Associations Between *FCGR3A* Polymorphisms and Susceptibility to Rheumatoid Arthritis: A Metaanalysis

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ABSTRACT. ***Objective.*** To investigate whether the Fcγ receptor (*FCG*R) polymorphism confers susceptibility to rheumatoid arthritis (RA).

Methods. We conducted metaanalyses on the associations between *FCG*R polymorphisms and RA susceptibility as determined using (1) allele contrast, (2) recessive models, (3) dominant models, and (4) contrast of homozygotes, using fixed or random effects models.

Results. A total of 10 separate comparisons were considered, which comprised 6 European and 4 Asian population samples. Metaanalysis of *FCG*R3A polymorphism revealed a significant association between the VV genotype and the risk of developing RA relative to the VF+FF genotype (OR 1.256, 95% CI 1.045–1.510, p = 0.015), with no evidence of between-study heterogeneity (p = 0.167). In subjects of European descent, a stronger association was observed between the VV genotype and RA than for the FF genotype (OR 1.374, 95% CI 1.101–1.714, p = 0.005). In Asians, no such association was found. Metaanalysis of the VV vs FF genotype revealed a significantly increased OR in Europeans (OR 1.399, 95% CI 1.107–1.769, p = 0.005), but not in Asians. No association was found between RA and the *FCG*R2A and *FCG*R3B polymorphisms in all subjects and in European and Asian populations, except for the NA22 vs NA11 of *FCG*R3B in Europeans.

Conclusion. No relation was found between the *FCG*R2A polymorphism and susceptibility to RA in Europeans or Asians. The *FCG*R3A polymorphism was found to be associated with RA in Europeans but not in Asians. The *FCG*R3B polymorphism was associated with RA susceptibility in Europeans. (First Release Oct 1 2008; J Rheumatol 2008;35:2129–35; doi:10.3899/jrheum.080186)

Key Indexing Terms:
FCγ RECEPTOR POLYMORPHISM RHEUMATOID ARTHRITIS METAANALYSIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that predominantly involves synovial joints and that affects up to 1% of adults worldwide[1]. Although the etiology of RA remains unsolved, RA has been established by twin and family studies to have a genetic component that has been estimated to contribute as much as 60% to development of RA[2,3]. Human leukocyte antigen (HLA) class II molecules have been most associated with RA, but family studies suggest that this association accounts for only one-third of genetic susceptibility, and that non-HLA genes are also involved in disease susceptibility[4].

It is well established that massive accumulations of B cells, macrophages, and dendritic cells occur in the RA synovium, and these cells express high levels of Fcγ receptors (*FCG*R) on their surfaces[5]. These receptors play an important role in the recognition of immune complexes that are abundant in RA. In human RA studies, elevated concentrations of FcγRII and FcγRIII in monocytes and macrophages have been associated with proinflammatory cytokine production and arthritis inflammation[6]. Thus, the activations of *FCG*R may be essentially required for the pathogenesis of RA.

*FCG*R genes map to 1q21-23, a linkage region for RA, and based on available information, *FCG*R genes are suspected of conferring susceptibility to RA[7]. The low-affinity receptors FcγRIIA, IIIA, and IIIB are called activating receptors, whereas FcγRIIB is an inhibitory receptor[8]. Moreover, FcγRIIA, FcγRIIIA, FcγRIIIB, and FcγRIIB are frequently coexpressed on the same cells, and thus provide a means for regulating signaling thresholds[9]. This molecular and expression diversity restricts specific biological properties to certain cell types. Activating functions include uptake and clearance of immune complexes, activation of phagocytes, antigen presentation, and antibody-dependent cellular cytotoxicity[8]. FcγRIIA is expressed on mononuclear phagocytes, neutrophils, and platelets. FcγRIIIA is expressed on natural killer cells, macrophages, T cells, a subset of monocytes, and mast cells. FcγRIIIB is selectively expressed on neutrophils and eosinophils. FcγRIIIB interacts with FcγRIIA in the phagocytosis of immune complexes and cellular activation, with signaling mediated through the

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immunoreceptor tyrosine-based activation motif (ITAM) of FcγRIIA[8,9]. FcγRIIB is the only immunoreceptor tyrosine-based inhibitory motif (ITIM)-containing receptor in the cytoplasmic tail; it abrogates cellular activation and plays a key role in the regulation of antibody production[8-10].

It has been estimated that the maximum distance between any of the low-affinity receptor genes is about 200 kb, which raises the possibility of linkage disequilibrium (LD)[10]. Further, single-nucleotide polymorphisms (SNP) of the 3 *FCG*R genes *FCG*R2A H/R131, *FCG*R3A F/V158, and *FCG*R3B NA1/NA2 exhibit biological functions that differ among *FCG*R genotypes[5]. Moreover, *FCG*R polymorphisms have been reported to be associated with RA susceptibility in some, but not all studies[11-21]. These controversial results may be due to small sample size, low statistical power, ethnicity, genotyping error, or clinical heterogeneity. To overcome the limitations of individual studies and resolve these inconsistent results, and to reduce the possibility that random errors produce false-positive or false-negative associations, we adopted a metaanalysis approach. Our aim was to determine whether *FCG*R polymorphisms confer susceptibility to RA.

MATERIALS AND METHODS

Identification of studies and data extraction. We performed a search for studies that examined the associations between *FCG*R polymorphisms and RA. Medline citation was used to identify articles in which *FCG*R polymorphisms were analyzed in patients with RA. In addition, combinations of keywords such as Fcgamma receptor, *FCG*R, Fc receptor, FCGR, IgG receptor, polymorphism, rheumatoid arthritis, and RA were entered as both Medical Subject Heading (MeSH) and text words. References in the studies identified were also investigated to identify additional studies not indexed by Medline. Genetic association studies that determined the distributions of *FCG*R genotypes in RA cases and controls were eligible for inclusion. Study inclusion criteria were as follows: (1) published before January 2008; (2) inclusion of original data; and (3) provision of enough data to calculate odds ratios. When a study reported results on different populations, we treated the results separately during the metaanalysis. We excluded the following: (1) studies that contained overlapping data; (2) studies in which numbers of null and wild genotypes or alleles could not be ascertained; and (3) studies that included family members because their analysis was based on linkage considerations.

The following information was extracted from each study: author, year of publication, ethnicity of the study population, demographics, genotype quality control, and number of cases and controls for the *FCG*R polymorphisms. Genotype quality control means that an original genotyping result is double-checked by another genotype method.

Evaluation of publication bias. Allele frequencies were calculated from genotype distributions. A chi-square test was used to determine if the observed genotype frequencies in the controls conformed to Hardy-Weinberg (H-W) expectations. Funnel plots are often used to detect publication bias. However, due to the limitations of funnel plotting, which requires a range of studies with varying sizes and subjective judgments, we evaluated publication bias using Egger's linear regression test[22], which measures funnel plot asymmetry using a natural logarithm scale of odds ratios.

Evaluations of statistical associations. We performed metaanalyses on the following: (1) allelic contrast and (2) homozygote contrast, and (3) the recessive and (4) dominant models. Point estimates of risk, odds ratios, and 95% confidence intervals were calculated for each study. We also assessed within- and between-study variations or heterogeneities using Cochran's Q-statistics, a heterogeneity test that assesses the null hypothesis that all studies evaluated the same effect. In addition, we quantified the effect of heterogeneity using I^2 values. I^2 ranges between 0% and 100% and represents the proportion of between-study variability that can be attributed to heterogeneity rather than chance[23]. I^2 values of 25%, 50%, and 75% are referred to as low, moderate, and high estimates. Fixed effects assume that genetic factors show similar effects on RA susceptibility across all investigated studies, and that observed variations between studies are caused by chance alone[24]. The random effects model assumes that different studies show substantial diversity and assess both within-study sampling errors and between-study variances[25]. If study groups show no heterogeneity, the fixed and random effects models produce similar results, and if not, the random effects model usually produces wider confidence intervals than the fixed effects model. The random effects model is used in the presence of significant between-study heterogeneity. Statistical manipulations were undertaken using the Comprehensive Meta-Analysis program (Biosta, Englewood, NJ, USA).

RESULTS

Studies included in the metaanalysis. Eleven studies concerning *FCG*R polymorphisms and RA were identified by Medline and manual searches[11-21]. Three studies were excluded due to family study data[21], data duplication[17], and data on only one *FCG*R3B polymorphism[20]. A total of 8 relevant studies met our inclusion criteria[11-16,18,19]. Two studies contained data on 2 different RA groups, and these were treated independently[15,16]. Therefore, a total of 10 separate comparisons were considered; these consisted of 6 European and 4 Asian population samples (Table 1). The Asian population was divided into a South East Asian group including Japanese and Taiwanese (Asian-1) and Indian and Pakistani populations (Asian-2).

Nine studies examined *FCG*R3A polymorphisms, 5 *FCG*R2A polymorphisms, 5 *FCG*R3B polymorphisms, and 3 *FCG*R2B polymorphisms. Because each different polymorphism was studied for *FCG*R2B polymorphisms, metaanalysis was performed on the *FCG*R3A, *FCG*R2A, and *FCG*R3B polymorphisms. Selected characteristics of the studies concerning the relationship between *FCG*R polymorphisms and RA are summarized in Table 1. Minor allele frequencies of *FCG*R polymorphisms in controls for the different populations are shown in Table 2.

Heterogeneity, publication bias, and statistical power. Some between-study heterogeneity was found during the metaanalyses, but no evidence of heterogeneity was found for VV vs VF+FF and VV vs FF analyses of *FCG*R3A and NA22 vs NA11 of *FCG*R3B polymorphisms in European studies. It was difficult to correlate the funnel plot, which is usually used to detect publication bias, as the number of studies included in the analysis was too small. Egger's regression test showed no evidence of publication bias in this metaanalysis of *FCG*R polymorphisms in overall groups (Egger's regression test p-values > 0.1). The distributions of *FCG*R genotypes in healthy control groups were consistent with the H-W equilibrium, except in the studies of Morgan, *et al*[16] and Brun, *et al*[11] on *FCG*R2A and

Table 1. Characteristics of individual studies included in the metaanalysis.

Study	Country	Ethnicity	RA/Control, n	Females with RA, %	*FCGR* Polymorphism(s)	Genotyping Method	Major Finding for Association
Morgan[16]	UK	European	147/129	82	2A, 3B	DS	NS
Kastbom[13]	Sweden	European	181/168	70.7	3A	DHLC, DS*	158VV in RA vs control (OR 1.9, p = 0.046)
Morgan[18]	UK	European	828/581	73	3A	DS	158VV in RA vs control (OR 1.53, p = 0.02)
Nieto[19]	Spain	European	117/142	86	3A	RFLP, DS*	158FF in RA vs control (OR 1.98, p = 0.01)
Milicic[15]	UK	European	398/289	NA	3A	RFLP, ASP*	NS
Brun[11]	Norway	European	114/96	71	2A, 3A, 3B	ASP	NS
Chen[12]	Taiwan	Asian-1	212/371	83.4	2A, 3A, 3B	ASP	NS
Kyogoku[14]	Japan	Asian-1	382/303	89.5	2A, 3A, 3B	SSCP, FRET, PHFA, ASP	NS
Morgan[16]	India/Pakistan	Asian-2	123/128	85	2A, 3A, 3B	DS	NS
Milicic[15]	India	Asian-2	63/93	NA	3A	RFLP, ASP*	NS

* Genotype quality control was done by additional method such as DS or ASP. DS: DNA sequencing, DHLC: denaturing high-performance liquid chromatography, RFLP: restriction fragment-length polymorphism, ASP: allele-specific polymerase chain reaction, SSCP: single-strand conformation polymorphism, FRET: fluorescence resonance energy transfer, PHFA: preferential homoduplex formation assay, NS: not significant, NA: not available.

Table 2. Minor allele frequency of *FCG*R polymorphism in controls for the different populations.

Population	*FCG*R2A, %	*FCG*R3A, %	*FCG*R3B, %
European	44.1	32.9	36.6
Asian-1	28.1	33.9	37.5
Asian-2	45.3	31.0	44.0

Kyogoku, *et al*[14] on *FCG*R3B. Deviation from H-W equilibrium among controls implies potential bias during control selection, or genotyping errors, but excluding the study that did not show H-W equilibrium among controls did not materially affect our overall results. Our metaanalysis had enough power (> 99%) to detect a small effect size (OR of 1.5) in the overall group, but some subgroup analysis by ethnicity had lower power in the metaanalyses of *FCG*R2A (73.0%) and *FCG*R3A (54.7%) in Europeans, and *FCG*R3A (52.6%) in the Asian-2 group.

Metaanalysis of FCGR2A polymorphisms and RA susceptibility. A summary of metaanalyses on the association between *FCG*R2A polymorphisms and RA is shown (Table 3). In the metaanalysis of *FCG*R2A polymorphisms, no association was found between RA and *FCG*R2A R allele in the overall population (OR 0.925, 95% CI 0.806–1.061, p = 0.263). Further, stratification by ethnicity failed to identify any association between *FCG*R2A polymorphisms and RA in the European or Asian groups (Table 3). In addition, no association between RA and the *FCG*R2A polymorphisms was found by metaanalyses using recessive and dominant models, and contrast of homozygotes.

Metaanalysis of FCGR3A polymorphisms and RA susceptibility. Metaanalysis revealed a significantly greater association between the VV genotype and the risk of developing RA than for the VF+FF genotype (OR 1.256, 95% CI 1.045–1.510, p = 0.015), with no evidence of between-study heterogeneity (p = 0.167; Table 4). Stratification by ethnicity indicated different associations between the *FCG*R3A polymorphisms and RA in Asians and Europeans. In subjects of European descent, an association between the VV genotype versus the VF+FF genotype was observed (OR 1.374, 95% CI 1.101–1.714, p = 0.005), and no evidence of between-study heterogeneity was found (p = 0.582; Figure 1). In subjects of Asian descent, no association was found between VV genotype and RA susceptibility. In a metaanalysis of the contrast of homozygotes, no association was found in overall or Asian subjects. Interestingly, however, metaanalysis of the VV versus the FF genotypes revealed significantly increased OR in Europeans (OR 1.399, 95% CI 1.107–1.769, p = 0.005), and no evidence of between-study heterogeneity was found (p = 0.202), which concurs with the result of metaanalysis of the relation between the VV genotype and RA in Europeans.

Metaanalysis of *FCG*R3B polymorphisms and RA. No association between RA and *FCG*R3B polymorphisms was found by metaanalyses using the allele contrast, recessive, and dominant models in the overall, the European, and the Asian populations, respectively, except for contrast of homozygotes (Table 5). Metaanalysis of the NA22 versus the NA11 genotypes revealed significantly decreased OR in Europeans (OR 0.173, 95% CI 0.100–0.301, p < 0.001).

DISCUSSION

In this metaanalysis, we combined data from published studies to evaluate the genetic associations between activating *FCG*R polymorphisms and susceptibility to RA. Our findings do not support an association between the *FCG*R2A and *FCG*R3B polymorphisms and RA susceptibility. Although there was heterogeneity among studies, no association between the *FCG*R2A and *FCG*R3B polymorphisms

Table 3. Metaanalysis of *FCG*R2A polymorphisms and association with RA.

Polymorphism	Population	No. of Studies	Test of Association OR	95% CI	p	Model	Test of Heterogeneity Q	p	I^2
*FCG*R2A	Overall	5	0.925	0.806–1.061	0.263	F	1.44	0.837	0
R vs H	Overall in HWE	3	0.945	0.804–1.110	0.490	F	0.62	0.733	0
	European	2	0.853	0.662–1.101	0.222	F	0.33	0.562	0
	Asian-1	2	0.958	0.794–1.148	0.623	F	0.56	0.452	0
RR vs RH+HH	Overall	5	0.932	0.722–1.203	0.587	F	5.71	0.222	29.9
(recessive)	Overall in HWE	3	0.839	0.600–1.172	0.303	F	3.19	0.202	33.4
	European	2	0.823	0.571–1.187	0.298	F	0.01	0.896	0
	Asian-1	2	0.893	0.407–2.146	0.873	F	3.15	0.076	0
RR+RH vs HH	Overall	5	0.904	0.776–1.053	0.195	F	1.85	0.763	0
(dominant)	Overall in HWE	3	0.934	0.784–1.113	0.447	F	0.35	0.836	0
	European	2	0.785	0.577–1.069	0.124	F	0.57	0.448	0
	Asian-1	2	0.950	0.782–1.155	0.607	F	0.20	0.651	0
RR vs HH	Overall	5	0.894	0.624–1.155	0.298	F	3.43	0.488	0
	Overall in HWE	3	0.877	0.595–1.294	0.509	F	2.43	0.296	17.8
	European	2	0.773	0.446–1.205	0.221	F	0.39	0.531	0
	Asian-1	2	0.895	0.554–1.444	0.648	F	2.41	0.120	586

HWE: Hardy-Weinberg equilibrium, F: fixed effects model, R: random effects model.

Table 4. Metaanalysis of *FCG*R3A polymorphisms and association with RA.

Polymorphism	Population	No. of Studies	Test of Association OR	95% CI	p	Model	Test of Heterogeneity Q	p	I^2
*FCG*R3A	Overall	9	1.037	0.890–1.208	0.645	R	21.9	0.005	63.6
V vs F	Genotype control*	3	1.017	0.736–1.404	0.921	R	8.54	0.014	76.6
	European	5	1.096	0.898–1.338	0.367	R	9.92	0.042	59.6
	Asian-1	2	0.946	0.797–1.122	0.524	F	2.00	0.156	50.2
	Asian-2	2	0.960	0.637–1.447	0.845	R	6.76	0.009	85.2
VV vs VF+FF	Overall	9	1.256	1.045–1.510	0.015	F	11.6	0.167	31.3
(recessive)	Genotype control*	3	1.390	1.013–1.908	0.041	F	1.90	0.386	0
	European	5	1.374	1.101–1.714	0.005	F	2.85	0.582	0
	Asian-1	2	1.080	0.750–1.556	0.678	F	1.34	0.247	25.4
	Asian-2	2	0.789	0.341–1.826	0.580	R	5.05	0.025	80.2
VV+VF vs FF	Overall	9	1.018	0.834–1.243	0.859	R	20.7	0.008	61.3
(dominant)	Genotype control*	3	0.912	0.564–1.474	0.706	R	9.96	0.007	79.9
	European	5	1.060	0.808–1.390	0.676	R	12.7	0.013	68.5
	Asian-1	2	0.882	0.703–1.106	0.276	F	1.09	0.295	8.71
	Asian-2	2	1.085	0.636–1.850	0.765	R	4.03	0.045	75.1
VV vs FF	Overall	9	1.168	0.864–1.579	0.312	R	16.4	0.037	51.2
	Genotype control*	3	1.237	0.696–2.196	0.468	R	5.40	0.067	63.0
	European	5	1.399	1.107–1.769	0.005	F	5.95	0.202	32.8
	Asian-1	2	1.007	0.685–1.480	0.971	F	1.64	0.200	39.1
	Asian-2	2	0.835	0.321–2.173	0.711	R	6.22	0.013	83.9

* European studies where genotype quality control was performed by additional method. HWE: Hardy-Weinberg equilibrium, F: fixed effects model, R: random effects model.

and RA susceptibility was found for any allele using homozygotes or recessive or dominant models in the overall group. The relative importance of the *FCG*R2A and *FCG*R3B polymorphisms in the development of RA may vary between ethnic groups, but ethnic-specific analysis revealed no association between the *FCG*R2A and *FCG*R3B polymorphisms and RA in the European or Asian groups, respectively, except for the analysis of NA22 versus NA11 of *FCG*R3B in Europeans. Kyogoku, *et al* demonstrated a lack of H-W equilibrium of *FCG*R3B, but not *FCG*R2A[14]. *FCG*R3B is subject to copy-number variation[26]; this is likely to be a major factor in the lack of H-W equilibrium and inconsistent results of different genetic models.

In contrast, metaanalysis of the *FCG*R3A polymorphisms revealed a significant association between the VV genotype and the risk of developing RA relative to the VF+FF genotype (OR 1.256, 95% CI 1.045–1.510, p = 0.015), with no evidence of between-study heterogeneity.

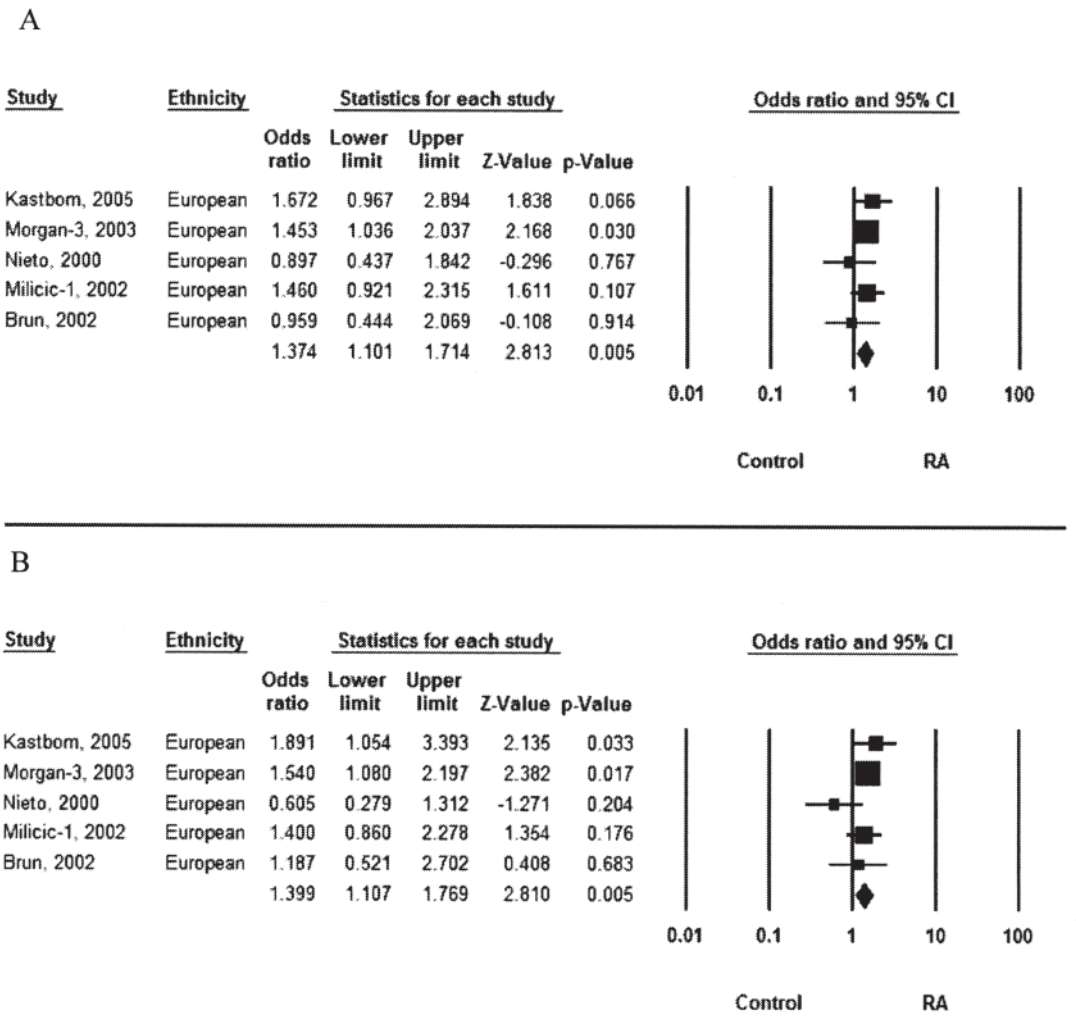

Figure 1. Odds ratios and 95% confidence intervals of individual studies and pooled data for the VV versus VF+FF (dominant model; A) and VV versus FF (homozygote contrast; B) for susceptibility to RA in European subjects.

Table 5. Metaanalysis of *FCG*R3B polymorphisms and association with RA.

Polymorphism	Population	No. of Studies	Test of Association OR	95% CI	p	Model	Test of Heterogeneity Q	p	I^2
FCGR3B	Overall	5	0.988	0.867–1.125	0.856	F	2.10	0.717	0
NA2 vs NA1	Overall in HWE	4	0.999	0.850–1.174	0.986	F	2.05	0.561	0
	European	2	0.963	0.738–1.257	0.783	F	1.02	0.310	2.84
	Asian-1	2	0.961	0.815–1.133	0.638	F	0.01	0.918	0
NA22 vs NA21+NA11	Overall	5	0.979	0.785–1.221	0.851	F	1.59	0.809	0
(recessive)	Overall in HWE	4	1.047	0.813–1.348	0.723	F	0.45	0.928	0
	European	2	1.104	0.763–1.598	0.599	F	0.30	0.580	0
	Asian-1	2	0.884	0.637–1.226	0.461	F	0.50	0.476	0
NA22+21 vs NA11	Overall	5	0.992	0.810–1.214	0.938	F	6.29	0.178	36.4
(dominant)	Overall in HWE	4	0.953	0.730–1.243	0.721	F	6.08	0.108	0
	European	2	0.674	0.374–1.213	0.188	F	1.91	0.166	47.8
	Asian-1	2	0.983	0.781–1.238	0.886	F	0.36	0.548	0
NA22 vs NA11	Overall	5	0.348	0.184–0.659	0.001	R	22.5	0.000	82.2
	Overall in HWE	4	0.342	0.143–0.818	0.016	R	22.0	0.000	86.4
	European	2	0.173	0.100–0.301	0.000	F	2.31	0.128	56.8
	Asian-1	2	0.571	0.217–1.518	0.263	R	7.85	0.005	87.2

HWE: Hardy-Weinberg equilibrium, F: fixed effects model, R: random effects model.

Stratification by ethnicity indicated a different association between the *FCG*R3A polymorphisms and RA in Asians and Europeans. In subjects of European descent, an association between the VV genotype and RA was observed, but in subjects of Asian descent this was not evident. Interestingly, analysis of the VV vs FF genotype revealed significantly higher OR in Europeans (OR 1.399, 95% CI 1.107–1.769, p = 0.005), and no evidence of between-study heterogeneity. These findings suggest that *FCG*R3A polymorphisms are associated with development of RA in Europeans, but not in Asians.

Our findings suggest that the low-affinity allele of the *FCG*R 3A (F158) may have a protective role in the development of RA in Europeans. *FCG*R3A F/V158 is known to have functional significance, and the F158 isoform binds IgG1 and IgG3 with lower affinity than the V158 isoform. The *FCG*R3A V158 allele may enhance capture of IgG opsonized pathogens or IgG immune complexes and feed them directly into the antigen-processing pathway, which results in more efficient presentation of arthritogenic peptides[27]. On the other hand, the *FCG*R3A F158 allele binds fewer immune complexes and could reduce inflammatory response[28]. However, whether the association between the *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. There has been evidence for LD between *FCG*R2A and *FCG*R3A, and *FCG*R2B and *FCG*R3B in RA as well as in SLE[16,29]. Evidence for LD at the *FCG*R locus could be expanded to other diseases.

Our study has some limitations. First, publication bias, heterogeneity, and confounding factors may have distorted the metaanalysis. Moreover, we could not draw funnel plots due to the small number of studies, and although we performed Egger's regression test, we could not eliminate the possibility of bias. Second, this metaanalysis included data from European and Asian patients, and thus our results are applicable only to these ethnic groups. Third, the numbers of studies performed on *FCG*R2A and *FCG*R3B polymorphisms were too small to achieve statistically meaningful results. Some metaanalyses had lower power. Interpretation of these data should be done carefully. More studies are needed to clarify the association between these polymorphisms and RA. Fourth, haplotype analysis may provide additional evidence for the presence of further unidentified polymorphic variants that are the true disease-susceptibility variants[16,30]. Morgan, *et al* revealed that *FCG*R2A, *FCG*R3A, and *FCG*R3B were not associated with RA. But the *FCG*R3A-*FCG*R3B 158V-NA2 haplotype was strongly associated with RA[16]. Haplotype analysis was not possible due to inadequate haplotype data in this metaanalysis. Fifth, *FCG*R polymorphisms may be associated with the severity of RA as well as susceptibility to RA. However, the small amount of data available did not allow metaanalysis on the association between the *FCG*R polymorphisms and the severity of RA.

Multiple genetic factors shape the RA phenotypes of an autoimmune disease with such complex traits. It might be difficult to identify the overall genetic effect of a single gene. The functional differences of *FCG*R3A 158 F/V polymorphisms may contribute to only part of the development of RA.

Metaanalysis offers a powerful means of organizing and synthesizing information on subtle yet clinically important genetic effects. This metaanalysis of published data revealed no relationship between the *FCG*R2A polymorphisms and susceptibility to RA in Europeans or Asians; but the *FCG*R3A polymorphism and the *FCG*R3B polymorphism were associated with development of RA in Europeans. However, the influence of *FCG*R polymorphisms on the pathogenesis of RA remains uncertain and must be determined by larger studies in different ethnic groups.

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