FCGR2A, *FCGR3A*, *FCGR3B* polymorphisms and susceptibility to rheumatoid arthritis: a meta-analysis

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Abstract

Objective

The aim of this study is to explore whether Fc gamma receptor (FCGR) polymorphisms are associated with the susceptibility to rheumatoid arthritis (RA).

Methods

We conducted a meta-analysis on the association between FCGR2A H131R (rs1801274), FCGR3A F158V (rs396991), and FCGR3B NA1/NA2 polymorphisms and RA susceptibility

Results

A total of seventeen studies reported in fourteen articles (4,418 patients with RA and 3,560 controls) were considered in our meta-analysis. In all of the study subjects, meta-analysis indicated an association between RA and FCGR2A R allele (OR=0.877, 95% CI=0.792–0.971, p=0.011). Stratification by ethnicity indicated an association between FCGR2A R allele and RA in Europeans (OR=0.816, 95% CI=0.687–0.968, p=0.020), but not in East Asians (OR=0.900, 95% CI=0.778–1.040, p=0.154). Meta-analysis revealed an association between RA and FCGR3A VV vs. FF genotype in all the study subjects (OR=1.210, 95% CI=1.067–1.479, p=0.006). Stratification by ethnicity indicated an association between FCGR3A VV genotype and RA compared to FF genotype in Europeans (OR=1.350, 95% CI=1.107–1.646, p=0.003), but not in East Asians and South Asians. No association was observed between RA and FCGR3B polymorphisms on performing the meta-analysis.

Conclusion

Although no relationship was found between the FCGR3B polymorphism and RA susceptibility, FCGR2A and FCGR3A polymorphisms were found to be associated with RA in Europeans, but not in Asians.

Key words

FCG receptor, polymorphism, rheumatoid arthritis, meta-analysis

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Received on October 24, 2014; accepted in revised form on January 23, 2015.

Funding: this study was supported in part by a grant of the Korea Healthcare technology R&D Project, Ministry for Health and Welfare, Republic of Korea (HI13C2124).

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly targets synovial joints and affects up to 1% of adults worldwide. Although the aetiology of RA is not fully understood, it is clear that RA has genetic components (1).

B cells, macrophages, and dendritic cells in the RA synovium express high levels of Fc gamma receptors (*FCG*Rs) on their surfaces (2). These receptors play a key role in the recognition of immune complexes. Elevated levels of *FCGR2* and *FCGR3* in monocytes and macrophages have been associated with proinflammatory cytokine production of the arthritic joints (3). Thus, activation of *FCG*Rs is involved in the pathogenesis of RA.

FCGR binding may initiate biological responses, such as phagocytosis and the processing of ICs (2). FCGR genes, mapped to 1q21-23, have functional polymorphisms (4). The low affinity receptors FCGR2A, 3A, and 3B are called activating receptors, whereas FCGR2B is an inhibitory receptor (2). Moreover, FCGR2A, 3A, and 3B, and FCGR2B are frequently coexpressed in the same cells, and thus provide a means for regulating signaling thresholds (5). Single nucleotide polymorphisms (SNPs) of the three FCGR genes, *i.e. FCGR2A* H131R (rs1801274), *FCGR3A* F158V (rs396991), and *FCGR3B* NA1/NA2, exhibit biological functions that differ among *FCGR* genotypes (6). Based on their biological functions, FCGR genes are suspected to facilitate the susceptibility to inflammatory diseases including RA (6-8). Individual studies based on small sample sizes have insufficient statistical power to detect positive associations and are not capable of demonstrating the absence of an association (9-12). Furthermore, the low statistical powers of individual studies could explain the contradiction in the published results (13, 14). On the other hand, meta-analysis integrates previous research, and increases the statistical power and resolution by pooling the results of independent analysis (15-17). In the present study, we explored whether *FCGR2A* H131R, *FCGR3A* F158V, and *FCGR3B* NA1/NA2 polymorphisms are associated with the susceptibilities to RA via a meta-analysis approach.

Methods

Identification of eligible studies and data extraction

We performed a search for studies that have examined the association between *FCG*R polymorphisms and RA. MEDLINE and EMBASE citations were used to identify articles that reported the analysis of *FCG*R polymorphisms in patients with RA. In addition, combinations of keywords, such as, 'Fc gamma receptor', '*FCG*R', 'polymorphism', 'rheumatoid arthritis', and 'RA' were entered as both Medical Subject Heading (MeSH) and text words. References in these identified studies were also investigated to identify additional studies not indexed by MEDLINE and EMBASE. Genetic association studies that determined the distribution of *FCG*R genotypes in RA cases and controls were included in the study. The inclusion criteria for the previous studies were: (1) published before January 2014; (2) the inclusion of original data; and, (3) the provision of adequate data to calculate odds ratios (OR). When a study reported results on different populations, we treated the results obtained separately during the meta-analysis. We excluded the following: (1) studies that contained overlapping data; (2) studies in which the numbers of null and wild genotypes or alleles could not be ascertained; and (3) studies that included data on family members because their analysis was based on linkage considerations. We conducted a systematic review and meta-analysis in accordance with the guidelines provided by the Cochrane review (9). Data regarding the methods and results of meta-analysis were extracted from the original studies by two independent reviewers. Discrepancy between the reviewers was resolved by consensus or a third reviewer. The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, number of cases and controls for *FCG*R polymorphisms. Allele frequencies were calculated from genotype distributions. Data extraction was performed by two in-

dependent reviewers, and discrepancy between the reviewers was resolved by consensus.

Evaluation of statistical associations

We performed meta-analysis using allelic contrast, homozygote contrast, recessive, and dominant models. Point estimates of risks, ORs, and 95% confidence intervals (CIs) were determined for each study. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities (18). The heterogeneity test was used to assess the probability of the null hypothesis that all studies were evaluating the same effect. When the significant Q-statistic ($p<0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis, but when heterogeneity was not indicated across studies, the fixed effects model was used. Fixed effects assume that genetic factors have similar effects on RA susceptibility across all studies and that observed variations between studies are caused by chance alone (19). The random effects model assumes that different studies show substantial diversity, and assesses both within-study sampling errors and between-study variances (20). The random effects model is used when significant between-study heterogeneity is observed. We quantified the effect of heterogeneity using a recently developed measure: $I^2 = 100\% \times (Q\text{-}df)/Q$ (21). I^2 ranges between 0% and 100%, and represents the proportion of inter-study variability attributable to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high estimates, respectively. Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

Evaluation of quality control and publication bias

A chi-squared test was used to determine whether observed genotype frequencies conformed to HWE (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). Funnel plots are used to detect publication bias, but they require a range of studies of varying sizes and subjective judgments. We evaluated publication bias using Egger's linear regression test (22), which measures funnel plot asymmetry on a natural logarithmic scale of ORs. When asymmetry was indicated, we used the 'trim and fill' method to adjust the summary estimate for observed bias (23).

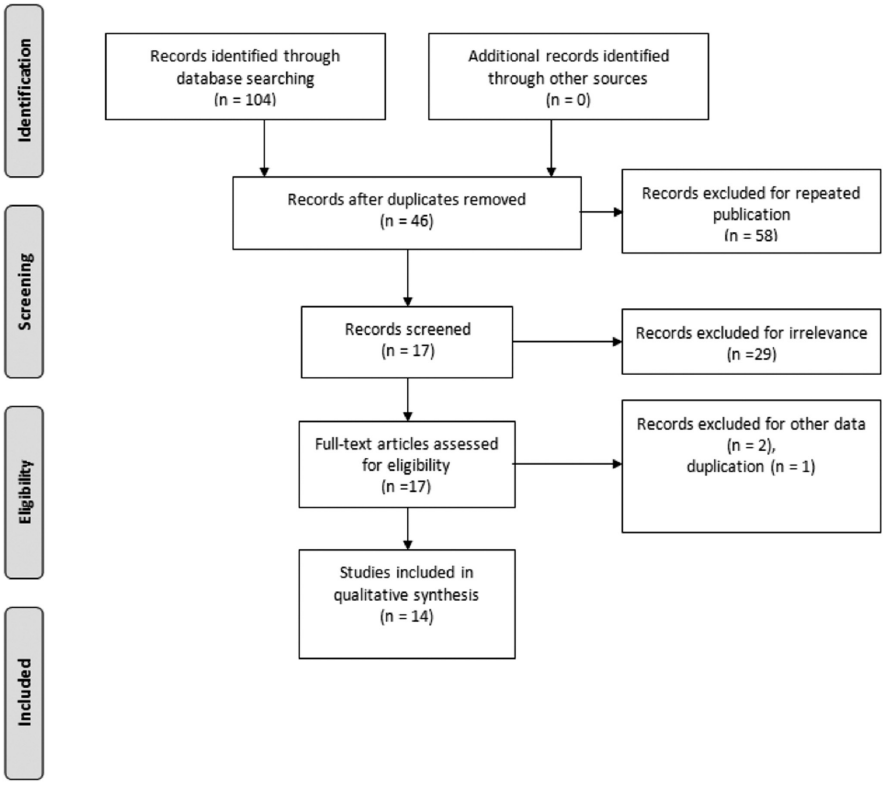

Fig. 1. Study flow chart.

Results

Studies included in the meta-analysis

One hundred and four studies were identified after electronic and manual searches. Of these, 17 were selected for a full-text review based on the title and abstract (24-40). Three studies were excluded because they were on other *FCGR* polymorphisms (38, 39), and they contained duplicate data (40). A total of fourteen relevant studies met the inclusion criteria (24-37) (Fig. 1). Three of the eligible studies contained data on two different RA groups (24, 29, 35), and these were treated independently. Therefore, a total of 17 separate comparisons were considered in our meta-analysis consisting of 4,418 patients with RA and 3,560 controls, involving nine Europeans, five East Asians, two South Asians, and one Tunisian (Table I). Ethnicity-specific meta-analysis was conducted on these populations. All the studies, except for one study, which showed only allele data of the polymorphisms (24), provided genotype data of the polymorphisms. Eleven studies examined *FCGR2A* polymorphisms, 13 *FCGR3A* polymorphisms, and 7 *FCGR3B* polymorphisms. Meta-analysis was performed on the *FCGR2A*, *FCGR3A*, and *FCGR3B* polymorphisms. Selected characteristics of the relationships found between *FCGR* polymorphisms and RA are summarised in Table I.

Meta-analysis of FCGR2A H131R polymorphism and RA susceptibility

A summary of meta-analysis findings on the association between *FCGR2A* H131R polymorphism and RA is provided in Table II. In all of the study subjects, meta-analysis indicated an association between RA and *FCGR2A* R allele (OR=0.877, 95% CI=0.792–0.971, p=0.011) (Table II). Stratification by ethnicity indicated an association between *FCGR2A* R allele and RA in Europeans (OR=0.816, 95% CI=0.687–0.968, p=0.020), but not in East Asians

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

Author (Ref)	Country	Ethnicity	Subjects		Polymorphisms studied	Association findings
			RA	Control		
Meziani-1, 2012 (24)	Japan	East Asian	238	184	FCGR2A	NS
Meziani-2, 2012 (24)	Germany/France	European	182	182	FCGR2A	FCGR2A (p=0.011)
Sfar, 2009 (25)	Tunisia	Tunisian	133	100	FCGR2A, 3A, 3B	NS
Thabet, 2009 (26)	Netherlands	European	945	388	FCGR3A	NS
Kobayashi, 2007 (27)	Japan	East Asian	86	100	FCGR2A, 3A, 3B	NS
Chen, 2006 (28)	Taiwan	East Asian	212	371	FCGR2A, 3A, 3B	NS
Morgan-1, 2006 (29)	UK	European	147	129	FCGR2A, 3B	NS
Morgan-2, 2006 (29)	India/Pakistan	South Asian	123	128	FCGR2A, 3A, 3B	NS
Matsumoto, 2005 (30)	Japan	East Asian	187	158	FCGR2A, 3A	NS
Kastbom, 2005 (31)	Sweden	European	181	168	FCGR3A	FCGR3A (p=0.046)
Morgan, 2003 (32)	UK	European	828	581	FCGR3A	FCGR3A (p=0.03)
Pawlik, 2002 (33)	Poland	European	82	148	FCGR2A	NS
Kyogoku, 2002 (34)	Japan	East Asian	382	303	FCGR2A, 3A, 3B	NS
Milicic-1, 2002 (35)	UK	European	398	289	FCGR3A	NS
Milicic-2, 2002 (35)	India	South Asian	63	93	FCGR3A	FCGR3A ((p<0.02)
Brun, 2002 (36)	Norway	European	114	96	FCGR2A, 3A, 3B	NS
Nieto, 2000 (37)	Spain	European	117	142	FCGR3A	FCGR3A (p=0.023)

Ref: reference; UK: United Kingdom; NS: not significant.

(OR=0.900, 95% CI=0.778–1.040, p=0.154) (Fig. 2, Table II). However, analysis using the dominant, recessive model, or homozygote contrast showed no association of *FCGR2A* H131R polymorphism and RA (Table II).

Meta-analysis of FCGR3A F158V polymorphism and RA susceptibility

Meta-analysis of *FCGR3A* F158V polymorphism showed no association between RA and *FCGR3A* V allele in all t study subjects (OR=1.106, 95% CI=0.960–1.274, p=0.162, Table III). Stratification by ethnicity indicated no association between *FCGR3A* V allele and RA in Europeans, East Asians, and South Asians (OR=1.182, 95% CI=0.966–1.446, p=0.104; OR=0.991, 95% CI=0.857–1.146, p=0.899; OR=0.907, 95% CI=0.398–2.019, p=0.816, respectively) (Table III).Analysis using the dominant and recessive model showed the same pattern for *FCGR3A* V allele (Table III). However, meta-analysis using homozygote contrast model revealed an association between RA and *FCGR3A* VV *versus* FF genotype in all study subjects (OR=1.210, 95% CI=1.067–1.479, p=0.006) (Table III). Stratification by ethnicity indicated an association between *FCGR3A* VV genotype and RA compared to FF genotype in Europeans (OR=1.350, 95% CI=1.107–1.646, p=0.003), but not in East Asians, and South Asians (OR=1.029, 95% CI=0.733–1.443, p=0.873; OR=0.602, 95% CI=0.063–5.723, p=0.658) (Fig. 3, Table III).

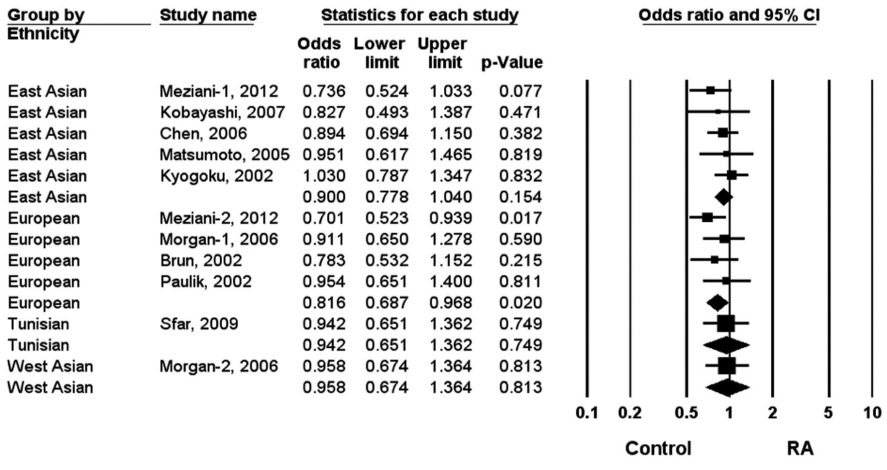

Fig. 2. ORs and 95% CIs of the individual studies and pooled data for the association between the R allele of FCGR2A R131H polymorphism and RA in each ethnic group.

Meta-analysis of FCGR3B NA1/NA2 polymorphism and RA susceptibility

Association between RA and *FCG*R3B polymorphisms was not found by meta-analysis using the allele contrast, recessive and dominant models, and homozygote contrast model in the overall, European, and East Asian populations, respectively (Fig. 4, Table IV).

Quality control, heterogeneity, and publication bias

The distribution of genotypes of *FCGR* polymorphisms in the control groups was consistent with the HWE, except for one study on *FCGR2A* polymorphism (30), 2 on *FCGR3A* polymorphism (26, 35), and 1 on *FCGR3B* polymorphism (29), which imply the potential bias in terms of control selection or genotyping errors. However, excluding the studies that did not show H-W equilibrium among controls did not affect our overall results (data not shown). Some between-study heterogeneity was found in the meta-analysis of *FCGR3A* polymorphism among all the study subjects, European, and South Asian groups. Accordingly, meta-analysis was performed using a random effects model in heterogeneous population (Table III). Publication bias causes a dispro-

Table II. Meta-analysis of the association between FCGR2A R131H polymorphism and RA.

Polymorphism	Population	No. of studies	Subject No.		Test of association			Test of heterogeneity			Publication bias
			RA	Control	OR	95% CI	*p*-value	Model	*p*-value	I^2	*p*-value
R *vs*. H allele	Overall	11	1,884	1,896	0.877	0.792-0.971	0.011	F	0.832	0	0.865
	European	4	524	552	0.816	0.687-0.968	0.020	F	0.946	0	
	East Asian	5	1,105	1,116	0.900	0.778-1.040	0.154	F	0.648	0	
RR+RH *vs*. HH (Dominant)	Overall	9	1,464	1,530	0.870	0.743-1.018	0.083	F	0.918	0	0.082
	European	3	342	370	0.804	0.568-1.133	0.210	F	0.551	0	
	East Asian	4	867	932	0.904	0.741-1.101	0.316	F	0.797	0	
RR *vs*. RH+HH (Recessive)	Overall	9	1,464	1,530	0.960	0.769-1.198	0.718	F	0.409	3.10	0.117
	European	3	342	370	0.907	0.650-1.264	0.564	F	0.865	0	
	East Asian	4	867	932	1.119	0.494-2.534	0.787	R	0.088	54.1	
RR *vs*. HH	Overall	9	1,464	1,530	0.886	0.683-1.148	0.358	F	0.532	0	0.126
	European	3	342	370	0.791	0.524-1.196	0.267	F	0.709	0	
	East Asian	4	867	932	0.945	0.598-1.493	0.808	F	0.119	48.6	

F: Fixed effect model; R: Random effect model.

portionate number of positive studies, and poses a problem for meta-analysis. Furthermore, evidence of publication bias was found for the meta-analysis of *FCGR2A* RR+RH genotype with RA in all the study subjects (Egger's regression test *p*-values = 0.082, Table II). However, the adjusted OR calculated using the trim and fill technique did not significantly affect the results.

Discussion

In our previous meta-analysis, we found that *FCG*R3A polymorphism was found to be associated with RA in Europeans but not in Asians (8). In the present study, we updated our meta-analysis by combining data from published studies to evaluate the genetic association between activated *FCG*R polymorphisms and RA susceptibility, and included six more studies with 1,853 RA additional patients and 1,260 additional controls (24-27, 30, 33).

Our findings do not support an association between *FCG*R3B polymorphisms and RA susceptibility. Association between *FCG*R3B polymorphisms and RA susceptibility was not found by the meta-analysis for any allele using homozygote, recessive, or dominant models in the overall group. The relative importance of *FCG*R3B polymorphisms in the development of RA may vary between ethnic groups. However, ethnic-specific meta-analysis did not reveal an association between *FCG*R3B polymorphisms and RA in the European or East Asian groups, respectively.

In contrast, meta-analysis of *FCG*R2A polymorphism revealed a significant association between the R allele of *FCG*R2A polymorphism and the risk of developing RA *versus* the H allele (OR=0.877, 95% CI=0.792–0.971, *p*=0.011), with no evidence of between-study heterogeneity. Stratification by ethnicity indicated a different association between *FCG*R2A polymorphism and RA in East Asian and Europeans. In subjects of European descent, an association between *FCG*R2A polymorphism and RA was observed, but in subjects of East Asian descent, this was not evident. These findings suggest that *FCG*R2A polymorphism is associated with the development of RA in Europeans, but not in East Asians. The findings of our meta-analysis suggest that the low-affinity allele of *FCG*R2A may have a protective role in the development of RA in Europeans. *FCGR2B* is widely distributed on leukocytes and platelets, and is the only inhibitory Fc receptor that has an immunoreceptor tyrosine-based inhibitory motif on the cytoplasmic tail (2). Deficiency of *FCGR2B* has been shown to be associated with severe inflammation triggered by immune complexes (41). A single nucleotide substitution in *FCGR2A* results in either a histidine (H) or arginine (R) at position 131 within the second Ig-like domain of the receptor (4). This polymorphism impacts the affinity of the receptor for IgG, with the R allele having a lower affinity (42).

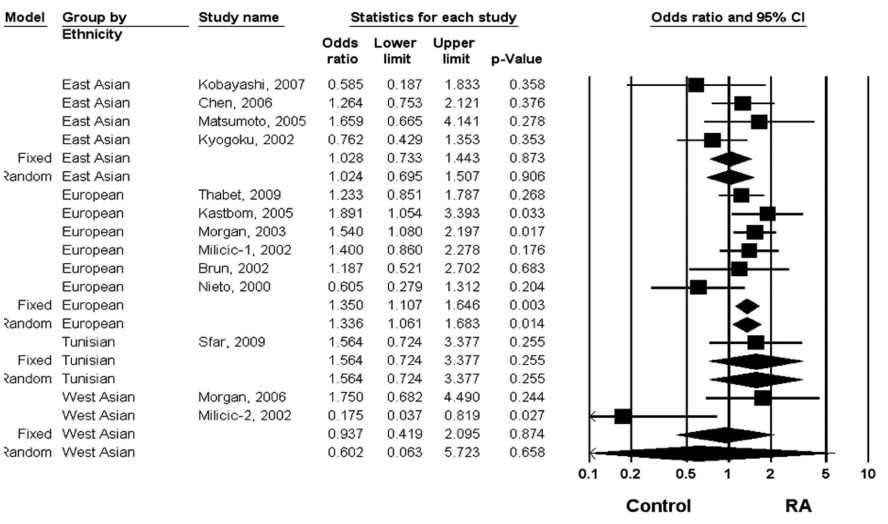

Fig. 3. ORs and 95% CIs of the individual studies and pooled data for the association between the VV *vs*. FF genotype of FCGR3A F158V polymorphism and RA in each ethnic group.

Table III. Meta-analysis of the association between FCGR3A F158V polymorphism and RA.

Polymorphism	Population	No. of studies	Subject no.		Test of association			Test of heterogeneity			Publication bias
			RA	Control	OR	95% CI	*p*-value	Model	*p*-value	I^2	*p*-value
V *vs*. F allele	Overall	13	3,640	2,965	1.106	0.960-1.274	0.162	R	0.000	67.5	0.315
	European	6	2584	1811	1.182	0.966-1.446	0.104	R	0.002	74.4	
	East Asian	4	867	932	0.991	0.857-1.146	0.899	F	0.236	29.3	
	South Asian	2	189	222	0.907	0.398-2.019	0.816	R	0.009	85.2	
VV+VF *vs*. FF (Dominant)	Overall	13	3,640	2,965	1.179	0.905-1.536	0.222	R	0.000	83.8	0.720
	European	6	2584	1811	1.292	0.811-2.058	0.282	R	0.000	91.3	
	East Asian	4	867	932	0.964	0.798-1.165	0.704	F	0.322	14.0	
	South Asian	2	189	222	1.049	0.464-2.372	0.909	R	0.045	75.1	
VV *vs*. VF+FF (Recessive)	Overall	13	3,640	2,965	1.071	0.835-1.373	0.589	R	0.011	53.5	0.491
	European	6	2584	1811	1.117	0.773-1.615	0.556	R	0.005	70.3	
	East Asian	4	867	932	1.068	0.773-1.475	0.691	F	0.354	7.88	
	South Asian	2	189	222	0.561	0.078-4.050	0.566	R	0.025	80.2	
VV *vs*. FF	Overall	13	3,640	2,965	1.210	1.067-1.479	0.006	R	0.093	36.2	0.110
	European	6	2584	1811	1.350	1.107-1.646	0.003	F	0.280	20.3	
	East Asian	4	867	932	1.029	0.733-1.443	0.873	F	0.303	17.6	
	South Asian	2	189	222	0.602	0.063-5.723	0.658	R	0.013	83.9	

F: Fixed effect model; R: Random effect model.

Neutrophils with the HH131 genotype of *FCGR2A* bind effectively to IgG2 with a three-fold higher phagocytosis rate and seven-fold higher bactericidal activity than neutrophils expressing the RR131 genotype (42).

Our meta-analysis of *FCG*R3A polymorphism indicated a significant association between the VV genotype of the *FCG*R3A polymorphism and the risk of developing RA versus the FF genotype (OR=1.210, 95% CI=1.067–1.479, *p*=0.006). Stratification by ethnicity indicated an association between *FCG*R3A polymorphism and RA in Europeans, but not in East Asians. *FCGR3A* shows a polymorphism that corresponds to a change of phenylalanine (F) to valine (V) at position 158 of Immunoglobulin-like domain 2. *FCGR3A* F158V is known to have functional significance (43). The *FCG*R3A V158 allele may enhance the capture of IgG opsonised pathogens or IgG immune complexes, and facilitate their direct entry into the antigen-processing pathway, which results in a more efficient presentation of arthritogenic peptides (44). On the other hand, the *FCG*R3A F158 allele binds fewer immune complexes and could reduce the inflammatory responses (45). However, whether the association between *FCG*R3A F/V158 polymorphism and RA susceptibility is due to a causal association or a LD with the true disease-causing polymorphism remains to be determined.

It is unclear why the association between *FCGR2A* H131R and *FCGR3A* F158V polymorphisms and RA susceptibility was found only in Europeans, but not in other ethnic groups such as East Asians and South Asians. Although the reasons for the difference remain unclear, it may be due to ethnic differences, smaller number of studies, lower statistical power, or type II error. Hence, further studies are needed to further clarify the reasons.

The present study has some limitations. First, publication bias, heterogeneity, and confounding factors may have distorted the meta-analysis. Second, this meta-analysis included data from European and Asian patients, and thus, our results are applicable to only these ethnic groups. Third, haplotype analysis may have provided more information and would have been more powerful than single polymorphism analysis. However, this analysis could not be employed due to inadequate haplotype data. Fourth, it would have been interesting to examine the association between the *FCG*R polymorphisms and disease pathogenesis and clinical features, and to stratify the data by gender or rheumatoid factor status. However, such studies could not be conducted because of the limited availability or unavailability of relevant data.

In conclusion, this meta-analysis of published data did not demonstrate a

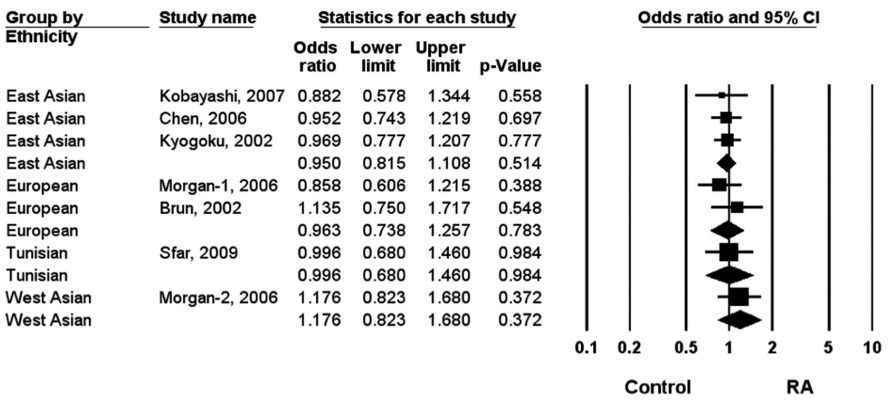

Fig. 4. ORs and 95% CIs of the individual studies and pooled data for the association between the NA allele of FCGR3B NA1/NA2 polymorphism and RA in each ethnic group.

Table IV. Meta-analysis of the association between FCGR3B NA1/NA2 polymorphism and RA.

Polymorphism	Population	No. of studies	Subject no.		Test of association			Test of heterogeneity			Publication bias
			RA	Control	OR	95% CI	*p*-value	Model	*p*-value	I^2	*p*-value
NA2 *vs*. NA1 allele	Overall	7	977	1,017	0.908	0.871-1.103	0.737	F	0.893	0	0.650
	European	2	261	216	0.963	0.738-1.257	0.783	F	0.310	2.84	
	East Asian	3	382	303	0.950	0.815-1.108	0.514	F	0.927	0	
NA2/NA2+NA2 /NA1 *vs*. NA1 /NA1(Dominant)	Overall	7	977	1,017	1.003	0.833-1.207	0.978	F	0.311	15.5	0.916
	European	2	261	216	0.674	0.374-1.213	0.188	F	0.166	47.8	
	East Asian	3	382	303	0.973	0.785-1.205	0.800	F	0.827	0	
NA2/NA2 *vs*. NA2/NA1+ NA1/NA1 (Recessive)	Overall	7	977	1,017	0.945	0.775-1.153	0.577	F	0.899	0	0.725
	European	2	261	216	1.104	0.763-1.598	0.599	F	0.580	0	
	East Asian	3	382	303	0.863	0.634-1.173	0.345	F	0.708	0	
NA2/NA2 *vs*. NA1/NA1	Overall	7	977	1,017	0.937	0.726-1.209	0.618	F	0.565	0	0.861
	European	2	261	216	0.747	0.400-1.397	0.361	F	0.175	45.5	
	East Asian	3	382	303	0.863	0.620-1.202	0.384	F	0.852	0	

F: Fixed effect model; R: Random effect model; NA: Not available.

relationship between *FCGR*3B polymorphisms and RA susceptibility in Europeans or Asians, but indicated that *FCGR2A* and *FCGR*3A polymorphisms are associated with the development of RA in Europeans. Nevertheless, the role of *FCGR* polymorphisms in the pathogenesis of RA remains ambiguous and must be determined by analysing larger studies in different ethnic groups.

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