CONCISE REPORT

Fc γ receptor IIa, IIIa, and IIIb polymorphisms of systemic lupus erythematosus in Taiwan

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Objective: To determine whether the distribution of Fc γ receptor IIa, IIIa, and IIIb polymorphisms confers a risk factor for disease susceptibility, and correlates with the clinical characteristics and serological parameters of patients with SLE in Taiwan.

Methods: Genotyping of Fc γ receptors IIa H/R131, IIIa F/V158, and IIIb NA1/NA2 was performed in 302 patients with SLE and 311 healthy blood donor controls. The distribution of Fc γ receptor IIa, IIIa, and IIIb genotypes in patients and controls was analysed. Frequencies of three Fc γ receptor polymorphisms were also compared between lupus patients with and without different clinical manifestations and autoantibodies.

Results: No significant skewing in the distribution of Fc γ RIIa H/R131, Fc γ RIIIa F/V158, and Fc γ RIIIb NA1/NA2 was found between patients and controls in Taiwan. The following clinical associations were found: Fc γ RIIIb NA1/NA1 protected against neuropsychiatric lupus ($p=0.028$) but conferred susceptibility to discoid rash ($p<0.005$); increased Fc γ RIIIa F/V158 was associated with infections ($p=0.039$); increased Fc γ RIIa H/R131 was associated with earlier onset of lupus ($p=0.01$).

Conclusion: Fc γ receptor IIa, IIIa, and IIIb polymorphisms may be responsible for the development of distinct manifestations of lupus patients in Taiwan, but there is no significantly skewed distribution in the susceptibility to lupus as a whole.

Binding of Fc γ Rs, integral surface membrane glycoproteins, with the Fc portion of IgG is a crucial mechanism for transmitting the stimulative or repressive immune responses. Fc γ R binding may initiate a plethora of biological responses, including phagocytosis, the facilitation of antigen presentation, and the processing of immune complexes.¹ Patients with systemic lupus erythematosus (SLE) exhibit the profound defect of phagocytosis in immune complex processing.²

Human SLE pedigree studies with genome-wide scans have mapped chromosome 1q21–24, in which the Fc γ R gene cluster is found as an important locus.^{3,4} The genetic heterogeneity of Fc γ R may have an impact on numerous autoimmune diseases and infections, especially lupus nephritis.⁵ Subsequent Fc γ R genetic association analysis of lupus disclosed controversial or discrepant results across various study groups, suggesting that ethnic and geographical factors may cause various disease susceptibilities and complexities of lupus.

Fc γ RIIa H/R131 polymorphism showed a significantly skewed distribution in several non-Caucasian lupus studies,

which might also influence the disease manifestations in Caucasian lupus patients.^{6,7} Recently, studies of Japanese and Korean lupus patients showed that Fc γ RIIa H/R131 polymorphism was an important genetic factor.^{8,9} Fc γ RIIIa F/V158 polymorphism has been shown to be an important susceptibility gene in Caucasian lupus studies.¹⁰ Fc γ RIIIb NA1/NA2 was also linked to lupus susceptibility in one Japanese population study and, in particular, in Caucasian patients with lupus nephritis.^{11,12}

In view of these positional and functional candidate gene approaches, the effects of genotype variants of three Fc γ Rs in Taiwan lupus patients were investigated.

PATIENTS AND METHODS

Characteristics of study groups

A total of 302 patients with SLE in Taiwan were studied. For this study, 311 healthy blood donors were selected as controls after a questionnaire survey to exclude autoimmune diseases. Patients enrolled in this study were prospectively followed up in the rheumatology clinics of Chang Gung Memorial Hospital. All the patients were evaluated by rheumatology specialists to verify that they fulfilled the 1982 and 1997 American College of Rheumatology criteria for SLE. Clinical manifestations of lupus and related serological findings were based on the American College of Rheumatology definition in the classification criteria. Patients were grouped as positive or negative according to presentation within the first year of lupus diagnosis. Associated infections during the course of the disease were all recorded, and were supported by positive culture.

Nucleic acid extraction and allele-specific polymerase chain reaction for Fc γ R genotyping

Genomic DNA was extracted from EDTA-anticoagulated peripheral blood using the DNA isolation kit. Each of the three primers was designed for allele-specific polymerase chain reaction for the genotyping of Fc γ RIIa H/R131, Fc γ RIIIa F/V158 and Fc γ RIIIb NA1/NA2 as previously described.¹³

Statistical analysis

The frequencies of the genotypes of the three Fc γ R polymorphisms in patients and controls were compared using a paired t test and a χ^2 test. Data were analysed with the SPSS statistic package for Windows, and Fisher's exact test applied. Distribution of the variant genotypes was also compared between lupus patients with and without different clinical manifestations and autoantibodies. A p value <0.05 was considered significant.

RESULTS

Clinical characteristics of SLE

This study enrolled 302 patients (91% women) with SLE from Taiwan with a mean age of lupus onset of 29.3 (11.5) years

Table 1 Frequencies of FcγRIIa, FcγRIIIa and FcγRIIIb alleles among 311 healthy controls and 302 patients with SLE with significant clinical association in Taiwan

Characteristics (n)	FcγRIIa			FcγRIIIa			FcγRIIIb		
	131HH (%)	131HR (%)	131RR (%)	158FF (%)	158FV (%)	158VV (%)	NA1/1 (%)	NA1/2 (%)	NA2/2 (%)
Normal (311)	41.8	46.3	11.9	42.8	46.9	10.3	38.3	46.6	15.1
SLE (302)	41.4	40.4	16.2	39.4	45.7	14.9	38.7	43.6	17.5
Age at onset									
<20* (57)	57.9	22.8	19.3	35.1	52.6	12.3	36.8	43.9	19.3
20–29 (123)	42.3	40.6	17.1	38.2	43.1	18.7	42.3	42.3	15.4
30–49 (73)	35.6	50.7	13.7	38.3	50.7	11.0	30.1	49.3	20.6
40–49 (29)	37.9	48.3	13.8	41.1	41.4	17.2	44.8	37.9	17.2
>50 (20)	45.0	40.0	15.0	60.0	30.0	10.0	45.0	25.0	30.0
Discoid rash									
Positive (66)	56.1†	33.3	10.6	39.4	48.5	12.1	53.0**	25.8	21.2
Negative (236)	39.8	42.4	17.8	39.4	44.9	15.7	34.7	47.5	17.8
Nephritis									
Positive (155)	38.7‡	47.1	14.2	41.3	41.9	16.8	43.2	38.7	18.1
Negative (147)	48.3	33.3	18.4	37.4	49.7	12.9	34.0	46.9	19.0
Neuropsychiatric									
Positive (36)	44.4	38.9	16.7	55.6§	36.1	8.3	19.4††	61.1	19.4
Negative (266)	43.2	40.6	16.2	37.2	47.0	15.8	41.4	40.2	18.4
Infection									
Positive (125)	43.2	38.4	18.4	43.2	37.6	19.2¶	40.0	44.8	15.2
Negative (177)	43.5	41.8	14.7	36.7	51.4	11.9	37.9	41.2	20.9

*p=0.01 (patients with age at onset <20 years compared with age at onset ≥20 years). †p=0.055; ‡p=0.051; §=0.095; ¶p=0.039; **p=0.005; ††p=0.028.

(range 11–77). Haematological disorders (233/302 (77.2%)) were the most common manifestation, followed by malar rash (206/302 (68.2%)) and arthritis (194/302 (64.2%)). One hundred and fifty five (51.3%) patients developed nephritis, 70 (23.2%) patients had nephrotic syndrome (proteinuria ≥3.5 gm/day), and 17 (5.6%) patients progressed to end stage renal disease. The incidence of other manifestations was as follows: 32.5% oral ulcer, 26.5% serositis, 25.8% vasculitis, 24.8% photosensitivity, 21.9% discoid rash, 13.9% Raynaud's phenomenon, and 11.9% neuropsychiatric manifestations. The age onset of lupus was most frequent from 20 to 29 years old (123 patients). In comparison with patients with age onset >20 years old, the patients with an earlier onset (age<20 years) had a higher frequency of FcγRIIa H/H131 (p=0.01) (table 1). No difference of clinical outcome was found for the three genotypes of FcγRIIa H/R131.

Distribution of FcγR genotyping between patients with SLE and healthy controls

This study found a relatively low incidence of FcγRIIa R/R131 (16.2% and 11.9%), FcγRIIIa V/V158 (14.9% and 10.3%), and FcγRIIIb NA2/NA2 (17.5% and 15.1%) in the lupus patients and healthy controls. Lupus susceptibility in patients and controls did not depend on the distribution of the three FcγR genotypes (table 1). Compared with FcγRIIIa F/F158 plus FcγRIIa H/H131, the combined genotype FcγRIIIa V/V158 plus FcγRIIa R/R131 was susceptible to SLE (p=0.019) (table 2). The combined genotype of FcγRIIIa F/F158 plus FcγRIIa R/R131 showed no difference from FcγRIIIa V/V158 plus FcγRIIa H/H131.

FcγR genotyping associations among different clinical manifestations

FcγR genotype distributions of lupus patients with and without various clinical manifestations were compared. Discoid rash was the only dermatological manifestation relevant to the polymorphism of Fcγ receptors. FcγRIIa H/

H131 and FcγRIIIb NA1/NA1 were susceptible to discoid rash. FcγRIIa H/H131 exhibited a protective role in the development of nephritis (p=0.055) but no significantly skewed distribution of FcγRIIIa V/F158 and FcγRIIIb NA1/NA2 polymorphisms was obtained. Lupus patients with neuropsychiatric involvement had a significantly lower frequency of FcγRIIIb NA1/NA1 than those without (p=0.028) (table 1). In comparison with FcγRIIIa F/F158 plus FcγRIIa H/H131, the combined genotype of FcγRIIIa V/V158 plus FcγRIIa R/R131 had a protective role in vasculitis (p=0.033) and oral ulcer (p=0.049) (table 2).

Associations of FcR genotypes with immunological variables

FcγRIIa H/R131, FcγRIIIa V/F158, and FcγRIIIb NA1/NA2 genotyping distributions for autoantibody positive and negative patients were analysed. No significant differences among the distribution of FcγRIIa H/R131, FcγRIIIa V/F158,

Table 2 Frequencies of FcγRIIa and FcγRIIIa combined genotypes among 311 healthy controls and 302 patients with SLE with significant clinical association in Taiwan

	IIa 158FF+ IIa 131HH	IIa 158VV+ IIa 131RR	p Value
Normal	64	3	0.019
SLE	67	13	
Vasculitis			0.033
Negative	50	13	
Positive	17	0	
Oral ulcer			0.049
Negative	44	12	
Positive	23	1	

and FcRIIb NA1/NA2 for anti-Smith, anti-RNP, anti-dsDNA, anticardiolipin, and hypocomplementaemia in the examined patients were seen.

FcR genotyping and infections

One hundred and twenty five lupus patients had 174 episodes of infection. Sixteen patients developed infections at lupus onset. Urinary tract infections (57 episodes) and herpes viral infections (37 episodes) were the most common infections in this study. Other infections were as follows: 26 cases of sepsis, 15 cases of skin wound infection, 9 cases of pneumonia, 3 cases of emphysema, 2 cases of biliary tract infections, 5 cases each of septic arthritis and meningitis. Nine episodes of fungus and five of tuberculosis infections were noted. The organisms most commonly found were 16 *E coli* infections of urinary tract infections, 10 *Salmonella* infections of sepsis, and 4 *Cryptococcus* infections of meningitis. The FcRIIIa V/V158 genotype was more frequently found in lupus patients who had with infections than those without (19.2% v 11.9%, $p = 0.039$).

DISCUSSION

FcR polymorphisms are the most important non-major histocompatibility complex lupus susceptibility loci. The inconsistencies among earlier lupus genetic association studies of FcR are attributable to many biases, including ethnic variation, population admixture, the production of various IgG subclass autoantibodies, distinct phenotypic expressions, and the confounding influence of other inherited factors. In a review of previous reports of FcR polymorphism, the significant association of disease susceptibility in lupus case-control studies was not noted in the following studies with larger populations.^{11–14} Thus, 302 Taiwanese lupus patients were enrolled and compared with 311 sex matched healthy controls in this study.

A review of published reports showed that the FcRIIa R/R131 genotype is susceptible to lupus, particularly lupus nephritis. However, Karassa *et al* in a meta-analysis study demonstrated that FcRIIa R/R131 had no clear effect on the development of nephritis in SLE. The Asian population has a lower frequency of FcRIIa R/R131 than populations of other ethnic origin.⁶ Similar low frequencies of FcRIIa R/R131 genotypes, 16.2% and 11.9%, were found in our lupus group and healthy control group, respectively. Manger *et al* demonstrated associations of various clinical symptoms and immunological disorders with FcR IIa H/R131 polymorphism.⁷ FcγIIa H/H131 was found to protect against the development of lupus nephritis in this study.

FcRIIIa F/V158 genotype is a susceptible gene, according to several Caucasian and Japanese studies^{10–13–14} but shows a distribution that is not significantly different between patients and controls in most Asian lupus studies. The distribution of the FcγRIIIa F/V158 polymorphism was reported to be associated with various clinical manifestations. FcγRIIIa V/V158 combined with FcRIIa H/H131 had a protective role for lupus nephritis in Korean and German studies.^{7–8} In this study, we could not find such an effect. Dijkstra *et al* found that lupus patients who presented with arthritis and/or serositis had a high frequency of FcRIIIa F/F158.¹² Interestingly, we found a trend towards an association of FcRIIIa F/F158 with neuropsychiatric manifestations.

FcRIIb NA2/NA2 polymorphism was related to lupus susceptibility and nephritis in a Japanese study. Subsequently, this association was claimed to involve perhaps another important FcRIIb polymorphism.¹⁴ Dijkstra *et al* also showed that FcRIIb NA1/NA1 was related to susceptibility to nephritis.¹² The FcRIIb NA1/NA2 genotype did not show a significantly skewed distribution of lupus susceptibility in

Taiwanese lupus patients. In this study, patients with FcRIIb NA1/NA1 may have been protected against central nervous system involvement. Unexpectedly, FcRIIa H/H131 and FcRIIb NA1/NA1 showed a high frequency in discoid rash.

FcRIIb NA1/NA2 and FcRIIa H/R131 have been shown to contribute to encapsulated bacterial infections with various neutrophil phagocytosis activities.¹⁵ In our study, there were few encapsulated bacteria infections, and FcRIIb NA1/NA2 and FcRIIa H/R131 polymorphisms had no significant role in patients with other associated infections. Interestingly, our lupus patients with infections had a higher frequency of the FcRIIIa V/V158 genotype. The result may be due to the high incidence of herpes virus and opportunistic infections in our lupus patients.

In conclusion, FcR IIa, IIIa, and IIb polymorphisms may contribute to clinical manifestations of lupus and related infections but do not indicate a significant susceptibility to lupus in Taiwanese patients.

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REFERENCES

- Salmon JE, Pricop L. Human receptors for immunoglobulin G: key elements in the pathogenesis of rheumatic disease. *Arthritis Rheum* 2001;**44**:739–50.
- Davies KA, Robson MG, Peters AM, Norsworthy P, Nash JT, Walport MJ. Defective Fc-dependent processing of immune complexes in patients with systemic lupus erythematosus. *Arthritis Rheum* 2002;**46**:1028–38.
- Moser KL, Neas BR, Salmon JE, Yu H, Gray-McGure C, Asundi N, *et al*. Genomes scan of human systemic lupus erythematosus: evidence for linkage on chromosome 1 q in African-American pedigrees. *Proc Natl Acad Sci USA* 1998;**95**:14869–74.
- Shai R, Quismorio FP, Li L, Kwon OJ, Morrison J, Wallace DJ, *et al*. Genome wide scan for systemic lupus erythematosus susceptibility genes in multiplex families. *Hum Mol Genet* 1999;**8**:639–44.
- Rasucu A, Repp R, Westerdal NAC, Kalden JR, Van De Winkel JGJ. Clinical relevance of Fc receptor polymorphism. *Ann N Y Acad Sci* 1997;**815**:282–95.
- Karassa FB, Trikalinos TA, Ioannidis JP. Role of the Fcγ receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. *Arthritis Rheum* 2002;**46**:1563–71.
- Manger K, Repp R, Jansen M, Geisselbrecht M, Wassmuth R, Westerdal NA, *et al*. Fcγ receptor IIa, IIIa, and IIb polymorphisms in German patients with systemic lupus erythematosus: association with clinical symptoms. *Ann Rheum Dis* 2002;**61**:786–92.
- Sato H, Iwano M, Akai Y, Nishino T, Fujimoto T, Shiiki H, *et al*. Fcγ receptor IIa polymorphism in Japanese patients with systemic lupus erythematosus. *Lupus* 2001;**10**:97–101.
- Yun HR, Koh HK, Kim SS, Chung WT, Kim DW, Hong KP, *et al*. Fcγ receptor IIa/IIIa polymorphism and its association with clinical manifestations in Korean lupus patients. *Lupus* 2001;**10**:466–72.

- 10 **Seligman VA**, Suarez C, Lum R, Inda SE, Lin D, Li H, *et al*. The Fc gamma receptor IIIA-158F allele is a major risk factor for the development of lupus nephritis among Caucasians but not non-Caucasians. *Arthritis Rheum* 2001;**44**:618–25.
- 11 **Hatta Y**, Tsuchiya N, Ohashi J, Matsushita M, Fujiwara K, Hagiwara K, *et al*. Association of Fc gamma receptor IIIB, but not of Fc gamma receptor IIA and IIIA polymorphisms with systemic lupus erythematosus in Japanese. *Genes Immun* 1999;**1**:53–60.
- 12 **Dijstelbloem HM**, Bijl M, Fijnheer R, Scheepers RH, Oost WW, Jansen MD, *et al*. Fc gamma receptor polymorphisms in systemic lupus erythematosus: association with disease and in vivo clearance of immune complexes. *Arthritis Rheum* 2000;**43**:2793–800.
- 13 **Edberg JC**, Langefeld CD, Wu J, Moser KL, Kaufman KM, Kelly J, *et al*. Genetic linkage and association of Fc gamma receptor IIIA (CD16A) on chromosome 1q23 with human systemic lupus erythematosus. *Arthritis Rheum* 2002;**46**:2132–40.
- 14 **Kyogoku C**, Dijstelbloem HM, Tsuchiya N, Hatta Y, Kato H, Yamaguchi A, *et al*. Fc gamma receptor gene polymorphisms in Japanese patients with systemic lupus erythematosus: contribution of FCGR2B to genetic susceptibility. *Arthritis Rheum* 2002;**46**:1242–54.
- 15 **Bredius RGM**, Fijen CAP, de Haas M, Kuijper EJ, Weening RS, van de Winkel JGJ, *et al*. Role of neutrophil Fc gamma receptor IIa (CD32) and Fc gamma receptor IIb (CD16) polymorphic forms in phagocytosis of human IgG1 and IgG3 opsonized bacteria and erythrocytes. *Immunology* 1994;**83**:624–30.

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