Association of Fcγ Receptor Polymorphisms with Adult Onset Still's Disease in Korea

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ABSTRACT. ***Objective.*** Fcγ receptors (FcγR) have important functions in the regulation of immune response and clearance of immune complex. High levels of immunoglobulins have been observed in patients with the active stage of adult onset Still's disease (AOSD), and high-dose intravenous immunoglobulin treatment has decreased the disease activity of AOSD. We investigated polymorphisms of FcγR as genetic factors influencing susceptibility or disease course of AOSD in Korea.

Methods. We genotyped the FcγRIIA H/R131, IIIA F/V176, and IIIB NA1/NA2 loci in 98 patients with AOSD and 151 healthy controls. Genotyping was performed using sequence-specific PCR. Patients with AOSD were subdivided into groups according to disease course: monocyclic systemic, polycyclic systemic, or chronic articular type. Allelic, genotypic, and haplotypic associations were analyzed by chi-square test.

Results. No significant skewing in any of the 3 FcγR polymorphisms was found between Korean AOSD patients and controls. FcγRIIA R/R131 and R/H131 genotype in patients with chronic articular-type disease was more frequent than in controls ($p = 0.006$ and $p_{corr} = 0.018$). No differences of genotypic and allelic frequencies were found between other disease course types and controls. Haplotype IIA R131-IIIA F176-IIIB NA2 was more frequent in AOSD patients than in controls ($p = 0.021$).

Conclusion. Although FcγR polymorphisms are not associated with development of AOSD in Koreans, the haplotype IIA R131-IIIA F176-IIIB NA2 may be associated with AOSD. Also, the FcγRIIA polymorphism may be associated with chronic articular-type AOSD. We need to identify whether these polymorphisms are associated with a response to anti-tumor necrosis factor agents in patients with AOSD. (First Release Dec 1 2008; J Rheumatol 2009;36:347–50; doi:10.3899/jrheum.071254)

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Adult onset Still's disease (AOSD) is a multisystemic inflammatory disorder. The etiology of AOSD remains unknown, although some infections have been suspected as disease initiators, especially in a genetically susceptible population, and aberrant induction of several cytokines may contribute to the pathogenesis[1]. The Fc receptor for IgG (FcγR) has various functions depending on the type of effector cell, including phagocytosis, immune complex (IC) clearance, cytokine release, and regulation of antibody production[2]. In the antigen-induced arthritis model, FcγR was a crucial factor in cartilage destruction and sustained inflammation[3]. Some patients with active AOSD showed elevated serum immunoglobulin concentrations, and circulating IC were sometimes observed[4]. Treatment with high-dose intravenous immunoglobulin (IVIG) induced remission of active AOSD by attenuating macrophage activity through FcγR[5].

Three functional polymorphisms have been reported for the low affinity FcγR: FcγRIIA, IIIA, and IIIB. Each polymorphism is located on the Fc-binding portion of the FcγR and alters affinity with various IgG subclasses. Each FcγR

has 2 codominantly expressed alleles: IIA R131 and H131, IIIA V176 and F176; and IIIB neutrophil antigen (NA)1 and NA2. The FcγRIIA H131, IIIA V176, and IIIB NA1 have higher affinity to immunoglobulins. These findings suggest that FcγR polymorphisms may influence the development and disease course of AOSD. Previously, FcγRIIA and IIIA polymorphisms were reported to have no association with AOSD, in a report from a single hospital[6]. Therefore, we recruited patients with AOSD from 5 university hospitals in Korea, and studied associations of FcγRIIA, IIIA, and IIIB polymorphisms with AOSD.

MATERIALS AND METHODS

A total of 98 patients with AOSD satisfied the Yamaguchi criteria[7] and 151 healthy controls were also enrolled. They were followed between May 1998 and March 2007. All information was obtained by interviews with patients and reviews of medical records, both retrospectively and prospectively. AOSD patients were subdivided according to the pattern of disease course, as reported, i.e., monocyclic systemic, polycyclic systemic, and chronic articular type[8]. Patients with disease duration < 1 year were excluded from the analysis of disease course. Written informed consent was obtained from all participants before enrollment.

Allele-specific polymerase chain reaction was performed as described for genotyping FcγRIIA H/R131[6], FcγRIIIA F/V176, and FcγRIIIB NA1/NA2[9].

To compare the frequencies of the genotypes, alleles, and haplotypes, we used chi-square tests (SPSS for Windows v.10.0; SPSS, Chicago, IL, USA). Haplotypic frequencies for multiple loci and the standardized disequilibrium coefficient (D') for the pairwise linkage disequilibrium test were calculated using the Arlequin program (http://cmpg.unibe.ch/software/arlequin3/)

RESULTS

Demographic characteristics are summarized in Table 1. All the genotypic and allelic frequencies of FcγR single-nucleotide polymorphisms (SNP) showed no significant differences between the AOSD patients and the controls (Table 2). There was significant skewing in the distribution of the FcγRIIA genotype between the chronic articular disease type and the controls (R/R131 and R/H131 vs H/H131, p = 0.006, p_{corr} = 0.018, OR 3.66, 95% CI 1.39–9.68). Also, the FcγRIIA R131 allele in the chronic articular disease type was more frequent than in controls, but this difference did not reach statistical significance (p = 0.025, p_{corr} = 0.075, OR 2.00, 95% CI 1.08–3.72; Table 3).

Table 1. Clinical characteristics of study subjects.

Characteristic	AOSD, n = 98	Controls, n = 151
Sex, F:M*	81:17	119:32
Mean age, yrs*	35.9 ± 10.9 (18–69)	35.0 ± 11.1 (17–68)
Disease duration, mo	55.9 ± 42.1 (1–153)	—
Clinical manifestations, n (%)		
Fever	98 (100.0)	
Joint symptom	90 (91.8)	
Rash	81 (81.7)	
Sore throat	70 (71.4)	
Lymphadenopathy	42 (42.9)	
Splenomegaly	32 (32.7)	
Hepatopathy	42 (42.9)	
Disease type, n = 88		
Monocyclic systemic, n (%)	28 (31.8)	
Polycyclic systemic, n (%)	35 (39.8)	
Chronic articular, n (%)	25 (28.4)	

* p > 0.05.

Haplotypes were constructed for 3 polymorphisms. The frequency of haplotype IIA R131-IIIA F176-IIIB NA2 in the AOSD patients was higher than that in the controls (p = 0.021, OR 2.35, 95% CI 1.11–4.95). In other haplotypic frequencies, no significant differences were found between the AOSD subjects and the controls. Weak linkage disequilibrium was observed between FcγRIIA and FcγRIIIA (D' 0.20), between FcγRIIA and FcγRIIIB (D' 0.45), and between FcγRIIIA and FcγRIIIB (D' 0.33).

DISCUSSION

FcγR plays important roles in immune modulation and IC clearance. In patients with active AOSD, concentrations of interleukin 1 (IL-1), IL-6, IL-18, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) were significantly increased[8]. Although these cytokines were typical Th1 cytokines, both Th1 and Th2 cells were capable of supporting B cell expansion and immunoglobulin production[10].

We observed no differences in genotypic or allelic frequencies of the 3 FcγR SNP between patients with AOSD and controls. However, haplotype IIA R131-IIIA F176-IIIB NA2 was more frequent in AOSD patients than in controls. These 3 alleles represent lower binding affinity with immunoglobulin. Lower binding FcγR alleles showed higher susceptibility for some infectious diseases; such infections might have a triggering effect on the pathogenic sequence of AOSD[11]. Further, natural killer cells and monocytes from patients with systemic lupus erythematosus (SLE) with FcγRIIIA V/V176 led to a larger flux in Ca^{++}, a greater degree of cell activation, and a more pronounced program of activation-induced cell death than FcγRIIIA F/F176[12]. We found that lower binding alleles were associated with Korean AOSD, similar to SLE[9,13]. The significance of IC in the pathogenesis of AOSD has not been proven, but prolonged survival of mononuclear cells and impaired handling of IC by mononuclear phagocyte systems might contribute in part to the pathogenesis of AOSD, based on the above findings.

We showed that FcγRIIA polymorphisms are associated with the chronic articular type of AOSD. Patients with chronic articular type AOSD have a more unfavorable prognosis than patients with the other disease-course types. Brun, *et al* reported that patients with FcγRIIA RR or RH genotype had significantly more aggressive rheumatoid arthritis[14]; they suggested that less effective IC clearance might contribute to the more unfavorable course. These 3 FcγR SNP were not in significant linkage disequilibrium, suggesting that the genetic contribution from FcγIIA in

Table 2. Allelic and genotypic frequencies of FcγRIIA, IIIA, and IIIB SNP in Korean AOSD patients and controls.

Locus		AOSD, n (%)	Controls, n (%)	p	OR (95% CI)
Allele					
FcγRIIA	R131	64 (32.7)	80 (26.5)	0.138	1.34 (0.91–1.99)
	H131	132 (67.3)	222 (73.5)		
FcγRIIIA	F176	137 (69.9)	223 (73.9)	0.336	0.823 (0.55–1.23)
	V176	59 (30.1)	79 (26.1)		
FcγRIIIB	NA2	90 (45.9)	135 (44.7)	0.789	1.05 (0.73–1.51)
	NA1	106 (54.1)	167 (55.3)		
Genotype					
FcγRIIA	R/R131	8 (8.2)	10 (6.6)		
	R/H131	48 (49.0)	60 (39.7)	0.251	
	H/H131	42 (42.9)	81 (53.6)		
	R/R131 + R/H131	56 (57.1)	70 (46.3)	0.096	1.54 (0.92–2.57)
FcγRIIIA	F/F176	45 (45.9)	79 (52.3)		
	V/F176	47 (48.0)	65 (43.0)	0.589	
	V/V176	6 (6.1)	7 (4.6)		
	F/F176 + V/F176	92 (93.8)	144 (95.3)	0.606	0.75 (0.24–2.28)
FcγRIIIB	NA2/NA2	19 (19.4)	30 (19.9)		
	NA1/NA2	52 (53.1)	75 (49.7)	0.855	
	NA1/NA1	27 (27.6)	46 (30.5)		
	NA2/NA2 + NA1/NA2	71 (72.4)	105 (69.5)	0.621	1.15 (0.66–2.02)

Table 3. Genotypic and allelic frequencies of FcγRIIA, IIIA, and IIIB SNP by disease course.

Disease Course	Locus		AOSD, n (%)	Controls, n (%)	p	p_{corr}*	OR (95% CI)
Monocyclic systemic, n = 28	FcγRIIA	R131	16 (28.6)	80 (26.5)	0.746	> 0.1	1.11 (0.58–3.09)
		R/R131 + R/H131	13 (46.4)	70 (46.3)	0.994	> 0.1	1.00 (0.45–2.25)
	FcγRIIIA	F176	38 (67.9)	223 (73.8)	0.354	> 0.1	0.75 (0.40–1.39)
		F/F176 + V/F176	27 (96.4)	144 (95.4)	0.802	> 0.1	1.31 (0.16–11.10)
	FcγRIIIB	NA2	29 (51.8)	135 (44.7)	0.328	> 0.1	1.33 (0.75–2.35)
		NA2/NA2 + NA1/NA2	21 (75.0)	105 (69.5)	0.561	> 0.1	1.31 (0.52–3.30)
Polycyclic systemic, n = 35	FcγRIIA	R131	20 (28.5)	80 (26.5)	0.723	> 0.1	1.11 (0.62–1.98)
		R/R131 + R/H131	19 (54.3)	70 (46.3)	0.397	> 0.1	1.37 (0.66–2.87)
	FcγRIIIA	F176	50 (71.4)	223 (73.8)	0.681	> 0.1	0.89 (0.50–1.58)
		F/F176 + V/F176	33 (94.3)	144 (95.4)	0.788	> 0.1	0.80 (0.16–4.04)
	FcγRIIIB	NA2	29 (41.4)	135 (44.7)	0.619	> 0.1	0.88 (0.52–1.48)
		NA2/NA2 + NA1/NA2	21 (60.0)	105 (69.5)	0.825	> 0.1	1.09 (0.49–2.47)
Chronic articular, n = 25	FcγRIIA	R131	21 (42.0)	80 (26.5)	0.025	0.075	2.00 (1.08–3.72)
		R/R131 + R/H131	19 (76.0)	70 (46.3)	0.006	0.018	3.66 (1.39–9.68)
	FcγRIIIA	F176	35 (70.0)	223 (73.8)	0.570	> 0.1	0.83 (0.43–1.60)
		F/F176 + V/F176	23 (92.0)	144 (95.4)	0.479	> 0.1	0.56 (0.11–2.86)
	FcγRIIIB	NA2	22 (44.0)	135 (44.7)	0.926	> 0.1	0.97 (0.53–1.78)
		NA2/NA2 + NA1/NA2	16 (64.0)	105 (69.5)	0.580	> 0.1	0.78 (0.32–1.89)

* Bonferroni correction.

chronic articular type AOSD might be independent from the other known FcγR SNP.

Our study was on a relatively large scale (98 patients with AOSD), considering the rarity of AOSD. But we could not evaluate whether the associated FcγR polymorphisms were functionally significant in clearance of immune complexes and the relationship between FcγR SNP and responsiveness to anti-TNF agents. Anti-TNF agents may have an effect via their IgG1 Fc fragment binding to FcγR[15]. The relationship of FcγR SNP and treatment outcome of anti-TNF agents in AOSD will be examined in future studies.

Although FcγR polymorphisms are not associated with AOSD in Koreans, the haplotype IIA R131-IIIA F176-IIIB NA2 may be associated with AOSD. Also, the FcγRIIA polymorphism may be associated with chronic articular type AOSD.

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