**CONCISE REPORT**

**Fcγ receptor Ila, Ila, and Ilib polymorphisms of systemic lupus erythematosus in Taiwan**


**Objective:** To determine whether the distribution of Fcγ receptor Ila, Ila, and Ilib 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 Fcγ receptors Ila H/R131, Ila F/V158, and Ilib NA1/NA2 was performed in 302 patients with SLE and 311 healthy blood donor controls. The distribution of Fcγ receptor Ila, Ila, and Ilib genotypes in patients and controls was analysed. Frequencies of three Fcγ receptor polymorphisms were also compared between lupus patients with and without different clinical manifestations and autoantibodies.

**Results:** No significant skewing in the distribution of Fcγ RIIa H/R131, Fcγ RIIa F/V158, and Fcγ RIIb NA1/NA2 was found between patients and controls in Taiwan. The following clinical associations were found: Fcγ RIIb NA1/NA1 protected against neuropsychiatric lupus (p = 0.028) but conferred susceptibility to discoid rash (p < 0.005); increased Fcγ RIIa F/V158 was associated with infections (p = 0.039); increased Fcγ RIIa H/H131 was associated with earlier onset of lupus (p = 0.01).

**Conclusion:** Fcγ receptor Ila, Ila, and Ilib 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.

**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 FcγR 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 FcγRIIa H/R131, FcγRIIa F/V158 and FcγRIIb NA1/NA2 as previously described.13

**Statistical analysis**
The frequencies of the genotypes of the three FcγR polymorphisms in patients and controls were compared using a paired t test and a χ² 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.
relevant to the polymorphism of Fc receptors. Discoid rash was the only dermatological manifestation without various clinical manifestations were compared. The combined genotype of FcRIIa H131 and FcγRIIb 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 FcγRIIa H131 and FcγRIIb NA1/NA2 polymorphisms was obtained. Lupus patients with neuropsychiatric involvement had a significantly lower frequency of FcγRIIb NA1/NA1 than those without (p = 0.028) (table 1). In comparison with FcγRIIa H131, the combined genotype of FcγRIIa V158 plus FcγRIIa R/R131 had a protective role in vasculitis (p = 0.033) and oral ulcer (p = 0.049) (table 2).

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

<table>
<thead>
<tr>
<th>Characteristics (n)</th>
<th>FcγRIIa</th>
<th>FcγRIIa</th>
<th>FcγRIIib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>131HH (%)</td>
<td>131HR (%)</td>
<td>131RR (%)</td>
</tr>
<tr>
<td>Normal (311)</td>
<td>41.8</td>
<td>46.3</td>
<td>11.9</td>
</tr>
<tr>
<td>SLE (302)</td>
<td>41.4</td>
<td>40.4</td>
<td>16.2</td>
</tr>
<tr>
<td>Age at onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years (57)</td>
<td>57.9</td>
<td>22.8</td>
<td>19.3</td>
</tr>
<tr>
<td>20-29 years (123)</td>
<td>42.3</td>
<td>40.6</td>
<td>17.1</td>
</tr>
<tr>
<td>30-49 years (73)</td>
<td>35.6</td>
<td>50.7</td>
<td>13.7</td>
</tr>
<tr>
<td>40-49 years (29)</td>
<td>37.9</td>
<td>48.3</td>
<td>13.8</td>
</tr>
<tr>
<td>&gt;50 years (20)</td>
<td>45.0</td>
<td>40.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Discoid rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (66)</td>
<td>56.1†</td>
<td>33.3</td>
<td>10.6</td>
</tr>
<tr>
<td>Negative (236)</td>
<td>39.8</td>
<td>42.4</td>
<td>17.8</td>
</tr>
<tr>
<td>Nephritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (155)</td>
<td>38.7†‡</td>
<td>47.1</td>
<td>14.2</td>
</tr>
<tr>
<td>Negative (147)</td>
<td>48.3</td>
<td>33.3</td>
<td>18.4</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (36)</td>
<td>44.4</td>
<td>38.9</td>
<td>16.7</td>
</tr>
<tr>
<td>Negative (266)</td>
<td>43.2</td>
<td>40.6</td>
<td>16.2</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (125)</td>
<td>43.2</td>
<td>38.4</td>
<td>18.4</td>
</tr>
<tr>
<td>Negative (177)</td>
<td>43.5</td>
<td>41.8</td>
<td>14.7</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FcγRIIa 158FF—lila 131HH</th>
<th>FcγRIIa 158VV—lila 131RR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>64</td>
<td>3</td>
<td>0.019</td>
</tr>
<tr>
<td>SLE</td>
<td>67</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>50</td>
<td>13</td>
<td>0.033</td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Oral ulcer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>44</td>
<td>12</td>
<td>0.049</td>
</tr>
<tr>
<td>Positive</td>
<td>23</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Distribution of FcγR genotyping between patients with SLE and healthy controls

This study found a relatively low incidence of FcγRIIa H/R131 (16.2% and 11.9%), FcγRIIa V/158 (14.9% and 10.3%), and FcγRIIb 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 FcγRIIa H131 and FcγRIIib NA1/NA1, FcγRIIa 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 FcγRIIa H131 and FcγRIIb NA1/NA2 polymorphisms was obtained. Lupus patients with neuropsychiatric involvement had a significantly lower frequency of FcγRIIb NA1/NA1 than those without (p = 0.028) (table 1). In comparison with FcγRIIa H131, the combined genotype of FcγRIIa V158 plus FcγRIIa R/R131 had a protective role in vasculitis (p = 0.033) and oral ulcer (p = 0.049) (table 2).

**Associations of FcγR genotypes with immunological variables**

FcγRIIa H/R131, FcγRIIa V/158, and FcγRIIb NA1/NA2 genotyping distributions for autoantibody positive and negative patients were analysed. No significant differences among the distribution of FcγRIIa H/R131, FcγRIIa V/158, and FcγRIIb NA1/NA2 genotypes were obtained.
and FcRIIIb NA1/NA2 for anti-Smith, anti-RNP, anti-dsDNA, anticardiolipin, and hypocomplementemia 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 live 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 FcRIIa V/V158 genotype was more frequently found in lupus patients who had with infections than those without (19.2% vs 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. 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. 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 FcRIIa H/R131 polymorphism. FcIIa H/H131 was found to protect against the development of lupus nephritis in this study.

FcRIIa F/V158 genotype is a susceptible gene, according to several Caucasian and Japanese studies but shows that FcRIIa V/V158 had no clear effect on the development of nephritis in SLE. The Asian population has a lower frequency of FcRIIa V/V158 than populations of other ethnic origin. Similar low frequencies of FcRIIa V/V158 were found in our lupus group and healthy control group, respectively. Dijstelbloem et al also found that lupus patients who presented with arthritis and/or serositis had a high frequency of FcRIIa F/F158. Interestingly, we found a trend towards an association of FcRIIa 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. Dijstelbloem et al also showed that FcRIIIb NA1/NA1 was related to susceptibility to nephritis. 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. 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 FcRIIa V/V158 genotype. The result may be due to the high incidence of herpes virus and opportunistic infections in our lupus patients.

In conclusion, FcRIIa, IIIa, and IIIb 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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