33)	0.575	21.4
single-C225	1.01 (0.94-1.09)	0.771	26.4	0.87 (0.66-1.15)	0.322	0.0
combined-C225	—	—	—	1.51 (1.05-2.17)	0.026	0.0
wt-Kras	—	—	—	1.29 (0.92-1.79)	0.137	0.0
mut-Kras	—	—	—	1.18 (0.61-2.28)	0.628	33.0
Irinotecan	—	—	—	1.51 (1.05-2.17)	0.026	0.0
Non-Irinotecan	1.01 (0.94-1.09)	0.771	26.4	0.87 (0.66-1.15)	0.322	0.0
Oxaliplatin	—	—	—	—	—	—
Non-Oxaliplatin	1.02 (0.94-1.10)	0.663	34.4	0.96 (0.74-1.23)	0.724	0.0

Table 4. FCGR3A polymorphism (VF+FF vs. VV) and cetuximab based treatment efficacy

	Response rate			DCR		
	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)
All	0.98 (0.68-1.42)	0.932	0.0	1.45 (1.04-2.05)	0.03	41.6
single-C225	1.03 (0.51-2.09)	0.933	14.4	1.66 (0.88-3.13)	0.116	28.7
combined-C225	0.97 (0.63-1.48)	0.881	0.0	0.81 (0.16-4.21)	0.807	74.9
wt-Kras	0.73 (0.28-1.90)	0.520	0.0	1.24 (0.42-3.68)	0.70	7.2
mut-Kras	0.11 (0.01-1.12)	0.062	0.0	0.56 (0.02-17.33)	0.74	65.4
Irinotecan	0.97 (0.30-3.10)	0.954	0.0	—	—	—
Non-Irinotecan	0.99 (0.67-1.45)	0.944	0.0	1.61 (1.13-2.29)	0.008	0.0
Oxaliplatin	—	—	—	—	—	—
Non-Oxaliplatin	0.98 (0.68-1.42)	0.932	0.0	1.45 (1.04-2.05)	0.03	41.6

Patients harboring the FCGR3A 158F allele had better DCR than those with the FCGR3 158VV genotype; however, no significant differences were observed in the clinical response rate or prognostic factors. The results of pooled-analysis showed that FCGR3A V allele carriers had a

Table 5. FCGR3A polymorphism (VF+FF vs. VV) and prognostic value of mCRC patients with cetuximab based treatment

	OS			PFS		
	HR (95% CI)	P	I^2 (%)	HR (95% CI)	P	I^2 (%)
All	0.88 (0.56-1.39)	0.593	50.8	0.85 (0.58-1.27)	0.434	66.6
single-C225	0.86 (0.65-1.14)	0.295	49.2	0.63 (0.30-1.33)	0.228	64.5
combined-C225	1.23 (0.39-3.94)	0.724	74.3	1.27 (0.70-2.32)	0.430	84.4
wt-Kras	——	——	——	1.29 (0.64-2.62)	0.478	82.8
mut-Kras	——	——	——	——	——	——
Irinotecan	1.23 (0.39-3.94)	0.724	74.3	——	——	——
Non-Irinotecan	0.86 (0.65-1.14)	0.295	49.2	0.76 (0.64-0.90)	0.001	0.4
Oxaliplatin	——	——	——	——	——	——
Non-Oxaliplatin	0.88 (0.56-1.39)	0.593	50.8	0.85 (0.58-1.27)	0.434	66.6

Table 6. FCGR3A polymorphism (VV+VF vs. FF) and cetuximab based treatment efficacy

	Response rate			DCR		
	OR (95% CI)	P	I^2 (%)	OR (95% CI)	P	I^2 (%)
All	0.68 (0.42-1.09)	0.106	0.6	1.16 (0.74-1.82)	0.51	45.4
single-C225	0.59 (0.35-0.99)	0.047	14.1	0.88 (0.51-1.53)	0.66	47.2
combined-C225	1.26 (0.41-3.93)	0.688	0.0	2.06 (0.92-4.61)	0.080	0.0
wt-Kras	0.81 (0.42-1.54)	0.520	0.0	0.46 (0.18-1.16)	0.10	0.0
mut-Kras	1.54 (0.15-15.91)	0.716	0.0	1.12 (0.25-4.91)	0.885	54.5
Irinotecan	1.26 (0.41-3.93)	0.688	0.0	2.06 (0.92-4.61)	0.080	0.0
Non-Irinotecan	0.59 (0.35-0.99)	0.047	14.1	0.88 (0.51-1.53)	0.66	47.2
Oxaliplatin	——	——	——	——	——	——
Non-Oxaliplatin	0.68 (0.42-1.09)	0.106	0.6	1.01 (0.63-1.64)	0.954	37.5

Table 7. FCGR3A polymorphism (VV+VF vs. FF) and prognostic value of mCRC patients with cetuximab based treatment

	OS			PFS		
	HR (95% CI)	P	I^2 (%)	HR (95% CI)	P	I^2 (%)
All	0.79 (0.64-0.97)	0.026	0.0	0.88 (0.70-1.12)	0.299	37.4
single-C225	0.82 (0.64-1.05)	0.117	0.0	0.98 (0.75-1.27)	0.87	0.0
combined-C225	0.70 (0.46-1.05)	0.086	48.2	——	——	——
wt-Kras	——	——	——	——	——	——
mut-Kras	——	——	——	——	——	——
Irinotecan	0.70 (0.46-1.05)	0.086	48.2	——	——	——
Non-Irinotecan	0.82 (0.64-1.05)	0.117	0.0	0.98 (0.75-1.27)	0.87	0.0
Oxaliplatin	——	——	——	——	——	——
Non-Oxaliplatin	0.79 (0.64-0.97)	0.026	0.0	0.88 (0.70-1.12)	0.299	37.4

better clinical response and OS than FCGR3A FF genotype carriers.

Our results indicated that FCGR3A 158V allele and FCGR2A 131R allele carriers had a better clinical response and FCGR3A 158F allele carriers had better DCR; however, the FCGR2A 131R allele and the FCGR3A 158F allele did not confer any benefits regarding OS or PFS. Moreover, the OS of FCGR 158V allele carriers was worse than that of patients with the FCGR 158FF genotype. One possible explanation for this phenomenon is that an increase in the tumor response rate does not always translate

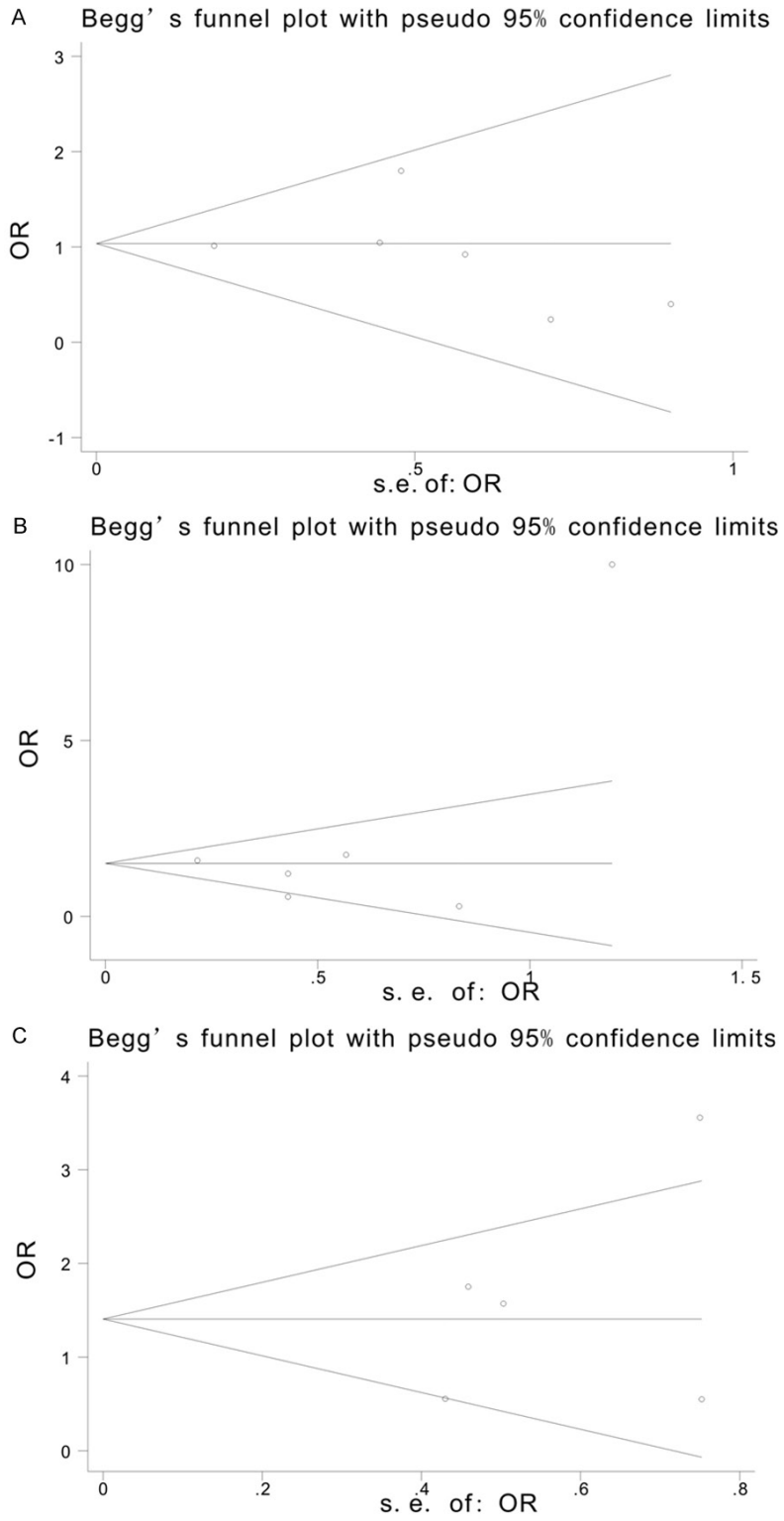

Figure 2. The plot chart of publication bias analysis. A. Funnel plot analysis of 6 studies on FCGR2A polymorphism (HR+RR vs. HH). B. Funnel plot analysis of 6 studies on FCGR3A polymorphism (VF+FF vs. VV). C. Funnel plot analysis of 5 studies on FCGR3A polymorphism (VV+VF vs. FF).

into overall survival benefits in patients with mCRC, especially after exposure to targeted therapies. This means that although patients treated with cetuximab may show an improved clinical response; this does not allow accurate prediction of the ultimate benefit on survival. In addition, the evaluation of cetuximab efficacy by radiographic imaging is limited because the effects of targeted chemotherapy do not always translate into a change in tumor size. For instance, bevacizumab, an angiogenesis inhibitor, can cause necrosis and cavitation without tumor shrinkage.

Pharmacogenetic studies have shown that these two genetic polymorphisms (H-131R and V158F) affect the binding affinity of receptors on immune cells to human IgGs. The FCGR2A-131H/H genotype has a higher affinity for human IgG2, and the FCGR3A V allele has a higher binding affinity for human IgG1. These results indicate that immune effector cells bearing the FCGR2A 131H allele or the FCGR3A 158V allele may mediate ADCC more effectively. Studies on the efficacy of IgG1-type monoclonal antibodies confirmed this hypothesis by demonstrating that that the FCGR2A 131HH genotype or the FCGR3A 158VV genotype increase efficacy of rituximab in lymphoma and trastuzumab in advanced breast cancer. However, our pooled analysis results were not consistent with these conclusions. We found that FCGR2A 131R allele carriers had a better clinical response and FCGR3A 158F allele carriers had a better DCR. This discrepancy could be attributed to the fact

that the biodistribution of moAbs in metastatic solid tumors is influenced by tumor burden, low vascularity, and high interstitial pressure, which may render ADCC ineffective because of poor distribution of the moAb itself.

In the present subgroup analysis, we found that patients who received cetuximab as single agent had improved clinical response rate or DCR, whereas the patients who received cetuximab combined with other chemotherapy drugs showed no benefits. There are two possible explanations for this discrepancy. First, all the studies included in the meta-analysis were retrospective studies, and most of the patients involved were exposed to chemotherapies as pretreatment. In patients who received cetuximab as a single agent, the immune effector cells such as NK cells may have been killed by cytotoxic drugs to varying degrees, which can influence the total ADCC effect of cetuximab. Moreover, the high affinity of the FCGR3A V-allele results in increased activation of tumor associated macrophages (TAMs) by cetuximab through cross-linking of the Fc gamma receptor. Therefore, the infiltration of TAMs could have been altered in patients who received chemotherapy prior to cetuximab, which may result in the release of mediators, such as VEGF and matrix metalloproteinase (MMPs), to the tumor microenvironment. A second possible explanation for this discrepancy is that in several studies, patients were treated with more than one type of IgG moAb, including bevacizumab and panitumumab in addition to cetuximab. For instance, Paez et al. [25] included patients treated with cetuximab or panitumumab as monotherapy or in combination with chemotherapy. In the study by Dahan et al. [28], 13 patients pre-treated with bevacizumab showed no response to cetuximab, and this subgroup had a significantly decreased specific survival compared with that of non-pretreated patients. In the study by Zhang et al. [27], patients received both cetuximab and bevacizumab. The identified molecular biomarker might select patients who would benefit either from an individual antibody or from combined anti-EGFR and anti-VEGF therapies, whereas it cannot specifically predict the efficacy of cetuximab. Therefore, combination regimens of targeted chemotherapies can influence the efficacy of cetuximab, which decreases the specificity of FCGR polymorphisms for the selection of patients.

Although both our meta-analysis and the studies included demonstrated that individual polymorphisms of FCGR2A and FCGR3A are limited as molecular biomarkers to predict the efficacy of cetuximab for the treatment of mCRC, several studies showed that the combined analysis of FCGR2A and FCGR3A polymorphism could enhance their predictive value regarding the efficacy of cetuximab. Moreover, combined analysis of KRAS mutation status and FCGR polymorphisms was performed in some studies. Bibeau et al. showed that a single FCGR polymorphism was not significantly associated with response to cetuximab, whereas patients with the FCGR2A 131HH and FCGR3A 158VV genotypes tended to show a better clinical response rate. The study by Zhang et al. suggested that the association between cetuximab efficacy and FCGR polymorphisms was more significant when the analysis was based on the combination of two polymorphisms (FCGR2A 131H allele and FCGR3A 158F allele compared with FCGR2A 131RR genotype or FCGR3A 158VV genotype) rather than an individual FCGR polymorphism.

The present meta-analysis had several limitations. First, most of the studies included were retrospective studies, which made variants patients selected and affected the overall pooled analysis. In addition, the sample size was small, and the patients received cetuximab as different line agents.

Conclusion

The present meta-analysis showed that the FCGR polymorphism is a predictor of the efficacy of treatment and the prognosis of patients with metastatic colorectal cancer treated with cetuximab.

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Disclosure of conflict of interest

None.

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References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Baselga J. The EGFR as a target for anticancer therapy-focus on cetuximab. Eur J Cancer 2001; 37 Suppl 4: S16-22.

[3] Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D'Haens G, Pinter T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009; 360: 1408-1417.

[4] Saltz LB, Meropol NJ, Loehrer PJ Sr, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004; 22: 1201-1208.

[5] Allegra CJ, Jessup JM, Somerfield MR, Hamilton SR, Hammond EH, Hayes DF, McAllister PK, Morton RF, Schilsky RL. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol 2009; 27: 2091-2096.

[6] Lievre A, Bachet JB, Boige V, Cayre A, Le Corre D, Buc E, Ychou M, Bouche O, Landi B, Louvet C, André T, Bibeau F, Diebold MD, Rougier P, Ducreux M,Tomasic G, Emile JF, Penault-Llorca F, Laurent-Puig P. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008; 26: 374-379.

[7] Desjarlais JR, Lazar GA, Zhukovsky EA, Chu SY. Optimizing engagement of the immune system by anti-tumor antibodies: an engineer's perspective. Drug Discov Today 2007; 12: 898-910.

[8] Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. N Engl J Med 2008; 358: 1160-1174.

[9] Cartron G, Dacheux L, Salles G, Solal-Celigny P, Bardos P, Colombat P, Watier H. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. Blood 2002; 99: 754-758.

[10] Wu J, Edberg JC, Redecha PB, Bansal V, Guyre PM, Coleman K, Salmon JE, Kimberly RP. A novel polymorphism of FcgammaRIIIa (CD16) alters receptor function and predisposes to autoimmune disease. J Clin Invest 1997; 100: 1059-1070.

[11] Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol 2003; 21: 3940-3947.

[12] McShane LM, Altman DG, Sauerbrei W, Taube SE, Gion M, Clark GM. REporting recommendations for tumor MARKer prognostic studies (REMARK). Breast Cancer Res Treat 2006; 100: 229-235.

[13] Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.

[14] Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005; 28: 123-137.

[15] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[16] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[17] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.

[18] Zhang W, Gordon M, Press OA, Rhodes K, Vallbohmer D, Yang DY, Park D, Fazzone W, Schultheis A, Sherrod AE, Iqbal S, Groshen S, Lenz HJ. Cyclin D1 and epidermal growth factor polymorphisms associated with survival in patients with advanced colorectal cancer treated with Cetuximab. Pharmacogenet Genomics 2006; 16: 475-483.

[19] Zhang W, Gordon M, Schultheis AM, Yang DY, Nagashima F, Azuma M, Chang HM, Borucka E, Lurje G, Sherrod AE, Iqbal S, Groshen S, Lenz HJ. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. J Clin Oncol 2007; 25: 3712-3718.

[20] Goncalves A, Esteyries S, Taylor-Smedra B, Lagarde A, Ayadi M, Monges G, Bertucci F, Esterni B, Delpero JR, Turrini O, Lelong B, Viens P, Borg JP, Birnbaum D, Olschwang S, Viret F. A polymorphism of EGFR extracellular domain is associated with progression free-survival in metastatic colorectal cancer patients receiving cetuximab-based treatment. BMC Cancer 2008; 8: 169.

[21] Graziano F, Ruzzo A, Loupakis F, Canestrari E, Santini D, Catalano V, Bisonni R, Torresi U, Floriani I, Schiavon G, Andreoni F, Maltese P, Rulli E, Humar B, Falcone A, Giustini L, Tonini G, Fontana A, Masi G, Magnani M. Pharmacogenetic profiling for cetuximab plus irinote-

can therapy in patients with refractory advanced colorectal cancer. J Clin Oncol 2008; 26: 1427-1434.

[22] Lurje G, Nagashima F, Zhang W, Yang D, Chang HM, Gordon MA, El-Khoueiry A, Husain H, Wilson PM, Ladner RD, Mauro DJ, Langer C, Rowinsky EK, Lenz HJ. Polymorphisms in cyclooxygenase-2 and epidermal growth factor receptor are associated with progression-free survival independent of K-ras in metastatic colorectal cancer patients treated with single-agent cetuximab. Clin Cancer Res 2008; 14: 7884-7895.

[23] Bibeau F, Lopez-Crapez E, Di Fiore F, Thezenas S, Ychou M, Blanchard F, Lamy A, Penault-Llorca F, Frebourg T, Michel P, Sabourin JC, Boissière-Michot F. Impact of Fc{gamma}RIIa-Fc{gamma}RIIIa polymorphisms and KRAS mutations on the clinical outcome of patients with metastatic colorectal cancer treated with cetuximab plus irinotecan. J Clin Oncol 2009; 27: 1122-1129.

[24] Garm Spindler KL, Pallisgaard N, Rasmussen AA, Lindebjerg J, Andersen RF, Cruger D, Jakobsen A. The importance of KRAS mutations and EGF61A>G polymorphism to the effect of cetuximab and irinotecan in metastatic colorectal cancer. Ann Oncol 2009; 20: 879-884.

[25] Paez D, Pare L, Espinosa I, Salazar J, del Rio E, Barnadas A, Marcuello E, Baiget M. Immunoglobulin G fragment C receptor polymorphisms and KRAS mutations: are they useful biomarkers of clinical outcome in advanced colorectal cancer treated with anti-EGFR-based therapy? Cancer Sci 2010; 101: 2048-2053.

[26] Pander J, Gelderblom H, Antonini NF, Tol J, van Krieken JH, van der Straaten T, Punt CJ, Guchelaar HJ. Correlation of FCGR3A and EGFR germline polymorphisms with the efficacy of cetuximab in KRAS wild-type metastatic colorectal cancer. Eur J Cancer 2010; 46: 1829-1834.

[27] Zhang W, Azuma M, Lurje G, Gordon MA, Yang D, Pohl A, Ning Y, Bohanes P, Gerger A, Winder T, Hollywood E, Danenberg KD, Saltz L, Lenz HJ. Molecular predictors of combination targeted therapies (cetuximab, bevacizumab) in irinotecan-refractory colorectal cancer (BOND-2 study). Anticancer Res 2010; 30: 4209-4217.

[28] Dahan L, Norguet E, Etienne-Grimaldi MC, Formento JL, Gasmi M, Nanni I, Gaudart J, Garcia S, Ouafik L, Seitz JF, Milano G. Pharmacogenetic profiling and cetuximab outcome in patients with advanced colorectal cancer. BMC Cancer 2011; 11: 496.

[29] Hu-Lieskovan S, Vallbohmer D, Zhang W, Yang D, Pohl A, Labonte MJ, Grimminger PP, Holscher AH, Semrau R, Arnold D, Dellas K, Debucquoy A, Haustermans K, Machiels JP, Sempoux C, Rödel C, Bracko M, Velenik V, Lenz HJ. EGF61 polymorphism predicts complete pathologic response to cetuximab-based chemoradiation independent of KRAS status in locally advanced rectal cancer patients. Clin Cancer Res 2011; 17: 5161-5169.

[30] Hsieh YY, Tzeng CH, Chen MH, Chen PM, Wang WS. Epidermal growth factor receptor R521K polymorphism shows favorable outcomes in KRAS wild-type colorectal cancer patients treated with cetuximab-based chemotherapy. Cancer Sci 2012; 103: 791-796.

[31] Park SJ, Hong YS, Lee JL, Ryu MH, Chang HM, Kim KP, Ahn YC, Na YS, Jin DH, Yu CS, Kang YK, Kim TW. Genetic polymorphisms of FcgammaRIIa and FcgammaRIIIa are not predictive of clinical outcomes after cetuximab plus irinotecan chemotherapy in patients with metastatic colorectal cancer. Oncology 2012; 82: 83-89.

[32] Rodriguez J, Zarate R, Bandres E, Boni V, Hernandez A, Sola JJ, Honorato B, Bitarte N, Garcia-Foncillas J. Fc gamma receptor polymorphisms as predictive markers of Cetuximab efficacy in epidermal growth factor receptor downstream-mutated metastatic colorectal cancer. Eur J Cancer 2012; 48: 1774-1780.

[33] Etienne-Grimaldi MC, Bennouna J, Formento JL, Douillard JY, Francoual M, Hennebelle I, Chatelut E, Francois E, Faroux R, El Hannani C, Jacob JH, Milano G. Multifactorial pharmacogenetic analysis in colorectal cancer patients receiving 5-fluorouracil-based therapy together with cetuximab-irinotecan. Br J Clin Pharmacol 2012; 73: 776-785.