CONSENSUS STATEMENT

Association between functional *FCGR3A* F158V and *FCGR2A* R131H polymorphisms and responsiveness to rituximab in patients with autoimmune diseases: a meta-analysis

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OBJECTIVES: To investigate the association between the functional Fc gamma receptor 3 A (*FCGR3A*) V158F and *FCGR2A* R131H polymorphisms and rituximab therapy in patients with autoimmune diseases.
METHODS: We searched the Medline, Embase, and Cochrane databases for relevant articles. We conducted a meta-analysis of the association between *FCGR3A* V158F and *FCGR2A* R131H polymorphisms and responsiveness to rituximab in patients with autoimmune diseases.
RESULTS: Eleven studies, consisting of 661 responders and 267 non-responders for *FCGR3A* V158F polymorphism and 156 responders and 89 non-responders for *FCGR2A R131H* polymorphism, were included. The meta-analysis revealed a significant association between the *FCGR3A* V allele and responsiveness to rituximab (odds ratio [OR] = 1.600, 95% confidence interval [CI] = 1.268–2.018, $P < 0.001$). Furthermore, associations were found using the dominant and homozygous contrast models. Subgroup analysis showed an association between the *FCGR3A* V allele and responsiveness to rituximab in European, RA, ITP, small (<50) and large (≥50) groups, and short- (≤6 months) and long-term follow-up periods (≥6 months). These associations were also found in recessive, dominant or homozygous contrast models. Meta-analysis revealed no association between the *FCGR2A* R allele and responsiveness to rituximab (OR = 1.243, 95% CI = 0.825–1.873, $P = 0.229$).
CONCLUSIONS: We demonstrated that the *FCGR3A* F158V polymorphism is associated with better responsiveness to rituximab therapy in patients with autoimmune diseases, indicating that individuals carrying the *FCGR3A* V allele will likely respond better to rituximab. However, *FCGR2A* R131H polymorphism was not associated with better response to rituximab.

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INTRODUCTION

A wide range of autoimmune diseases impact about 5% of people worldwide. Their absence of self-tolerance results in immune-mediated tissue damage and is one of their defining traits [1]. Autoimmune disorders have a variety of biochemical and clinical signs, but they all share the same pathological mechanisms, such as abnormal B-cell regulation. The necessity of biological treatments that suppress B cells in individuals with intractable autoimmune disease has been shown by the crucial role of B cells in illness. Using antibody-dependent cell-mediated cytotoxicity, the hybrid monoclonal antibody, rituximab, mainly attacks B cells. (ADCC) (4). The Fc gamma receptors (FCGR) on natural killer cells, particularly FcRIIIa, initiate ADCC [2]. Although rituximab is one of the most successful treatments for autoimmune illness, it does not work for everyone [3–5]. The causes of this lack of response are unknown. It would be possible to foresee a patient's response to rituximab, which would remove needless medication, lower expenses for treatment, and significantly improve patient care.

In the identification of immunological complexes, FCGRs play a vital function [6]. Their biochemical reaction has been associated with mutations in the genes encoding FCGRs, which change their preference for the Fc region and include FCGR2A and FCGR3A. A single nucleotide substitution at position 596 results in either valine (V158) or phenylalanine (F158) at position 158, which is the source of the FCGR3A V158F (rs396991) variant. (F158V) [7]. High IgG binding of the FCGR3A V158 variant is associated with a more potent immune response, which is mediated by complement-dependent cytotoxicity, cellular cytotoxicity, and apoptosis [7]. A similar change is made by the FCGR2A R131H (rs1801274) mutation, which changes the amino acid from arginine (R) to histidine at position 131 (H) (R131H). IgG and H131R interact differentially; H131 has a stronger attraction for IgG compared to R131 [8]. Therefore, genomic differences unique to biological agents that regulate the action of FCGR3A and FCGR2A may affect the biological effectiveness [8]. Numerous studies have looked into the relationship between FCGR3A V158F and FCGR2A R131H SNPs and the reactivity to rituximab therapy, because of their significance in the pathogenesis of autoimmune disorders [9–19]. However, the results of these inquiries remain unclear. These variations could be caused by clinical heterogeneity, inadequate statistical strength, or insufficient group size. As a result, we carried out a meta-analysis to get around the constraints of each research and clarify the differences [20–22]. In individuals with autoimmune disorders, we looked at the associations between

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rituximab reactivity and the FCGR2A R131H and FCGR3A V158F polymorphisms.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We considered all studies that examined the association between *FCGR3A* F158V and *FCGR2A* R131H polymorphisms and responsiveness to biologics in patients with autoimmune diseases. A literature search was conducted using the Medline, Embase, and Cochrane Library databases. References within individual publications were reviewed to identify additional studies that were not indexed in the electronic databases. The following keywords and terms were searched: "Fc gamma receptor," "*FCGR3A*," "*FCGR2A*," "polymorphism," "rituximab," and "autoimmune disease." No language restrictions were applied. A study was included in the analysis if it: (1) was published before November 2022, (2) presented original data (ensuring independence among the studies), and (3) provided sufficient data to calculate odds ratios (ORs). The exclusion criteria were as follows: (1) inclusion of duplicate data, (2) containment of unextractable data, and (3) study of other polymorphisms. Two independent reviewers searched the literature and extracted the data from the original studies. Discrepancies between the reviewers were resolved by consensus. The following information was extracted from each article: author identification, year of publication, country of study, biologic names, follow-up duration, response criteria used, and genotypes or alleles of *FCGR3A* F158V and *FCGR2A* R131H polymorphisms in responders and non-responders.

Evaluation of statistical associations

We estimated the overall contrast between the V and F (allelic effect), VV vs. VF + FF (recessive), VV + VF vs. FF (dominant), and VV + FF (homozygote contrast) models of *FCGR3A* F158V polymorphism in response to biologics. Similarly, we estimated the overall contrast between the H and R, HH vs. HR + RR, HH + HR vs. RR, and HH vs. RR models of *FCGR2A* R131H polymorphism in response to rituximab. Point estimates of risk, ORs, and 95% confidence intervals (CI) were calculated for each included study. Cochran's Q-test was used to assess within- and between-study variations, heterogeneity, and the null hypothesis that all studies evaluated the same effect. The heterogeneity effect was quantified using the I^2 statistic, which ranges from 0% to 100% and provides an estimate of the total point estimate variability attributable to heterogeneity rather than chance [23]. I^2 values of 25%, 50%, and 75% were designated as low, moderate, and high heterogeneity, respectively. The fixed-effects model assumes that a genetic factor has a similar effect on responders across all included studies and that the observed variation among the studies is caused by chance alone [24]. Conversely, the random-effects model assumes that different studies have substantial diversity and assesses both within-study sampling errors and between-study variances [25]. The two models show similar results when the study groups are homogeneous. However, when the groups are heterogeneous, the random-effects model usually provides wider CIs than the fixed-effects model. The random-effects model and is best used when significant between-study heterogeneity is present [25]. Statistical analyses were performed using the Comprehensive Meta-Analysis Program (Biostat, Englewood, NJ, USA).

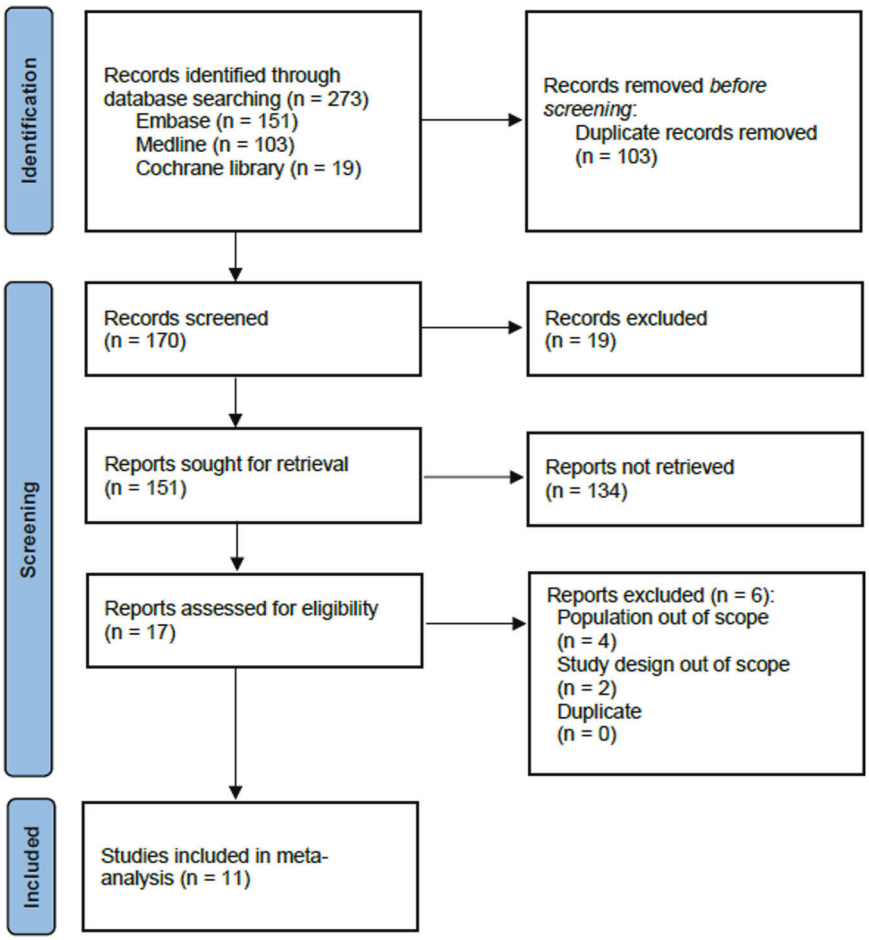

Fig. 1 PRISMA diagram for the literature identification and isolation of the appropriate studies.

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

Study	Country	Ethnicity	Disease	Sample size (N)		No. of subjects	Response criteria	Studied polymorphism(s)	Follow-up period	Study quality
				R	NR					
Morales, 2019 [9]	Spain	European	RA	8	30	38	EULAR	FCGR3A F158V/ FCGR2A R131H	18 months	6
Ellithy, 2018 [10]	Egypt	Arab	ITP	37	13	50	Remission	FCGR2A R131H	3 months	5
Pal, 2017 [11]	Hungary	European	RA	36	16	52	EULAR	FCGR3A F158V	6 months	5
Cartin-Ceba, 2016 [12]	USA	Unknown	AAV	70	26	96	Remission	FCGR3A F158V/ FCGR2A R131H	6 months	6
Stork, 2014 [13]	Netherlands	European	IgM-polyneuropathy	12	15	27	Sensory score	FCGR3A F158V	12 months	5
Quartuccio, 2014 [14]	Italy	European	RA	146	66	212	EULAR	FCGR3A F158V	6 months	7
Zhu, 2013 [15]	China	Asian	ITP	29	9	38	Remission	FCGR3A F158V/ FCGR2A R131H	12 months	5
Kastbom, 2012 [16]	Sweden	European	RA	130	47	177	EULAR	FCGR3A F158V	3–6 months	7
Ruyssen-Witrand, 2012 [17]	France	European	RA	90	21	111	EULAR	FCGR3A F158V	6 months	7
Robledo, 2012 [18]	Spain	European	Autoimmune diseases	116	16	132	ACR/EULAR	FCGR3A F158V	6 months	7
Cooper, 2012 [19]	UK	European	ITP	25	23	48	Remission	FCGR3A F158V/ FCGR2A R131H	52 weeks	5

RA rheumatoid arthritis, *ITP* immune thrombocytopenic purpura, *AAV* antineutrophil cytoplasmic antibodies-associated vasculitis, *IgM* immunoglobulin M, *R* responder, *NR* non-responder, *UK* United Kingdom, *USA* United States of America, *ACR* American College of Rheumatology, *EULAR* European League Against Rheumatism.

Exploring study quality, heterogeneity, and publication bias

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of each study was given a score [26]. The highest score is 9, and a score in the range of 5–9 is considered to be of high methodological quality. Although funnel plots are often used to detect publication bias, they require diverse study types with varying sample sizes. Furthermore, the interpretation of the plots are subjective. Therefore, we evaluated publication bias using Egger's linear regression test [27], which uses a natural logarithm scale of ORs to measure funnel plot asymmetry.

RESULTS

Studies included in the meta-analysis

Electronic and manual searches identified 273 eligible studies, of which 17 were selected for full-text review based on the title and abstract details. Six of these 17 studies were excluded because they did not include patients with autoimmune diseases, had no data, or reported other polymorphisms. Finally, 11 studies, consisting of 661 responders and 267 non-responders for the *FCGR3A* V158F polymorphism and 156 responders and 89 non-responders for *FCGR2A R131H* polymorphism, that met the inclusion criteria were included [9–19, 28] (Fig. 1). Sixteen separate comparison groups were considered in the meta-analysis. The sample sizes in the studies ranged from 29 to 302. Eleven studies considered *FCGR3A* F158V polymorphism and five studies investigated the *FCGR2A* polymorphism. The follow-up period ranged from 3 to 18 months. The quality assessment scores of the included studies ranged from 5 to 7, indicating high quality (Table 1). There was no excluded study based on a low NOS score. The characteristics of these studies are summarized in Table 1.

Association between *FCGR3A* V158F polymorphism and responsiveness to rituximab

The meta-analysis revealed a significant association between the *FCGR3A* V allele and responsiveness to rituximab (OR = 1.600, 95% CI = 1.268–2.018, $P < 0.001$) (Table 2, Fig. 2). Furthermore, associations were found using the dominant and homozygous contrast models (Table 2). Subgroup analysis showed an association between the *FCGR3A* V allele and responsiveness to rituximab in European, RA, ITP, small (<50) and large (≥50) groups, and short- (≤6 months) and long-term (>6 months) follow-up periods (Table 2, Supplementary Fig.). These associations were also found in recessive, dominant or homozygous contrast models (Table 2).

Association between the *FCGR2A* R131H polymorphism and responsiveness to rituximab

The meta-analysis revealed no association between the *FCGR2A* R allele and responsiveness to rituximab in any study participant (OR = 1.243, 95% CI = 0.825–1.873, $P = 0.229$) (Table 3, Fig. 3). Furthermore, no associations were found between the recessive, dominant, and homozygous contrast models (Table 3). Subgroup analysis showed no association between the *FCGR2A* R allele and responsiveness to rituximab in European, RA, ITP, AAV, small (<50) and large (≥50) groups, and short- (≤6 months) and long-term (≥6 months) follow-up periods (Table 3, Supplementary Fig.).

Heterogeneity and publication bias

Between-study heterogeneity was found in the subgroup meta-analysis of *FCGR3A* V158F and *FCGR2A R131H* polymorphisms (Table 2); however, there was no such heterogeneity in the allelic meta-analysis (Tables 2 and 3). Funnel plots showed symmetry, while Egger's regression analysis showed no evidence of publication bias for the *FCGR* polymorphisms addressed (Egger's regression test *P*-values > 0.1), indicating no publication bias in this meta-analysis (Fig. 4).

Table 2. Meta-analysis of *FCGR3A* F158V polymorphisms with responsiveness to rituximab in patients with autoimmune disease.

Gene, Polymorphism	Group	No. of studies	Total sample size		Test of association			Test of heterogeneity		
			R	*NR*	*OR*	95% CI	*P*	Model	*P*	I^2 (%)
FCGR3A F158V polymorphism V vs. F	Overall	10	661	267	1.600	1.268–2.018	< 0.001	F	0.142	33.1
	European	9	632	258	1.676	1.204–2.333	0.002	R	0.097	40.5
	RA	5	410	180	1.431	1.081–1.894	0.012	F	0.182	35.8
	ITP	2	54	32	2.350	1.199–4.607	0.013	F	0.507	0
	Others	3	197	55	2.018	0.925–4.802	0.076	R	0.100	56.4
	Number <50	4	74	77	2.091	1.249–3.500	0.005	F	0.330	12.5
	Number ≥50	6	587	190	1.494	1.152–1.938	0.002	F	0.120	42.7
	Follow-up ≤6 M	6	587	190	1.494	1.152–1.938	0.002	F	0.120	42.7
	Follow-up >6 M	3	45	68	2.198	1.236–3.906	0.007	F	0.193	39.1
VV + VF vs. FF (Dominant)	Overall	10	661	267	1.828	1.324–2.523	< 0.001	F	0.577	0
	European	9	632	258	1.843	1.325–2.563	< 0.001	F	0.481	0
	RA	5	410	180	1.746	1.184–2.577	0.005	F	0.450	0
	ITP	2	54	32	2.225	0.770–6.434	0.140	F	0.497	0
	Others	3	197	55	1.940	0.978–3.847	0.058	F	0.200	37.8
	Number <50	4	74	77	2.217	0.980–5.012	0.056	F	0.841	0
	Number ≥50	6	587	190	1.764	1.242–2.505	0.002	F	0.262	22.9
	Follow-up ≤6 M	6	587	190	1.764	1.242–2.505	0.002	F	0.262	22.9
	Follow-up >6 M	3	45	68	2.581	0.977–6.813	0.056	F	0.773	0
VV vs. VF + FF (Recessive)	Overall	10	661	267	1.882	0.875–4.050	0.106	R	0.021	53.8
	European	9	632	258	1.846	0.806–4.228	0.147	R	0.013	58.6
	RA	5	410	180	1.174	0.351–3.926	0.795	R	0.015	67.5
	ITP	2	54	32	4.902	1.292–18.59	0.019	F	0.477	0
	Others	3	197	55	2.257	0.842–6.048	0.106	F	0.285	20.3
	Number <50	4	74	77	3.939	1.418–10.94	0.009	F	0.338	10.9
	Number ≥50	6	587	190	1.429	0.562–3.634	0.454	R	0.028	60.2
	Follow-up ≤6 M	6	587	190	1.429	0.562–3.634	0.454	R	0.028	60.2
	Follow-up >6 M	3	45	68	4.415	1.402–13.90	0.011	F	0.203	37.2
VV vs. FF	Overall	10	661	267	2.383	1.140–4.983	0.021	R	0.080	41.6
	European	9	632	258	2.392	1.070–5.347	0.034	R	0.584	0
	RA	5	410	180	1.640	0.549–4.905	0.376	R	0.066	54.5
	ITP	2	54	32	6.200	1.338–28.73	0.020	F	0.353	0
	Others	3	197	55	2.511	0.876–7.195	0.087	F	0.227	32.6
	Number <50	4	74	77	4.856	1.490–15.83	0.009	F	0.353	8.07
	Number ≥50	6	587	190	1.864	0.785–4.424	0.158	R	0.086	48.2
	Follow-up ≤6 M	6	587	190	1.864	0.785–4.424	0.158	R	0.086	48.2
	Follow-up >6 M	3	45	68	5.948	1.512–23.40	0.011	F	0.231	31.8

FCGR3A Fc gamma receptor 3 A, *RA* rheumatoid arthritis, *ITP* immune thrombocytopenic purpura, *F* fixed effects model, *R* random effects model, *R* responder, *NR* non-responder, *OR* odds ratio, *CI* confidence interval, *P* *P*-value, I^2 between-study variability attributable to heterogeneity, *M* months.

DISCUSSION

Our meta-analysis revealed that patients with the FCGR3A 158 V variation reacted to rituximab more favorably than those with the FCGR3A 158 F variety. However, the rituximab reaction was not correlated with the FCGR2A R131H mutation. To the best of our knowledge, this is the first meta-analysis to compile the data on the relationship between the FCGR3A V158F and FCGR2A R131H polymorphisms and rituximab response in individuals with autoimmune diseases. It also establishes the utility of the FCGR3A F158V polymorphism in predicting rituximab response. Our meta-analysis shows a paucity of reliable pharmacogenetic data on the FCGR2A R131H variation in autoimmune disease patients, though. We concentrated on the FCGR2A and FCGR3A polymorphisms due to their role in ADCC and the abundance of papers looking into their relationship with rituximab response in autoimmune disorders.

Our study's findings, which further support the idea that genetic variants in FCGR3A, which have been linked to decreased FCGR affinity, are linked to rituximab reactivity, may be explained by FCGR binding and complement interactions. In comparison to the 158 F isoform, the 158 V isoform has a greater propensity for binding to IgG1 and IgG3 [29]. The FCGR3A 158 V variations may enhance the acquisition of the IgG-opsonized pathogen or IgG immune complex, which enters directly into the antigen-

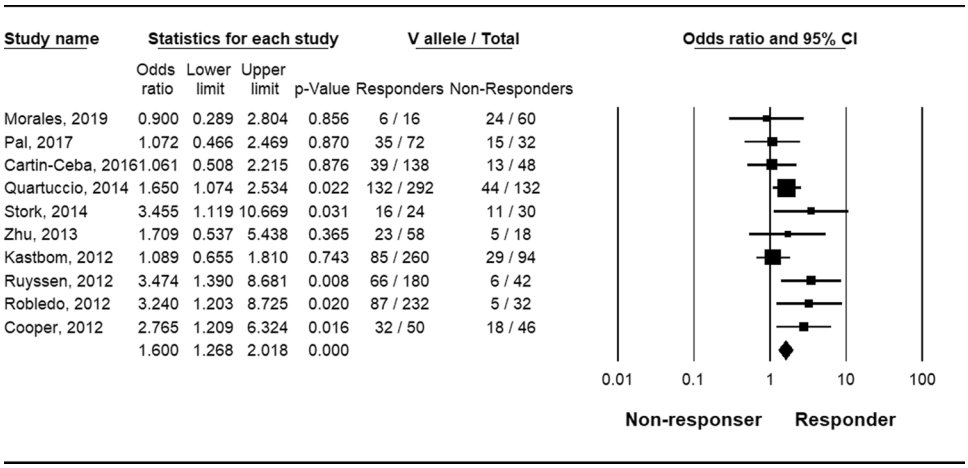

Fig. 2 ORs and 95% CIs of the individual studies and pooled data for the associations between the *FCGR3A* V allele and responsiveness to rituximab in patients with autoimmune diseases. OR odds ratio, CI confidence interval, FCGR Fc gamma receptor.

Table 3. Meta-analysis of *FCGR2A* R131H polymorphisms with responsiveness to rituximab in patients with autoimmune disease.

Gene, Polymorphism	Group	No. of studies	Total sample size		Test of association			Test of heterogeneity		
			R	*NR*	*OR*	95% CI	*P*	Model	*P*	I^2 (%)
FCGR2A R131H polymorphism R vs. H	Overall	5	156	89	1.243	0.825–1.873	0.229	F	0.563	0
	European	3	90	67	1.015	0.615–1.677	0.954	F	0.584	0
	RA	1	8	30	0.641	0.207–1.989	0.442	NA	NA	NA
	ITP	3	119	50	1.513	0.824–2.780	0.182	F	0.535	0
	AAV	1	70	26	1.235	0.653–2.338	0.516	NA	NA	NA
	Number <50	3	136	48	0.997	0.513–1.939	0.994	F	0.424	0
	Number ≥50	2	20	41	1.423	0.845–2.397	0.185	F	0.451	0
	Follow-up ≤6 M	2	107	39	1.423	0.845–2.397	0.185	F	0.451	0
	Follow-up >6 M	2	20	41	0.738	0.328–1.663	0.464	F	0.727	0

FCGR2A Fc gamma receptor 2 A, *RA* rheumatoid arthritis, *ITP* immune thrombocytopenic purpura, *AAV* antineutrophil cytoplasmic antibodies-associated vasculitis, *F* fixed effects model, *R* responder, *NR* non-responder, *OR* odds ratio, CI confidence interval, *P* *P*-value, I^2 between-study variability attributable to heterogeneity, *NA* not available, *M* months.

processing pathway [30], leading to a more effective display of the arthritogenic peptides. In comparison, the FCGR3A 158 F gene binds to fewer immune complexes and may even suppress inflammation reactions [7, 31]. Individuals with the high affinity V gene are more effectively reduced from peripheral B cells by rituximab. Rituximab insensitivity may be predicted by low FCGR3A mRNA.

The genome q21-q23 risk areas for inflammatory diseases have been found, and the potential genes there are the FCGR2A genes [32, 33]. The susceptibility to biologic treatment may be impacted by alleles linked to autoimmune disease risk [34]. Furthermore, the FCGR2A R131H mutation impacts either H or R at location 131 within the receptor's second Ig-like region, making it physiologically important [34]. As a consequence, the curative reaction is reduced when the high-affinity H gene enhances the removal of biologics from the bloodstream. The FCGR2A R131H mutation was not linked to a heightened rituximab reaction, according to our meta-analysis. However, because of the small sample size, we could not rule out type II errors. The FCGR3A V158F statistics for rituximab are not unique to autoimmune illness because it is also used to treat cancer [30].

The statistical discrepancy between the FCGR3A V158F variant's dominant and recessive modes of action is a hot subject in the area of genetic epidemiology. This difference has been seen in numerous studies, with some citing a dominant impact and others a genetic effect. The possible molecular processes that might be causing this disparity have been the subject of a number of theories, though they are still not completely known. Additional hereditary or external variables may alter how the FCGR3A V158F variation affects illness risk. Another reason for the difference between the dominant and recessive theories is that the FCGR3A V158F variation may have complicated and context-dependent effects on the Fc receptor's functionality. The immunological processes of immune complex uptake and antibody-dependent cellular killing are both mediated by the Fc receptor. Depending on the existence of other immunological components, the specific virus or antigen met, or both, the FCGR3A V158F variant's impact on these activities may vary.

There are a few limitations on this research. First, because of the small sample size, a publishing bias may have had an impact on the findings of our meta-analysis, especially those of the subgroup analysis. Second, the meta-analysis might have been impacted by variability and influencing variables. The duration of the breaks between exams differed. (from 3 to 18 months). Furthermore, we were unable to take into consideration factors that may have affected the reaction to biologics in this research, including

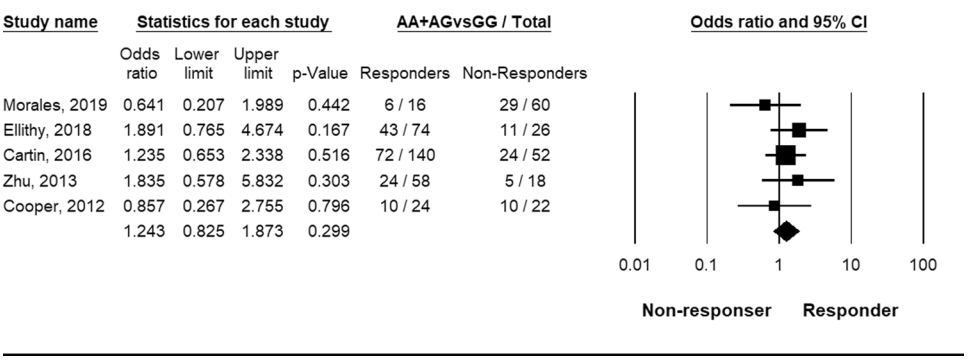

Fig. 3 ORs and 95% CIs of the individual studies and pooled data for the associations between the *FCGR2A* the R allele and responsiveness to biologics in patients with autoimmune diseases. OR odds ratio, CI confidence interval, FCGR Fc gamma receptor.

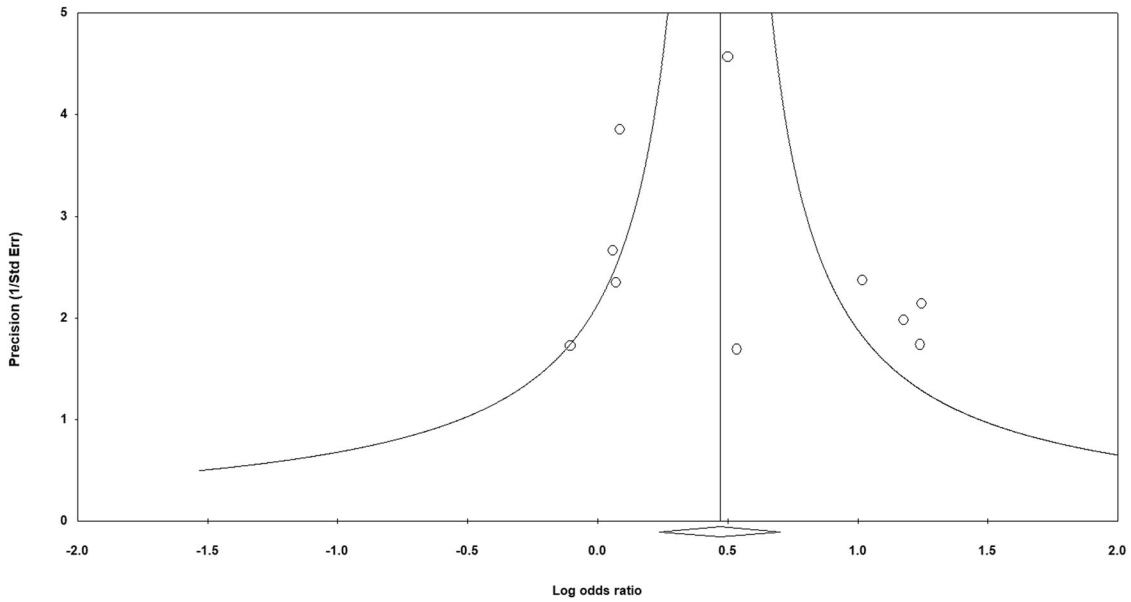

Fig. 4 Funnel diagram of studies evaluating the relationship between the associations between the *FCGR3A* V allele and responsiveness to rituximab in patients with autoimmune diseases (Egger's regression test, $p = 0.307$).

gender, rheumatoid factor status, illness length, and initial DAS28. The meaning of the response phenotype varied between research, and illness seriousness and response phenotype intensity also added to the variety of results. Thirdly, the findings cannot be applied to other groups because the bulk of the data used in this meta-analysis originated from European countries. The proportional impacts of FCGR3A and FCGR2A SNPs on disease risk and treatment reaction may change depending on the gene rates of these polymorphisms, which differ between racial groups.

The results of the current research showed that the FCGR3A V158F variant is related to rituximab response, which implies that people who carry the FCGR3A V gene may respond to rituximab more favorably. In individuals with autoimmune diseases, the FCGR2A R131H mutation was not linked to an improved reaction to rituximab therapy. As a result, identifying the genetic variation in individuals with autoimmune disorders may make it easier to tailor treatments based on the likelihood that they will respond to rituximab. In order to determine the prognostic value of these SNPs in individuals with autoimmune disorders, additional research is necessary.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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