Immunoglobulin G Fc-Receptor (FcγR) IIA, IIIA, and IIIB Polymorphisms Related to Disease Severity in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Fc receptors for IgG (FcγR) modulate immune responses. FcγR are expressed on various leukocytes and contain allelic polymorphisms with different capacity for IgG binding and phagocytosis. We investigated the distribution of FcγRIIA, FcγRIIIA, and FcγRIIIB polymorphisms in rheumatoid arthritis (RA) and whether they were related to disease expression and severity.

Methods. Ninety-six controls and 114 patients fulfilling American College of Rheumatology (ACR) criteria for RA were genotyped for FcγRIIA, IIIA, and IIIB using polymerase chain reaction. Physician's global assessment of RA type estimated RA disease expression. In addition, usual measures of disease activity were recorded.

Results. The genotype and allele frequencies did not differ significantly between the RA patients and the controls. Patients homo or heterozygous for the FcγRIIA arginine (R) allele had significantly more aggressive RA and swollen joints than patients homozygous for the FcγRIIA histidine (H) allele. Although there was a tendency of more severe disease among patients homo or heterozygous for the FcγRIIIA valine allele, there were no significant findings with the disease activity for the FcγRIIIA and FcγRIIIB genotypes.

Conclusion. FcγRIIA is implicated as a possible disease modifying gene in RA. Individuals homozygous for the FcγRIIA R allele have less efficient binding of IgG2 subclasses than individuals homozygous for the H allele. Less effective processing of circulating immune complexes in RA patients homozygous for the FcγRIIA R allele may therefore contribute to a more unfavorable course. (J Rheumatol 2002;29:1135–40)

Key Indexing Terms:
RHEUMATOID ARTHRITIS FC-RECEPTORS DISEASE SEVERITY GENETICS

Autoimmune mechanisms are considered to play an important role in the pathogenesis of rheumatoid arthritis (RA)[1]. Receptors for the Fc portion of IgG (FcγR) are important in modulating immune responses[2], and FcγR polymorphisms have been implicated as genetic factors that may influence the susceptibility to autoimmune disease[3].

Three FcγR subtypes have been identified (FcγRI or CD64, FcγRII or CD32, and FcγRIII or CD16). These subtypes are encoded by several genes on chromosome 1[3,4]. FcγRI binds IgG with high affinity, whereas the others are all low affinity receptors. The low affinity receptors FcγRIIA, IIIA, and IIIB are called activating receptors, whereas the FcγRIIB is an inhibitory receptor[5]. It is estimated that the maximum distance between any of the low affinity receptor genes is about 200 kb, which makes it possible that the receptors are in linkage disequilibrium[6,7].

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The FcγRIIA, IIIA, and IIIB receptors are expressed on various leukocytes and contain allelic polymorphisms. The FcγRIIA allele containing histidine (H) at position 131 has higher affinity for IgG2 than the variant containing arginine (R), whereas the FcγRIIIA valine (V) or FcγRIIIB neutrophil antigen (NA) 1 alleles have higher affinity for IgG1 and IgG3 than the FcγRIIIA phenylalanine (F) or the FcγRIIIB NA2 alleles[8-10].

FcγR genotypes have been implicated as factors that may modify disease susceptibility or disease phenotype in various autoimmune conditions. Although studies do not all agree, associations have been reported for systemic lupus erythematosus[11], Wegener's granulomatosis[12], myasthenia gravis[13], multiple sclerosis[14], and Guillain-Barré syndrome[15,16].

There are few clinical studies on FcγR genotypes and RA disease susceptibility or expression. A preliminary study on FcγRIIA reported no associations[17]. The evidence regarding FcγRIIIA is not consistent, as studies have identified all 3 genotypes as disease susceptibility factors[18,19]. However, one of these studies showed that the FcγRIIIA V allele was associated with nodular RA, which is considered a more severe disease subset[19]. Immunohistochemical and *in vitro* cell studies have suggested that FcγRIIIA and B may play a role in susceptibility to tissue damage in RA[20-22]. FcγRIII also seems to

be crucial in triggering murine collagen-induced autoimmune arthritis, and lack of FcγRII may augment the arthritis[23]. Murine FcγRII is functionally equivalent to human FcγRIIB.

We investigated the distribution of FcγRIIA, FcγRIIIA, and FcγRIIIB polymorphisms in patients with RA and controls and studied whether these allelic variants were related to disease expression and severity in RA.

MATERIALS AND METHODS

Patients and controls. During 1998, 114 consecutive RA outpatients of the Department of Rheumatology of Haukeland University Hospital in Bergen were included in the study. The diagnosis of RA was established according to the revised criteria of the American College of Rheumatology[24]. Patient and physician global assessments of disease activity, morning stiffness, pain last week, Health Assessment Questionnaire score, and 28-joint count of tender and swollen joints were recorded[25]. The joints were scored on a 4 point scale according to severity[26].

Roentgenograms of hands and wrists were ordered if no recent pictures were available (from within 12 mo of the investigation). After taking all available clinical, laboratory, and radiologic information into account, the investigator also recorded a global assessment of type of RA (1: low grade, 2: intermediate, and 3: aggressive). This global assessment served as an estimate of RA disease expression. Ninety-six unrelated blood donors with no known disease from the same geographic area served as controls.

Laboratory tests. Routine laboratory tests included measurement of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, and platelets.

FcγR genotyping. Genomic DNA was purified from peripheral blood leukocytes using QIAamp DNA Blood Mini Kits 50 (Qiagen GmbH, Hilden, Germany) according to the manufacturer's instructions. Polymerase chain reaction (PCR) for FcγRIIA was modified from Botto, *et al*[27]. Five oligonucleotide primers were used. Two primers from the T cell receptor Vα22 gene (Ctrl-1: 5'-GAT TCA GTG ACC CAG ATG GAA GGG-3' and Ctrl-2: 5'-AGC ACA GAA GTA CAC CGC TGA GTC-3') amplified a fragment of 270 bp and were used as an internal positive control. The other primers bound to sequences in the FcγRIIA gene. EC2-131R (5'-CCA GAA TGG AAA ATC CCA GAA ATT CTC TCG-3') and EC2-131H (5'-CCA GAA TGG AAA ATC CCA GAA ATT CTC TCA-3') were allele-specific primers. In cooperation with the antisense downstream primer TM1 (5'-CCA TTG GTG AAG AGC TGC CCA TGC TGG GCA-3'), these primers amplified a 980 bp fragment. Two separate PCR reactions were performed for genotyping of each individual. The 25 μl of PCR reaction mixture contained 100 ng of genomic DNA, 2.5 μl of 10× PCR buffer (Applied Biosystems, Foster City, CA, USA), 57.5 nmol of $MgCl_2$, 1 nmol of each of the 4 dNTP, 1.1 pmol of each of the 2 control primers, 0.011 nmol of the other 3 primers, and 1.75 U of Taq DNA polymerase (Applied Biosystems). PCR conditions were denaturation for 5 min at 94°C, followed by 45 cycles of 94°C for 45 s, 63°C for 30 s, and 72°C for 1.5 min, and a final extension step at 72°C for 10 min.

PCR for FcγRIIIA was modified from Koene, *et al*[10]. The allele-specific primers [KIM-G (V): 5'-TCT CTG AAG ACA CAT TTC TAC TCC CTA C-3' and KIM-1 (F): 5'-TCT CTG AAG ACA CAT TTC TAC TCC CTA A-3'] amplified a 160 bp fragment with their antisense downstream primer A013 (5'-ATA TTT ACA GAA TGG CAC AGG-3'). The control primers were Ctrl 1 and Ctrl 2 (see FcγRIIA), amplifying a 270 bp piece of DNA. Again, 2 PCR procedures were required for genotyping of a subject. Reactions were performed with 175 ng of genomic DNA in a 25 μl reaction volume, containing 2.5 μl of PCR Gold Buffer, 62.5 nmol of $MgCl_2$, 1.25 nmol of each of the 4 dNTP, 11.9 pmol of KIM-G (V), 66.4 pmol of KIM-G (F), 15.4 pmol of A013, 1.1 pmol of each of the two control primers and 0.5 U of Ampli Taq Gold (Applied Biosystems). PCR conditions were denaturation for 10 min at 94°C, 32 cycles of 95°C for 30 s, 57°C for 20 s, and 72°C for 25 s, and a final extension step at 72°C for 7 min.

PCR for FcγRIIIB was modified from Bux, *et al*[28]. Two human growth hormone (HGH) primers (HGH-I: 5'-CAG TGC CTT CCC AAC CAT TCC CTT A-3' and HGH-II: 5'-ATC CAC TCA CGG ATT TCT GTT GTG TTT C-3') were used as internal positive controls, amplifying a 439 bp fragment. The NA1-specific primer (5'-CAG TGG TTT CAC AAT GTG AA-3') gave a 141 bp fragment, and the NA2-specific (5'-CAA TGG TAC AGC GTG CTT-3') amplified a 219 bp piece. The reverse primer (5'-ATG GAC TTC TAG CTG CAC-3') did not discriminate between the 2 allotypes. Since there was a substantial difference in length between the NA1-specific and NA2-specific reaction products, both alleles could be detected in the same reaction. The reaction mixture (volume 25 μl) contained 100 ng of genomic DNA, 3.7 μl of 10 × PCR buffer, 25.0 nmol of $MgCl_2$, 1 nmol of each of the 4 dNTP, 4.0 pmol of each of the 2 control primers, 0.013 nmol of the NA1 and NA2 primers, 0.025 nmol of the reverse primer, and 0.5 U of Taq DNA polymerase. PCR conditions were denaturation for 3 min at 94°C followed by 30 cycles of 94°C for 1 min, 57°C for 2 min, and 72°C for 1 min, and a final extension step at 72°C for 10 min.

After electrophoresis in 1.5% agarose gel and staining with ethidium bromide, the amplification products were visualized with ultraviolet light.

Statistical analysis. Data were frequently not normally distributed and we used the median and the interquartile range (IQR) as measures of central tendency and dispersion. Differences between groups were tested with the Kruskal-Wallis test. A chi-square test was applied to categorical variables, and the odds ratio (OR) and 95% confidence interval (95% CI) were computed for 2 × 2 tables. For FcγRIIIA, previous studies indicated a more severe disease among patients with the V/V and V/F genotypes[19], and a separate analysis was carried out with these 2 groups combined versus the group with the F/F genotype, in a cross tabulation with aggressive RA versus low grade RA. Based on the analyses of the associations between disease activity measures and the FcγRIIA genotypes, a comparable analysis with the genotypes R/R and R/H combined were performed. Associations beween measures of disease activity and FcγR genotypes were also studied using multiple logistic regression, and the OR and 95% CI were computed for any significant associations. The statistical analyses were performed using SPSS Release 9.0.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the study population. Eighty-two of the 114 patients with RA (71%) were women and 32 (29%) were men. The median age was 66.0 years (IQR 54.3–73.0) and the median disease duration was 8.7 years (IQR 4.1–17.5). Eighty-six patients (74%) were rheumatoid factor positive. The median value of CRP was 11.0 mg/l, ESR 25.0 mm/h, hemoglobin 12.8 g/l, swollen joint score 13.0, tender joint score 28.5, duration of morning stiffness 15.0 min, and Health Assessment Questionnaire score 1.25. Ninety-two patients (79%) used cytotoxic or disease modifying antirheumatic drugs, and 42 (36%) used peroral steroids.

The global assessment of type of RA was validated relative to measures of disease activity. This variable adequately reflected the general activity of the disease (Table 1).

Distribution of FcγR genotypes and allele frequencies. The different FcγRIIA, FcγRIIIA, and FcγRIIIB genotypes and allele frequencies did not differ significantly between the RA patients and controls (Table 2).

FcγR associations with clinical and laboratory variables of disease activity. Although not significant for most of the variables, there was a trend of higher disease activity among patients with the FcγRIIA R allele (Table 3). The significant findings regarding swollen joints did not persist after correc-

Table 1. Clinical and laboratory associations with the global assessment of type of rheumatoid arthritis. Values are median (interquartile range).

Variables of Disease Activity	Type of RA Low Grade, N = 38	Medium, N = 43	Aggressive, N = 33	p*
Age, yrs	70.5 (52.0–77.0)	64.0 (52.8–71.5)	66.0 (58.8–73.0)	0.22
Disease duration, yrs	5.7 (3.1–15.0)	10.8 (4.9–20.8)	9.3 (5.5–17.0)	0.11
Morning stiffness, min	7.5 (0.0–60.0)	30.0 (0.3–115.0)	60.0 (0.0–120.0)	0.08
Tender joint score	4.0 (0.0–8.0)	9.0 (4.0–15.5)	9.0 (3.0–21.5)	0.002
Swollen joint score	6.5 (2.0–12.0)	14.0 (7.0–26.0)	28.0 (14.5–34.3)	< 0.001
Doctor assessment, VAS	17.5 (9.0–23.0)	36.0 (21.8–51.5)	63.0 (46.3–71.0)	< 0.001
Patient assessment, VAS	28.0 (8.3–47.5)	46.0 (23.3–62.5)	39.0 (25.0–59.3)	0.03
Pain last week, min	17.5 (6.0–41.0)	43.5 (20.3–60.8)	47.5 (27.0–66.8)	0.004
HAQ score	0.88 (0.25–1.63)	1.25 (0.75–1.75)	1.75 (1.13–2.25)	0.001
ESR, mm/h	20.0 (11.8–35.5)	26.0 (17.0–42.0)	36.0 (20.8–61.0)	0.003
C-reactive protein, mg/l	4.0 (3.0–9.5)	13.5 (5.3–38.0)	24.0 (10.8–39.0)	< 0.001
Hemoglobin, g/l	13.2 (12.4–13.9)	12.7 (12.1–13.7)	12.7 (11.5–13.6)	0.20
RF titer	128 (8–512)	64 (8–320)	128 (56–640)	0.13
Current MTX dose, mg	7.5 (7.5–10.6)	10.0 (7.5–15.0)	15.0 (7.5–15.0)	0.05

VAS: Visual analog scale; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate.
* Kruskal-Wallis test for significance.

Table 2. Distribution of Fcγ receptor (FcγR) genotypes and allele frequencies.

	Fcγ Receptor Genotype, n (%)*			Allele Frequencies**		Total
	R/R	R/H	H/H	R	H	
IIA						
Patients	36 (31.6)	46 (40.4)	32 (28.1)	0.52	0.48	114
Controls	33 (34.4)	45 (46.9)	18 (18.8)	0.58	0.42	96
	* Chi-square = 2.54, p = 0.28; ** Chi-square = 1.54, p = 0.24					
	F/F	F/V	V/V	F	V	
IIIA						
Patients	44 (39.3)	51 (45.5)	17 (15.2)	0.62	0.38	112
Controls	43 (48.3)	32 (36.0)	14 (15.7)	0.66	0.34	89
	* Chi-square = 2.05, p = 0.36; ** Chi-square = 0.77, p = 0.40					
	NA1/NA1	NA1/NA2	NA2/NA2	NA1	NA2	
IIIB						
Patients	14 (12.3)	48 (42.1)	52 (45.6)	0.33	0.67	114
Controls	11 (12.6)	41 (47.1)	35 (40.2)	0.36	0.64	87
	* Chi-square = 0.62, p = 0.74; ** Chi-square = 0.36, p = 0.60					

tion for multiple comparisons. However, in a multivariate logistic regression model based on the variables of Table 3 with FcγRIIA as the dependent variable (R/R and R/H genotypes combined), a significant association was found between swollen joints and the FcγRIIA R genotypes (OR = 1.06, 95% CI: 1.01–1.11).

Corresponding analyses for the FcγRIIIA and FcγRIIIB alleles showed no trends or significant differences.

FcγR associations with disease expression. Cross tabulations of the FcγR genotypes versus RA disease type showed a non-significant trend towards more aggressive disease among patients with the FcγRIIA genotypes containing the R allele (Table 4).

Further analyses were performed comparing the group with aggressive RA with the group with low grade RA. The odds ratio for aggressive disease of the FcγRIIA R/R and R/H genotypes combined versus the H/H genotype was 3.64 (95% CI: 1.05–12.63). A comparable result was found when only

Table 3. Clinical and laboratory associations with FcγRIIA genotypes. Values are mean rank [median (interquartile ranges)].

	FCγRIIA R/R, N = 36	R/H, N = 46	H/H, N = 32	p*
Variable of disease activity				
Morning stiffness, min	58.4 [15.0 (0.0–120.0)]	58.6 [30.0 (0.0–90.0)]	51.4 [15.0 (0.0–60.0)]	0.57
Tender joint score	64.2 [7.5 (3.0–29.0)]	59.0 [8.0 (4.0–12.0)]	47.8 [4.5 (0.0–10.8)]	0.11
Swollen joint score	66.0 [17.5 (6.5–32.0)]	58.4 [13.0 (6.0–27.0)]	46.6 10.0 (4.0–17.3)]	0.05
Doctor assessment, VAS	62.5 [36.0 (18.3–65.3)]	61.1 [33.0 (19.0–55.0)]	46.8 [24.0 (14.8–43.5)]	0.09
Patient assessment, VAS	48.6 [40.5 (18.5–59.8)]	47.7 [41.5 (15.8–59.3)]	39.9 [29.0 (9.0–60.0)]	0.44
Pain last week, min	55.6 [37.5 (18.0–53.0)]	58.1 [35.0 (16.8–66.3)]	47.6 [26.0 (6.5–47.5)]	0.36
HAQ score	57.3 [1.38 (0.75–1.75)]	55.6 [1.13 (0.75–1.75)]	55.0 [1.00 (0.25–2.25)]	0.95
ESR, mm/h	51.5 [22.0 (13.3–34.8)]	65.6 [33.0 (20.0–52.3)]	47.6 [22.0 (10.0–35.0)]	0.04
C-reactive protein, mg/l	55.0 [10.0 (3.3–37.8)]	60.5 [17.0 (4.3–41.8)]	50.7 [10.0 (4.0–27.0)]	0.42
Hemoglobin, g/l	56.4 [12.9 (12.1–13.6)]	57.1 [13.0 (12.1–13.6)]	57.5 [12.7 (12.0–13.9)]	0.99
RF titer	51.3 [64 (8–224)]	62.9 [128 (8–512)]	56.7 [96 (14-448)]	0.27
Current MTX dose, mg	33.1 [12.5 (7.5–15.0)]	31.5 [10.0 (7.5–15.0)]	29.3 [10.0 (7.5–12.5)]	0.83

* Kruskal-Wallis test for significance.

homozygotes were analyzed (R/R versus H/H, OR = 4.14, 95% CI: 1.05–16.29). The odds ratio for aggressive disease of the FcγRIIIA V/V and V/F genotypes combined versus the F/F genotype was 2.51 (95% CI: 0.94–6.66). However, the results were not significant. No trends or significant results were found in the analyses of the FcγRIIIB genotypes.

DISCUSSION

Although progress has been made in recent years, much is still unclear regarding the etiology and pathogenesis of RA. Knowledge about factors that predispose to disease or influence disease expression may shed new light on the etiopathogenesis and indicate directions for future research. Such factors include rheumatoid factor, which may be associated with a more severe disease[29], interleukin-1, and tumor necrosis factor-α, which are considered important in the pathogenesis of RA[30], and the shared epitope of the DRB1 RA susceptibility genes[31]. Further, FcγR genes have been implicated in the susceptibility and severity of the disease[17-19].

The genotype and allele frequencies of the FcγRIIA, IIIA, and IIIB did not differ significantly between patients and controls. The distribution of genotypes in our study is similar to that described in other caucasoid populations[32]. Our results indicate that FcγRIIA, IIIA, and IIIB polymorphisms are not

Table 4. Cross tabulations of the FcγRIIA, FcγRIIIB, and FcγRIIIA genotypes versus RA disease type. Values are numbers (%) of patients with each genotype within each RA disease type category.

	FcγRIIA* R/R	RH	H/H	Total	FcγRIIIA** F/F	F/V	V/V	Total	FcγRIIIB*** NA1/NA1	NA1/NA2	NA2/NA2	Total
Disease type												
Low grade	11 (28.9)	14 (36.8)	13 (34.2)	38 (100.0)	21 (56.8)	10 (27.0)	6 (16.2)	37 (100.0)	7 (18.4)	16 (42.1)	15 (39.5)	38 (100.0)
Medium	11 (25.0)	18 (40.9)	15 (34.1)	44 (100.0)	12 (27.9)	24 (55.8)	7 (16.3)	43 (100.0)	5 (11.4)	21 (47.7)	18 (40.9)	44 (100.0)
Aggressive	14 (43.8)	14 (43.8)	4 (12.5)	32 (100.0)	11 (34.4)	17 (53.1)	4 (12.5)	32 (100.0)	2 (6.3)	11 (34.4)	19 (59.4)	32 (100.0)
Total	36	46	32	114	44	51	17	112	14	48	52	114

* Chi-square = 6.24, p = 0.18. ** Chi-square = 8.89, p = 0.06. *** Chi-square = 4.79, p = 0.31.

associated with susceptibility for RA. The results of previous studies regarding FcγRIIIA as a susceptibility marker for RA are inconsistent, as all 3 FcγRIIIA genotypes have been found to be increased in RA[18,19]. Therefore, larger population as well as family-based association studies are needed.

Griffiths, *et al*[17] have reported on FcγRIIA polymorphisms in RA. In this preliminary study comprising 115 patients of various ethnic groups, no associations were found with disease severity as defined by the presence of RF, extraarticular manifestations, and bone erosions. In the present study, however, there was a non-significant trend of higher disease activity among patients with the R/R and R/H genotypes. Significant correlations were found only with the clinical variable swollen joints, and with physician global assessment of disease type. This last variable was constructed for the express purpose of evaluating variation in disease expression and severity, and the patients were racially homogeneous. Thus, the 2 studies do not seem directly comparable, and as both studies are relatively small, statistical power may have been insufficient to detect small differences in genotype and allele frequencies. This may explain why significant associations were found for swollen joints but not for the other variables of RA disease activity. The results of the present study should, however, be interpreted with caution, since no correction was applied for examining 3 genes, and some of the significant findings were from analyses of subgroups.

There was a non-significant association between the FcγRIIIA V/V and V/F genotypes and the aggressive disease type. This finding is in accordance with that of Morgan, *et al*[19], who found that the V allele was associated with nodular RA. However, we found no associations with disease activity and the FcγRIIIB genotypes.

The possible effects of FcγRIIA on the disease expression in RA may be related to the immune functions of these receptors. FcγR are important in a broad range of immune responses such as antibody-dependent cellular cytotoxicity, endocytosis, phagocytosis, release of inflammatory mediators, and augmentation of antigen presentation, depending on the identity of the FcγR-expressing cell[5]. FcγRIIA R/R has a lower affinity and confers a less effective phagocytosis of IgG2 opsonized particles than FcγRIIA H/H[3,8]. This may therefore be associated with diminished processing and clearance of immune complexes in patients homozygous for the R allele. Such immune complexes might theoretically constitute contributing factors for the perpetuation of inflammation in RA. In addition, there are indications that FcγRIIA R/R increases the risk of infectious disease, including chronic types such as adult periodontitis[3]. Hypothetically, persistent triggering with bacterial antigens might influence inflammatory activity in RA.

In conclusion, our results implicate FcγRIIA as a possible disease modifying gene in RA. This finding may provide additional insights into the pathogensis of this and other autoimmune diseases. Further, prognostic markers may be helpful in both counselling and treating patients in their early stages of the disease.

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