Polymorphism of the FcγRIIa IgG Receptor in Patients with Lupus Nephritis and Glomerulopathy

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ABSTRACT. ***Objective.*** FcγRIIa is a low affinity receptor that has 2 codominantly expressed alleles, R131 and H131, which differ in their ability to bind immunoglobulin G (IgG) subclasses. Cells expressing H131 bind more efficiently complexed IgG2 than those expressing the R131 variant. The FcγRIIa polymorphism has been shown to be associated with lupus nephritis. We evaluated the relevance of FcγRIIa gene polymorphism in the development of lupus immune complex mediated nephritis, as well as its clinical and histological characteristics, by comparing the genotype and allelic distribution of this receptor in lupus nephritis to ethnically matched Brazilian patients with primary glomerulonephritis.

Methods. Patients with lupus nephritis (n = 76) and patients with diagnosis of primary glomerulonephritis (n = 63) established by kidney biopsies were recruited. FcγRIIa genotyping was performed by polymerase chain reaction with allele-specific primers to distinguish between the 2 allelic forms (H131 and R131).

Results. We observed a skewed frequency of genotype FcγRIIa-R/R131 and the R131 allele in patients with lupus nephritis compared to primary glomerulopathies ($p < 0.05$), which disappeared when we compared this population with lupus nephritis only to the group with proliferative glomerulonephritis (IgA nephropathy, membranoproliferative glomerulonephritis, and mesangial proliferative glomerulonephritis). No association was found between genotype distribution and histological class of lupus nephritis or renal insufficiency available at the beginning and end of followup. We found an association of genotype FcγRIIa-R/R131 with higher antinuclear antigen titers and complement 3 consumption ($p < 0.05$).

Conclusion. The skewed distribution of FcγRIIa genotypes with the predominance of homozygous R/R131 genotype observed in patients with lupus nephritis over nonproliferative idiopathic glomerulonephritis emphasizes its importance as a heritable risk factor for immune complex mediated renal injury in Brazilian patients with lupus. (J Rheumatol 2006;33:523–30)

Key Indexing Terms:
AUTOIMMUNITY Fc RECEPTORS GLOMERULONEPHRITIS
IMMUNOGLOBULIN LUPUS NEPHRITIS

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a local inflammatory process provoked by immune complex deposition within tissues. Although there are diverse mechanisms involved in the formation of immune complexes, both high serum concentrations of circulating immune complexes (facilitating their deposition) and *in situ* immune complex formation play important roles in the development of the disease[1]. SLE involves polyclonal activation with increased immunoglobulin synthesis, especially IgG[2]. It has also been shown that, among the various IgG subclasses, IgG1 and IgG2 predominate in cases of lupus nephritis[3].

Concerning glomerular immune deposits in lupus nephritis, findings in the literature are not entirely uniform. While some investigators report predominance of IgG1 and IgG2[4], others report that IgG2 and IgG3 are more commonly found[5]. However, despite the lack of consensus, prevalence of a given IgG subclass in circulation does not necessarily translate to greater deposits of that particular immunoglobulin in the kidney.

Circulating immune complexes are removed through the complement system and through the FcγR receptors, which bind to the Fc portion of IgG. Immune complex clearance in patients with lupus is reduced due to, among other factors, impaired phagocytosis related to allelic variants of Fcγ receptors[6].

There are 3 classes of Fcγ receptors: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16). They differ in function and cell distribution, as well as in IgG (and IgG subclass) binding capacity[7].

Three isoforms of the FcγRII receptor have been identified: FcγRIIa, FcγRIIb, and FcγRIIc. The FcγRIIa is present in mononuclear phagocytes, neutrophils, and platelets, and pos-

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sesses 2 codominantly expressed alleles, R131 (arginine) and H131 (histidine). These alleles differ from each other at amino acid position 131 and in their capacity to bind to IgG2. The FcγRIIa-H/H131 is the only IgG receptor that binds efficiently to IgG2 in humans, while the FcγRIIa-R/R131 binds poorly[8].

Studies of FcγRIIa receptor polymorphism in SLE have yielded inconclusive results. A recent metaanalysis showed that the R/R131 homozygote is directly correlated with a 1.3-times greater risk of development of SLE, but indicated no connection with lupus nephritis[9]. On the other hand, other lupus nephritis studies have shown that the H131 allele and the FcγRIIa-H/H131 genotype are less frequent in Korean patients[10], whereas the allele FcγRIIa-R131 prevails in Caucasian patients[11]. It has also been shown that there is a correlation between FcγRIIa receptor polymorphism and level of proteinuria, suggesting a similar correlation with renal disease severity[10,12].

Zuñiga, *et al*[5] studied the relation between genotypes and renal immune deposits and reported that the FcγRIIa-R131 genotype may impair the removal of circulating immune complexes and trigger phagocytic activity, thereby releasing inflammatory mediators within glomeruli. However, the authors showed no connection between these genotypes and histological classes of proliferative and nonproliferative lupus nephritis.

A study by Bazilio, *et al*[13] in our laboratory showed a predominance of the FcγRIIa-R/R131 genotype in patients with lupus nephritis compared to the general population. The authors also found a tendency (nonsignificant) for higher rates of renal insufficiency within patients with this genotype than within the general population.

We analyzed the relationship between the FcγRIIa-R/R131 genotype and disease severity in patients with lupus nephritis and primary glomerulopathies, as well as possible relationships between the genotype and aspects of renal histology. Disease severity was assessed at study onset (defined as the day of renal biopsy) and at the last followup examination.

MATERIALS AND METHODS

Seventy-six patients with lupus nephritis and 63 with primary glomerulopathies were selected for study. With the exception of those under dialysis at other centers within the city of São Paulo, all patients were monitored at the University of São Paulo Hospital das Clínicas Nephrology Outpatient Clinic. All patients with SLE fulfilled the American College of Rheumatology 1982 revised criteria for the disease. All adult patients (over age 18 years) of both sexes undergoing followup in the Nephrology Division between June 2002 and June 2003 were enrolled. Patient exclusion criteria were the presence of diabetes, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV). Patient followup ranged from 6 months to 10 years.

Patients with lupus nephritis were divided into 2 ethnic groups: Caucasians (n = 64) and Afro-South Americans (n = 12). All patients except 5 had histopathological diagnosis by kidney biopsies according to the 1982 World Health Organization (WHO) classification criteria for lupus nephritis. Thus, subclasses V-c and V-d are included under class V (membranous lupus nephritis). Patients' distribution by lupus nephritis histopathological class was as follows: 42 (55.3%) with diffuse proliferative glomerulonephritis (WHO class IV), 28 (36.8%) with membranous glomerulonephritis (WHO class V), one (1.3%) with chronic glomerulosclerosis (WHO class VI), and no histological diagnosis for 5 patients (6.6%), who did not undergo biopsy.

Clinical and laboratory indicators, together with a regular outpatient recall system scheduled by the attending physicians, were used to evaluate the patients under treatment in the Nephrology Department of the Hospital das Clínicas. Conventional immune suppression drugs were administered according to clinical and laboratory criteria established to evaluate disease progression. The most commonly employed therapeutic regimens for patients with class IV included oral and intravenous corticosteroids and intravenous cyclophosphamide, both administered according to the criteria adopted by the Nephrology Department, as advocated by Steinberg, *et al*[14], and in accord with the protocol devised by the US National Institutes of Health. For patients with class V we used the protocol devised by Austin, *et al*[15] with oral corticoids.

Over the course of this study, laboratory testing was periodically performed to determine serum levels of creatinine, complement, antinuclear antigen (ANA), and anti-double-stranded DNA; to analyze blood cell counts; to measure total proteins and protein fractions; to measure anticardiolipin and lupus anticoagulant antibody (LAC); to quantify proteinuria; and to perform urinalysis. ANA was determined using immunofluorescence in HEp-2 cells, anti-dsDNA by means of immunofluorescence using *Crithidia luciliae* as substrate, complement by radial immunodiffusion, anticardiolipin antibody by ELISA, and LAC by coagulometric method.

Clinical and laboratory data were compiled from patient charts. Baseline values were defined as those obtained nearest the time of renal biopsy and final values as those obtained in the last followup examination prior to June 2003. Evaluation periods ranged from 6 months to 10 years. Renal insufficiency was defined as serum creatinine ≥ 1.4 mg/dl at the end of study. Some laboratory data from patients undergoing dialysis outside the Hospital das Clínicas could not be assessed.

As controls, we selected 63 patients with primary glomerulopathies, also under treatment at the Nephrology Outpatient Clinic. Of these 63 patients, 22 (34.9%) had been diagnosed with membranous glomerulonephritis (MG), 17 (27%) with focal segmental glomerulosclerosis (FSGS), 10 (15.9%) with IgA nephropathy (IgAN), 6 (9.5%) with membranoproliferative glomerulonephritis (MPGN), 5 (7.9%) with minimal change disease (MCD), and 3 (4.8%) with mesangial proliferative glomerulonephritis (MesPGN). For purposes of comparison, patients were divided into 2 groups: proliferative glomerulonephritis (those with MPGN, IgAN, or MesPGN) and nonproliferative glomerulonephritis (those with MG, FSGS, or MCD). Patients with primary glomerulopathies were also divided into 2 ethnic groups: Caucasians (n = 53) and Afro-South Americans (n = 10). As with the lupus nephritis patients, patients with diabetes, hepatitis B, hepatitis C, or HIV were excluded. All other variables were identical to those used in the lupus nephritis group.

The Research Ethics Committee of the University of São Paulo approved the study protocol and all patients gave written informed consent.

The characteristics of each group are shown in Table 1.

Analysis of FcγRIIa polymorphism with genomic polymerase chain reaction (PCR). Peripheral blood samples (3 ml) were drawn in EDTA syringes, and

Table 1. Demographic characteristics and clinical and laboratory findings.

	Lupus nephritis	Glomerulopathies
Age, yrs	27.92 ± 9.64	36.76 ± 13.64*
Sex, female: male	68:8	35:28*
Initial creatinine, mg/dl	2.10 ± 2.02	1.27 ± 0.79*
Final creatinine, mg/dl	2.45 ± 2.57	1.80 ± 1.97
Initial proteinuria, g/24 h	5.77 ± 6.80	5.11 ± 5.25
Final proteinuria, g/24 h	1.33 ± 1.33	2.24 ± 2.62*
Followup, mo	34.37 ± 31.36	54.13 ± 34.46*

* $p < 0.05$ (t test). Results expressed as mean ± SD (standard deviation).

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genomic DNA was isolated using a GFX™ Genomic Blood DNA purification kit (Amersham Pharmacia Biotech, Piscataway, NJ, USA). A 1 kb fragment of the FcγRIIa gene, containing exon 4 and parts of exon 5 separated by an intron, was amplified with PCR using the specific primers P63 5'(forward) CAA GCC TCT GGT CAA GGT C–3' and RII anti-sense 5'(reverse) CAA TGA CCA CAG CCA CAA TG–3', as described[10]. Exon 4 encodes the extracellular domain of FcγRIIa, where there is functional polymorphism resulting from a base nucleotide substitution (A to G) at position 494. For initial PCR, we used 100 ng of genomic DNA, in a reaction volume of 25 µl and containing 2.5 µl of 10× PCR buffer, 0.75 µl (50 mM) of $MgCl_2$, 0.5 µl (100 µM) of dNTP nucleotide mixture, 0.5 µl (10 pmol/µl) of each primer (P63 and RII), and 0.25 µl (5 IU/µl) of Taq polymerase (Invitrogen®). PCR was performed in a Biometra Personal 48 thermocycler under the following conditions: 94°C for 3 min, 29 cycles of denaturation at 94°C for 30 s, annealing at 55°C for 1 min, and extension at 72°C for 40 s before a final extension at 72°C for 5 min.

The product of the initial PCR was submitted to nested PCR using the following primers: 494A 5'(forward) AAA TCC CAG AAA TTC TCC CA-3', 494G 5'(forward) AAA TCC CAG AAA TTC TCC CG-3', and P52 anti-sense 5'(reverse) GAA GAG CTG CCC ATG CTG-3'. The first 2 primers provide adequate specificity to identify polymorphism because they differ from one another in their base (A for allele H131 and G for allele R131). This second reaction was performed using 1 µl of the product obtained in the first reaction, 10× PCR buffer, 0.7 µl (50 nM) of $MgCl_2$, 0.5 µl (100 µM) of dNTP nucleotide mixture, 0.5 µl (10 pmol/µl) of each primer (P52 and 494A in PCR-2; P52 and 494G in PCR-3), as well as 0.25 µl (5 IU/µl) of Taq polymerase (Invitrogen). The total reaction volume was 25 µl. Nested PCR was performed under conditions as follows: 94°C for 3 min, 10 cycles of denaturation at 94°C for 30 s, annealing at 62°C for 1 min, and extension at 72°C for 40 s, before a final extension at 72°C for 5 min.

The amplified products of both PCR and nested PCR were analyzed by electrophoresis in a 1.2% agarose gel containing ethidium bromide. Photodocumentation was performed using a Biometra system and BioDocAnalyze software (Biometra, Göttingen, Germany; Figures 1 and 2).

Cloned plasmids (kindly provided by Dr. J.G.J. van de Winkel, Immunology Department, Utrecht University Medical Center, Utrecht, The Netherlands) were used to adjust the reactions, and the genotype of each sample was validated only after 2 independent PCR assays.

Statistical analysis. Categorical data are expressed as absolute (n) and relative (%) frequencies. For matrices in which the results were genotypic, the chi-square test for trend was used. For square (2×2) matrixes, the chi-square test with Yates's correction was used.

Continuous variables are expressed as mean ± standard deviation of the sample. For independent variables, Student's unpaired t test was used. In comparing 2 or more groups, ANOVA for categorical variables was used together with Student-Newman-Keuls post-test and are also expressed as mean ± standard deviation of the sample. Student's paired t test was used to compare initial versus final (longitudinal) patient status.

The α risk adopted for the entire study period was ≤ 5% ($p \leq 0.05$).

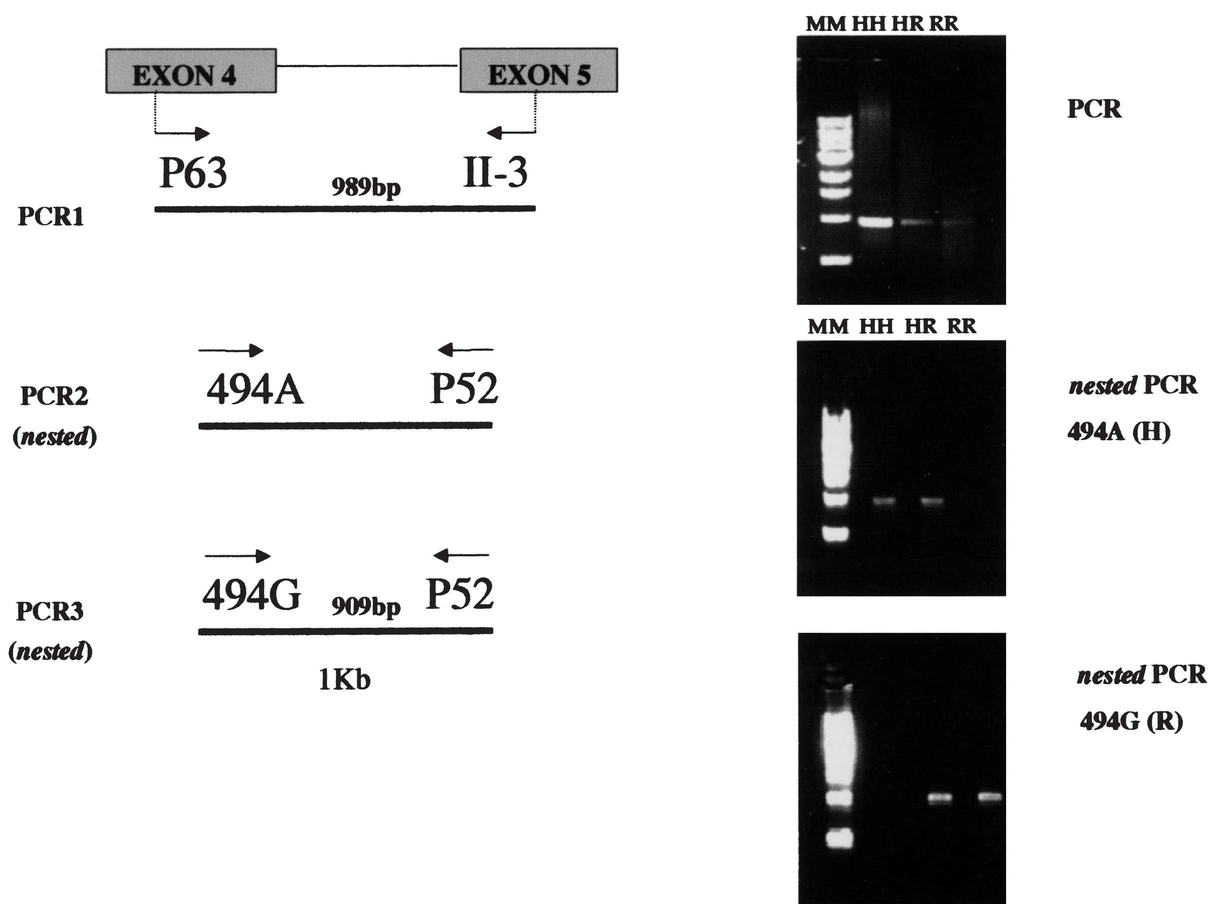

Figure 1. Analysis of amplified plasmid DNA product using PCR and nested PCR with primers specific for FcγRIIa-H131 (494A) or FcγRIIa-R131 (494G). Products were analyzed by electrophoresis on agarose gel and show possible combinations for PCR, nested PCR with 494A, and nested PCR with 494G: H/H131, H/R131, and R/R131, respectively.

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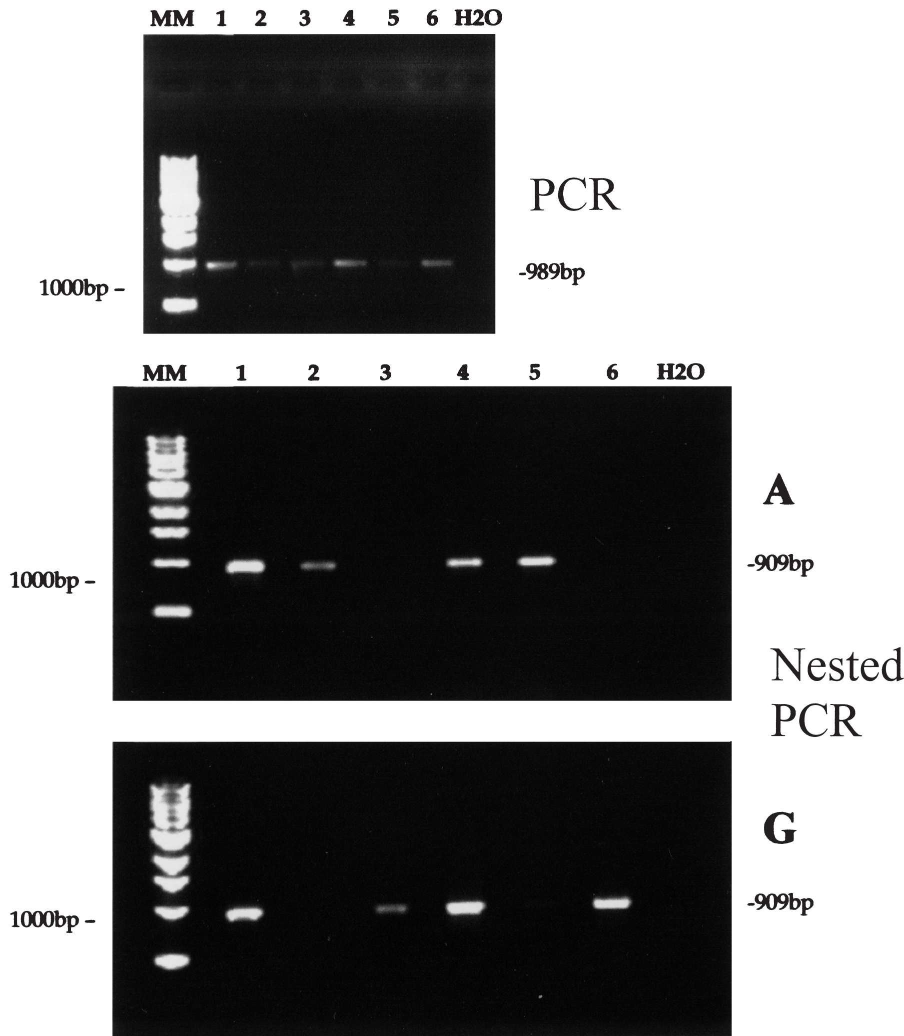

Figure 2. Analysis of amplified DNA product from 6 patients with lupus nephritis using PCR and nested PCR with primers specific for FcγRIIa-H131 (494A) or FcγRIIa-R131 (494G). Products were analyzed by electrophoresis on agarose gel and show possible combinations for the 6 patients: H/R131, H/H131, R/R131, H/R131, H/H131, and R/R131, respectively.

RESULTS

Analyzing the distribution of FcγRIIa receptor polymorphism in the 76 patients with lupus nephritis in comparison with the 63 glomerulopathy patients, lupus nephritis was found to correlate with both the FcγRIIa-R/R131 genotype and the R131 allele distribution ($p < 0.05$; Table 2).

When the population of patients with glomerulopathies was divided between proliferative and nonproliferative dis-

Table 2. Distribution of FcγRIIa genotypes and alleles in patients with lupus nephritis, all glomerulopathy patients, and in the proliferative and nonproliferative glomerulopathy subgroups.

Disease Type	Genotypes R/R n (%)	R/H n (%)	H/H n (%)	p*	Alleles R131	H131	p**
GP, n = 63	15 (23.8)	33 (52.4)	15 (23.8)	< 0.05	0.50	0.50	< 0.05
Proliferative GP, n = 19	6 (31.6)	8 (42.1)	5 (26.3)	0.22	0.53	0.47	0.27
Nonproliferative GP, n = 44	9 (20.5)	25 (56.8)	10 (22.7)	< 0.05	0.49	0.51	< 0.05
Lupus nephritis, n = 76	32 (42.1)	33 (43.4)	11 (14.5)		0.64	0.36	

* Chi-square test for trend (vs lupus nephritis). ** Chi-square test with Yates correction (vs lupus nephritis).

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ease types and the genotype distribution of the receptor was compared to that of patients with lupus nephritis, the FcγRIIa-R/R131 receptor was more frequently found in patients with lupus nephritis than in those with nonproliferative glomerulopathies only (42.1% R/R131 and 14.5% H/H131 vs 20.5% R/R131 and 22.7% H/H131, respectively). No such difference was found between lupus nephritis and proliferative glomerulopathy patients (42.1% R/R131 and 14.5% H/H131 vs 31.6% R/R131 and 26.3% H/H131; Table 2). The same results were found for the R131 allele.

In the histological analysis of FcγRIIa receptor genotype distribution, no statistically significant difference was found between lupus nephritis classes IV and V (42.9% R/R131 and 19% H/H131 vs 39.3% R/R131 and 3.6% H/H131, respectively; Table 3). As for clinical variables of lupus patients by genotype, no significant differences in epidemiologic data, proteinuria, or serum creatinine (either initial or final) were found between genotypes (Table 4).

Using serum creatinine to evaluate renal function (renal insufficiency defined as serum creatinine ≥ 1.4 mg/dl), 28 (36.8%) of the 76 lupus nephritis patients were found to have renal insufficiency by the study endpoint (Table 5). No correlation was found between the FcγRIIa-R/R131 genotype and renal insufficiency assessed in the final followup examination (with renal insufficiency: 42.9% R/R131 and 21.4% H/H131; without renal insufficiency: 41.7% R/R131 and 10.4% H/H131). Of the same 76 patients, 18 (23.6%) progressed to endstage renal disease and required dialysis. Comparing those requiring dialysis with those not requiring dialysis, no correlations with genotypes were found (dialysis: 44.5% R/R131 and 22.2% H/H131; no dialysis: 41.4% R/R131 and 12.1% H/H131). When separately analyzing the evolution of class IV and class V patients — defining PCr ≥ 1.4 mg/dl as endpoint — we found no association between polymorphism and worse outcome (Tables 6 and 7).

Table 3. Polymorphism of the FcγRIIa receptor by lupus nephritis histological class.

	Genotype, n (%)			
	R/R	R/H	H/H	p*
Class IV, n = 42	18 (42.9)	16 (38.1)	8 (19)	
Class V, n = 28	11 (39.3)	16 (57.1)	1 (3.6)	0.47

* Chi-square test for trend.

Table 5. FcγRIIa polymorphism and renal failure in lupus nephritis: all patients.

	Genotype, n (%)			
	R/R	R/H	H/H	p*
Serum creatinine				
< 1.4 mg/dl, n = 48	20 (41.7)	23 (47.9)	5 (10.4)	
≥ 1.4 mg/dl, n = 28	12 (42.9)	10 (35.7)	6 (21.4)	0.34

* Chi-square test for trend.

A study comparing immunological activity of patients with lupus nephritis and genotype showed significant correlations between FcγRIIa-R/R131 and markers of lupus activity (ANA > 1/100 and low levels of C3). No correlation was found between the FcγRIIa genotypes and antiphospholipid antibodies (Table 8).

DISCUSSION

A study by Bazílio, *et al*[13] showed that healthy controls presented genotype distributions of 21% R/R131 and 27% H/H131. This was different from the distribution reported in Japanese blood donors (> 50% H/H131 and < 10% R/R131)[16]. However, similar proportions were found in a study of French Caucasian subjects (18% R/R131 and 31% H/H131)[17], as well as in a study of Chinese subjects (16% R/R131 and 26% H/H131)[18]. Thus, our protocol did not focus on a normal population — as previously studied — but instead on patients with primary glomerulopathies. We found that such patients present a genotype distribution similar to that seen in our healthy individuals: 23.8% R/R131 and 23.8% H/H131 versus 21% R/R131 and 27% H/H131, respectively.

We found the R/R131 genotype was more prevalent in patients with lupus nephritis (42.1%) than in glomerulopathy patients (23.8%). A similar distribution was seen in relation to the R131 allele (lupus nephritis, 0.64; glomerulopathy, 0.50; $p < 0.05$).

These findings are in agreement with those obtained in studies of European and Afro-American lupus patients[11,19]. However, some investigators have stated that there is no correlation between FcγRIIa polymorphism and renal lesions[18,20].

Table 4. FcγRIIa polymorphism and clinical and laboratory findings in patients with lupus nephritis.

	Genotype		
	R/R	R/H	H/H
Age, yrs	25.70 ± 9.02	30.56 ± 10.44	26.91 ± 7.70
Sex, female:male	28:4	30:3	10:1
Initial serum creatinine, mg/dl	1.88 ± 1.86	2.11 ± 1.97	2.70 ± 2.67
Final serum creatinine, mg/dl	2.55 ± 2.62	2.06 ± 2.40	3.34 ± 2.91
Initial proteinuria, g/24 h	5.69 ± 5.63	6.22 ± 5.25	5.64 ± 2.71
Final proteinuria, g/24 h	1.69 ± 1.35	1.01 ± 1.29	1.43 ± 1.25

ANOVA; results expressed as mean ± SD (standard deviation).

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Our findings support hypotheses regarding receptor involvement in impaired clearance of immune complexes in patients with lupus nephritis. Therefore, as described by Salmon, *et al*[6], clearance of circulating immune complexes via the mononuclear phagocytic system is compromised in patients with SLE and can result in immune complex deposition and inflammatory processes in tissues and organs, especially in cases of lupus glomerulonephritis. The FcγR receptors play important roles in immune complex clearance. One of the mechanisms involved could be reduced receptor expression, together with the dysfunction described in cases of SLE[21]. Another potential mechanism is Fcγ receptor polymorphism, which has been implicated in impaired clearance of circulating immune complexes[6].

The Fcγ RIIa has 2 codominant alleles, the R131 and the H131, which differ from each other in their capacity to bind to human IgG2. The homozygous H/H131 binds efficiently with immune complexes containing IgG2, while R/R131 binds poorly. The IgG2 subclass plays an important role in the pathogenesis of lupus glomerulonephritis[3]. High levels of circulating immune complexes containing IgG2 are found in lupus patients with renal activity, although not in those presenting extrarenal activity[3]. Zuñiga, *et al*[5] demonstrated that IgG2 and IgG3 were the prevailing subclasses in immune deposits from renal biopsies obtained from lupus nephritis patients, and these subclasses were correlated with the Fcγ RIIa-R/R131 genotype.

When we considered patients with proliferative separately from those with nonproliferative glomerulopathies, we identified segregation of the R/R131 genotype in patients with proliferative forms (31.6% R/R131 and 26.3% H/H131), which is similar to the distribution observed in lupus nephritis patients. In contrast, no such segregation was found in patients with nonproliferative glomerulopathies (20.5% R/R131 and 22.7% H/H131).

Table 6. FcγRIIa polymorphism and renal failure in lupus nephritis: class V patients.

	Genotype, n (%)			
	R/R	R/H	H/H	p*
Serum creatinine				
< 1.4 mg/dl, n = 26	11 (42.3)	14 (53.9)	1 (3.8)	
≥ 1.4 mg/dl, n = 2	0	2 (100)	0	0.33

* Chi-square test for trend.

Table 7. FcγRIIa polymorphism and renal failure in lupus nephritis: class IV patients.

	Genotype, n (%)			
	R/R	R/H	H/H	p*
Serum creatinine				
< 1.4 mg/dl, n = 22	9 (40.9)	9 (40.9)	4 (18.2)	
≥ 1.4 mg/dl, n = 20	9 (45)	7 (35)	4 (20)	0.92

* Chi-square test for trend.

Our findings allow us to make inferences regarding common immunopathological mechanisms involved in the glomerular proliferation seen in both lupus nephritis and primary glomerulopathy. In the group of patients with proliferative glomerulopathies, which included those with MPGN, mesPGN, and IgAN (all presenting low or nonexistent levels of circulating IgG immune complexes), clearance of circulating immune complexes is probably irrelevant. The most likely mechanism is direct stimulation of tissue proliferation with the participation of this receptor. In support of this hypothesis, Zuñiga, *et al*[5] recently described the role played by inflammatory activation of polymorphonuclear neutrophils and monocytes by C-reactive protein (CRP) binding with the FcγRIIa-R/R131 receptors, resulting in strong cellular activation and consequent liberation of cytokines, free radicals, and proteases. Therefore, any CRP present in the glomerular immune deposit would exacerbate the damage. The authors also found positive immunostaining for CRP, which, although faint in samples from MPGN and acute diffuse glomerulonephritis, was pronounced in lupus nephritis. Other investigators have also emphasized the importance of CRP, which binds to C1q and activates the classic complement pathway, identifying it as an additional factor contributing to tissue damage[22].

Our results from the histological analysis of SLE patients (WHO classification) showed genotype distribution to be similar in both class IV patients (42.9% R/R131 and 19% H/H131) and class V patients (39.3% R/R131 and 3.6%

Table 8. FcγRIIa polymorphism and lupus activity measures.

Genotype	ANA > 1/100, n (%)	Anti-dsDNA-positive, n (%)	Low C3, n (%)	Antiphospholipid-positive, n (%)
R/R	23 (47.9)	17 (47.2)	23 (52.3)	8 (38.1)
R/H	23 (47.9)	17 (47.2)	18 (40.9)	10 (47.6)
H/H	2 (4.2)	2 (5.6)	3 (6.8)	3 (14.3)
p	< 0.05	0.09	< 0.05	0.89

Results of chi-square test for trend. ANA: antinuclear antigen; anti-dsDNA: anti-double-stranded DNA; C3: complement component 3.

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H/H131). Sato, *et al*[23] evaluated 69 biopsies from patients with lupus nephritis and found no correlation between FcγRIIa receptor polymorphism and lupus nephritis histology, although most patients (n = 32) were categorized as class I or II, with only 23 class III and class IV patients and 13 class V patients. Similarly, Dijstelbloem, *et al*[24] found no prevalence of the FcγRIIa-R/R131 genotype in patients with class III or class IV lupus nephritis. The number of class V patients was too small for comparisons (n = 7).

We also studied genotype distribution in relation to the indexes of lupus nephritis activity and chronicity established by the WHO, and found no segregation by genotype. Zuñiga, *et al*, however, found that lupus nephritis patients presenting chronicity indexes greater than 4 in renal biopsy results also had the FcγRIIa-R/R131 genotype more frequently in comparison to the predicted values (41% R/R131 and 5% H/H131 vs 25% R/R131 and 25% H/H131).

Our renal function findings suggest that there was no genotype segregation that might determine severity of lupus nephritis at the onset of the study (initial serum creatinine) or over the course of the study (serum creatinine measured at the final followup examination). We also found there was no genotype segregation associated with disease progression to chronic renal insufficiency requiring dialysis. Manger, *et al*[12] also observed a similarity in renal function among the various genotypes represented in the group of lupus patients they studied. They observed an early-onset reduction in renal function among patients with the FcγRIIa-R/R131 genotype. Similarly, Song, *et al* found no relationship between genotype and creatinine clearance[10]. Thus, no relationship between clinical patterns of patients with lupus and FcγRIIa receptor polymorphism could be established in our study. The receptor seems only to influence predisposition to nephropathy, but not its evolution. Other SLE factors, such as the complement system and other IgG subclasses, can also alter the course of disease in these patients.

Comparing immunological activity in lupus nephritis patients according to genotype, we found significant correlations between FcγRIIa-R/R131 genotype and the lupus activity markers (ANA > 1/100 and low C3). Manger, *et al*[12] also reported a relationship between FcγRIIa receptor polymorphism and immunological activity, showing correlations between the FcγRIIa-R/R131 genotype and hypocomplementemia and the presence of antiribonucleoprotein antibody.

In conclusion, abnormal distribution of FcγRIIa alleles, especially the FcγRIIa-R/R131 genotype, may contribute to the pathogenesis and development of renal disease in SLE. The association seems to be related to the proliferative component resulting from the presence of immune complexes in the disease. We identified no relationship between polymorphism and clinical evolution of patients; however, we did find that polymorphism affects markers of immune activity.

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