

Role of the Fc γ Receptor IIa Polymorphism in Susceptibility to Systemic Lupus Erythematosus and Lupus Nephritis

A Meta-Analysis

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Objective. To assess the impact of the Fc γ receptor type IIa (Fc γ RIIa)–R/H131 polymorphism on the risk for systemic lupus erythematosus (SLE) and development of lupus nephritis.

Methods. A meta-analysis was performed based on the Medline and Embase databases (last retrieval August 2001), assessment of bibliographies of pertinent articles, and additional data gathered after contact with primary investigators.

Results. A total of 25 comparisons from 17 studies involving R/H131 genotyping of 1,405 patients with lupus nephritis, 1,709 SLE patients without nephritis, and 2,580 non-SLE controls were included. No association between RR genotype and risk of lupus nephritis relative to both other genotypes (odds ratio [OR] 1.05, 95% confidence interval [95% CI] 0.88–1.27) was demonstrated in the total meta-analysis or in any racial subgroup. The RR genotype was more frequent in SLE patients as a whole (OR 1.30, 95% CI 1.10–1.52) and in SLE patients without nephritis (OR 1.27, 95% CI 1.04–1.55) compared with disease-free controls. A potential dose–response relation between the R131 allele and the risk of SLE was also identified, with an OR of 1.23 for RR versus RH (95% CI 1.03–1.46). The OR was 1.55 for RR versus HH (95% CI 1.21–1.98). There was no

significant heterogeneity between racial subgroups. The population-attributable fractions of SLE cases due to the Fc γ RIIa-R131 allele were 13%, 40%, and 24% in subjects of European, African, and Asian descent, respectively.

Conclusion. The Fc γ RIIa-R/H131 polymorphism represents a significant risk factor for SLE but has no clear effect on susceptibility for lupus nephritis.

Genetic polymorphisms of the receptors for the Fc portion of IgG (Fc γ R) have been proposed as heritable risk factors for susceptibility to infectious and autoimmune diseases (1,2). Best studied is the biallelic polymorphism of the low-affinity Fc γ RIIa stimulatory isoform (3). Fc γ RIIa displays codominant variants that bear either an arginine or a histidine at amino acid position 131 in the extracellular domain (R131 and H131, respectively). These variants differ in their ability to bind human IgG2. H131 is the high-binding allele, R131 is low-binding, and heterozygotes have intermediate function (4). Because IgG2 is a poor activator of the classical complement pathway, the H131 allele seems essential for handling IgG2 immune complexes (ICs).

Given the potential consequences of the Fc γ RIIa-R/H131 polymorphism for IC clearance, it has been hypothesized that the Fc γ RIIa-R131 allele may confer susceptibility to systemic lupus erythematosus (SLE) (4), the prototypic human IC-mediated autoimmune disease. It has also been hypothesized that this polymorphism may affect the incidence of specific manifestations of SLE, particularly lupus nephritis (4–9), or may negatively influence disease outcome (10,11).

Despite early hypothesis-generating investigations suggesting that the R131 allele may be related to lupus nephritis in particular (4,5), subsequent investiga-

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tions (7,10–19) performed in several ethnic groups yielded apparently inconclusive results regarding the magnitude (or even the presence) of disease susceptibility conferred by this polymorphism. In most such studies, the sample size was limited. Moreover, individual studies did not have enough power to detect dose–response relationships and determine whether RR homozygotes differ from RH heterozygotes in terms of disease susceptibility. Given the amount of accumulated data, a quantitative synthesis of the evidence using rigorous methods has become necessary (20). To address these issues, we conducted a comprehensive meta-analysis of results from all available studies regarding an association between the Fc γ RIIa-R/H131 polymorphism and development of SLE and/or lupus nephritis.

METHODS

Identification and eligibility of relevant studies. We considered all controlled studies that examined the association of the Fc γ RIIa-R/H131 polymorphism with SLE and/or lupus nephritis. Sources included Medline and Embase, with the last search occurring in August 2001. The search was based on combinations of “systemic lupus erythematosus,” “rheumatic diseases,” “connective tissue disease,” “autoimmune disease,” “polymorphism,” “allele,” “genetics,” “Fc receptor,” and “Fc γ receptor.” Nonfamilial studies were eligible if they had determined the distribution of Fc γ RIIa alleles in both SLE patients and a control group of individuals without SLE. Studies comparing the frequency of Fc γ RIIa alleles among SLE patients with nephritis and SLE patients without nephritis were also eligible. The references of retrieved articles were also screened.

The search included reports in English, French, German, or Italian and was complemented by contact with experts, to avoid publication bias. We also communicated with the investigators of original studies, to obtain clarifications and any additional data that were missing from the published reports. The contributing investigators were asked to comment on the final data synthesis.

Data extraction. Two investigators independently extracted the data. The following information was sought from each study: first author’s name, journal and year of publication, country of origin, type of study design, racial ancestry of the study population (European descent [including Hispanics], African descent, and Asian descent), selection of control groups, criteria used for the diagnosis of SLE, definition of nephritis, demographics, total sample size, and the total number of SLE patients (including those with nephritis and those without nephritis) and control subjects for each Fc γ RIIa genotype. Furthermore, we examined whether matching had been used, whether it had been specifically mentioned that personnel who performed the genotyping were blinded to the clinical status of subjects, and whether the genotyping method had been validated. Finally, when data from an individual study were reported separately for populations that were of

similar racial descent but from different geographic locations, the division of data was sustained.

Meta-analysis methods. The meta-analysis examined the contrasts of SLE patients with lupus nephritis versus those without nephritis, patients with SLE versus non-SLE controls, and SLE patients without nephritis versus non-SLE controls. The following key genotype contrasts were evaluated: RR versus RH and HH combined, RR versus RH, and RR versus HH. The first contrast corresponds to recessive genetic modeling for the putative effect of the R131 allele, the second allows assessment of whether there is a dose–response relationship between the R131 allele and SLE or lupus nephritis, and the third examines the 2 homozygous states. Estimates for the contrast of RH versus HH were consistent with those of the other analyses (details not shown). The odds ratio (OR) was used as the metric of association, because these studies typically used case–control designs.

For each comparison and genetic contrast, we estimated between-study heterogeneity using the chi-square–based Q statistic (21). Heterogeneity was considered significant at a *P* value less than 0.10. Study-specific data were combined using both fixed (22) and random effects (23) models. The latter models incorporate between-study heterogeneity and provide wider confidence intervals (CIs) when results of the constituent studies differ among themselves. In the absence of between-study heterogeneity, the 2 methods provide identical results, although random effects models are more appropriate when between-study heterogeneity is present. Unless stated otherwise, random effects estimates are provided.

We performed cumulative meta-analysis and recursive cumulative meta-analysis (24–26) to evaluate whether the combined OR changed over time as more data on each comparison and contrast were accumulated. Inverted funnel plots (27) were examined as diagnostics for heterogeneity related to the sample size of each study. Subgroup analyses estimated subgroup-specific ORs defined by race. Subgroup estimates were tested for heterogeneity between subgroups. Finally, sensitivity analyses were limited to those studies that used specific definitions of disease and methods of genotyping.

Attributable fraction. The proportion of SLE cases attributed to the R131 allele (attributable fraction) is given as

$$\frac{[PR_1 \times (R_1 - 1)] + [PR_2 \times (R_2 - 1)]}{1 + [PR_1 \times (R_1 - 1)] + [PR_2 \times (R_2 - 1)]}$$

where PR_1 and R_1 are the prevalence of and summary relative risk associated with RH heterozygosity (as compared with HH homozygosity), and PR_2 and R_2 are the prevalence of and summary relative risk associated with RR homozygosity (as compared with HH homozygosity) (28). Because SLE is rare in the general population, the case–control-derived OR is an excellent approximation of the population relative risk (29). Genotype prevalence data are derived from the included study comparisons. Separate attributable fraction values were obtained for subjects of different racial descent.

Software. Analyses were conducted using SPSS version 10.0 (SPSS, Chicago, IL) and Meta-Analyst (Joseph Lau, Boston, MA). *P* values are 2-tailed.

Table 1. Characteristics of studies included in the meta-analysis*

Reference/year, country	Ethnic group	No. of SLE patients		No. of non-SLE controls	R allele frequency		
		Total	Analyzed (nephritis/non-nephritis)		Nephritis	Non-nephritis	Non-SLE controls
Salmon et al (4)/1996, US	African American	257	257 (117/140)	139	0.64	0.58	0.47
	Caucasian American	266	266 (115/151)	103	0.51	0.52	0.50
Botto et al (12)/1996, UK	English	215	215 (31/184)	259	0.50	0.57	0.55
	Afro-Caribbean	70	70 (16/54)	77	0.59	0.63	0.55
	Chinese	46	46 (not provided)	49	Not provided	Not provided	0.31
Smyth et al (13)/1997, UK	English/other Caucasian†	81	81 (19/62)	66	0.47	0.60	0.53
	Greek	42	42 (19/23)	52	0.50	0.46	0.38
	Korean	73	73 (44/29)	64	0.52	0.48	0.37
Song et al (6)/1998, Korea	Korean	108	108 (47/61)	187	0.53	0.40	0.49
Manger et al (10)/1998, Germany	German	70	70 (45/25)	87	0.53	0.54	0.47
Koene et al (14)/1998, Netherlands	Dutch/American	81	76 (52/24)	217	0.18	0.25	0.20
Hatta et al (15)/1999, Japan	Japanese	195	195 (71/124)	283	0.68	0.54	0.55
Norsworthy et al (7)/1999, UK	Multinational, mainly Caucasian						
Yap et al (17)/1999, Malaysia	Chinese	175	175 (122/53)	108	0.41	0.40	0.45
	Malay	50	50 (23/27)	50	0.26	0.41	0.37
Oh et al (18)/1999, US‡	African American	77	63 (46/17)	69	0.59	0.44	0.57
Dijstelbloem et al (11)/2000, Netherlands	Dutch	230	230 (108/122)	154	0.52	0.54	0.47
Michel et al (31)/2000, France	French	80	80 (23/57)	183	0.46	0.61	0.44
D'Alfonso et al (19)/2000, Italy	Italian	172	84 (25/59)	87	0.38	0.43	0.44
Sato et al (32)/2001, Japan	Japanese	90	90 (83/7)	96	0.56	0.50	0.38
Zuniga et al (8)/2001, US	Mexican/Central American	67	67 (46/21)	53	0.63	0.64	0.53
Seligman et al (33)/2001, US	Caucasian American	286	262 (76/186)	–	0.55	0.54	–
	Mexican	116	103 (48/55)	–	0.55	0.60	–
	Asian	101	97 (57/40)	–	0.48	0.51	–
	African American	71	61 (30/31)	–	0.50	0.56	–
Yun et al (9)/2001, Korea	Korean	300	299 (142/157)	197	0.41	0.33	0.33

* For the systemic erythematosus (SLE) patients who were analyzed, both genotype and clinical information was available.

† Other Caucasian subjects included 13 Irish, 20 from Southern/Eastern Europe, 2 Australian, and 1 South African.

‡ In this study, a definition of nephritis was not provided; for the purposes of our analysis, we selected only patients with proteinuria.

RESULTS

Characteristics of eligible studies. Twenty-eight comparisons from 20 studies addressing the relationship between FcγRIIa-R/H131 and susceptibility to SLE and/or the development of lupus nephritis were identified (4–19,30–33). Three reports (5,16,30) were excluded because of extensive overlapping with other included publications. In addition, 13 patients labeled as “other” ethnicity (not specified) in one study (33) were excluded from the analysis. The meta-analysis therefore included 25 (4,6–15,17–19,31–33) eligible comparisons; 21 of these comparisons (4,6–15,17–19,31,32) had data evaluating the relationship between the FcγRIIa-R/H131 polymorphism and susceptibility to SLE, and 24 (4,6–15,17–19,31–33) had data on lupus nephritis versus SLE without nephritis (Table 1).

A large number of ethnic groups were represented (Table 1). In all but 2 studies (13,18), SLE patients fulfilled the American College of Rheumatology (ACR) 1982 revised criteria (34). One of these studies

(13) did not clarify the criteria used for the diagnosis of SLE, and the other (18) included patients based on a clinical diagnosis (96% of them also met ≥ 4 of the ACR criteria). Most studies uniformly used the relevant ACR criterion for the definition of renal disease, but some alternative definitions, such as biopsy-proven lupus nephritis (12,31), or certain laboratory findings, alone (18,32) or in common with specific histologic features on renal biopsy (7,8,19,33), were also used. One study (17) did not clarify which criteria were utilized.

In 5 comparisons (8,14,15,17,32), patients with lupus nephritis comprised $>60\%$ of the total SLE cohort, suggesting overselection of nephritis cases. Variable case-to-control ratios were used in the eligible comparisons. With 2 exceptions (17,33), no study provided details about whether any matching of cases and controls (other than by race) had been performed. No study indicated whether the personnel who performed the genotyping were blinded to the clinical status of patients. For 19 comparisons, the genotyping method

Table 2. Summary odds ratios (ORs) for the association of systemic lupus erythematosus (SLE) or lupus nephritis with *FcγRIIA*-specific genotypes (random effects model)

Comparison group	No. of comparisons	RR vs. RH + HH		RR vs. RH		RR vs. HH	
		OR (95% confidence interval)	No. of subjects	OR (95% confidence interval)	No. of subjects	OR (95% confidence interval)	No. of subjects
SLE nephritis vs. SLE without nephritis	24	1.05 (0.88–1.27)	3,114	1.01 (0.84–1.22)	2,369	1.07 (0.81–1.42)	1,550
European descent	13	0.96 (0.73–1.26)	1,803	0.96 (0.74–1.24)	1,423	0.94 (0.65–1.35)	901
African descent	4	1.12 (0.75–1.69)	451	1.02 (0.66–1.57)	376	1.47 (0.70–3.09)	232
Asian descent	7	1.28 (0.84–1.95)	860	1.20 (0.77–1.88)	570	1.23 (0.69–2.20)	417
SLE vs. disease-free controls	21	1.30 (1.10–1.52)	5,217	1.23 (1.03–1.46)	3,724	1.55 (1.21–1.98)*	2,717
European descent	11	1.27 (1.07–1.50)	2,952	1.24 (1.04–1.49)	2,235	1.38 (1.09–1.75)	1,533
African descent	3	1.19 (0.63–2.23)*	675	1.00 (0.55–1.83)*	542	1.95 (1.00–3.81)	354
Asian descent	7	1.28 (0.83–1.98)	1,590	1.13 (0.67–1.90)*	947	1.64 (0.81–3.32)†	830

* $0.01 < P < 0.10$ for heterogeneity.

† $P < 0.01$ for heterogeneity.

had previously been validated ($n = 8$) or was validated during the study, either by sequencing or by comparing it with a previously validated method ($n = 11$). In 6 comparisons (8,14,17,19,32), there was no specific reference to validation, even though a novel or modified assay was used for genotype analysis.

In total, the meta-analysis included genotyping of 1,405 SLE patients with nephritis, 1,709 SLE patients without nephritis, and 2,580 non-SLE controls. The H131 allele was more highly represented among non-SLE controls of Asian descent than among those of other racial descent (Table 1); frequencies were 0.45–0.62 in non-SLE controls of European descent (4,7,8,10–14,19,31), 0.43–0.53 in those of African descent (4,12,18), and 0.55–0.80 in those of Asian descent (6,9,12,15,17,32). Overall, the prevalence of RR homozygosity was 26%, 29%, and 9% in the 3 racial subgroups, respectively. The prevalence of RH heterozygosity in these subgroups was 48%, 45%, and 46%, respectively. The distribution of genotypes in all disease-free control groups was always consistent with Hardy-Weinberg equilibrium (all P values were >0.10).

Meta-analysis. Overall effects. We found no evidence of an association between the RR genotype and the risk of lupus nephritis (Table 2 and Figure 1). No association was discerned when RR was contrasted with RH or HH separately. When only the 14 comparisons (2,025 subjects) that met the ACR criterion for the definition of nephritis were analyzed, the results did not change substantially. The random effects OR estimate for the risk of developing lupus nephritis was 0.99 in RR homozygous patients compared with both other genotypes combined (95% CI 0.81–1.23), with no evidence of between-study heterogeneity ($P = 0.75$). The results

were also similar when we excluded studies that lacked fully documented validation of the genotyping methods used. Among the 18 comparisons that remained following this exclusion, the OR for nephritis was 1.04 (95% CI 0.84–1.29) in RR homozygotes versus other subjects (no significant heterogeneity).

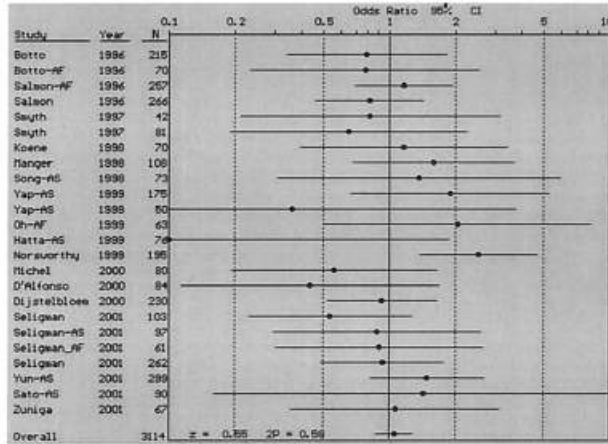
In contrast, we documented a significant association between the homozygous RR genotype and the risk of developing SLE ($P = 0.0016$) relative to both other genotypes combined, with no evidence of between-study heterogeneity ($P = 0.2$) (Table 2 and Figure 1). Moreover, the summary estimates for RR versus RH suggested the presence of a dose effect. R131 homozygotes were at greater risk for SLE compared with RH heterozygotes (OR 1.23). A maximal effect was seen when RR homozygotes were contrasted with HH (OR 1.55), while the OR for RH versus HH was 1.28. As expected, we also found consistently significant skewing toward RR homozygosity in SLE patients without nephritis when compared with disease-free controls (OR for RR versus other genotypes 1.27, 95% CI 1.04–1.55; $P = 0.15$ for heterogeneity; data not shown). The results were very consistent when we excluded studies that lacked recorded validation of the genotyping methods used (OR 1.36 for RR versus other genotypes [95% CI 1.12–1.64; no significant heterogeneity]).

Racial subgroup analyses: lupus nephritis. No differences in genotype distribution between SLE patients with nephritis and those without nephritis were observed in any of the racial subgroups. There was no significant heterogeneity between races in this regard (Table 2).

Racial subgroup analyses: SLE susceptibility. The RR genotype was clearly overrepresented among SLE patients of European descent. Such subjects also showed

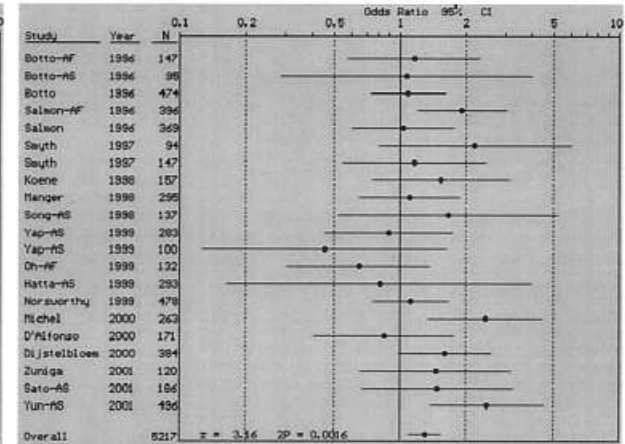
SLE Nephritis vs SLE without Nephritis

RR vs RH + HH

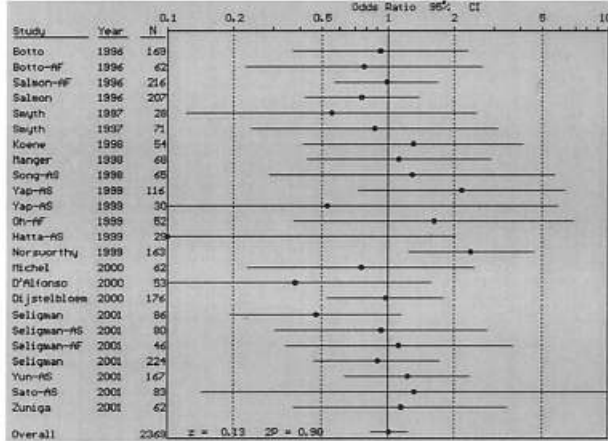


SLE vs Disease-free Controls

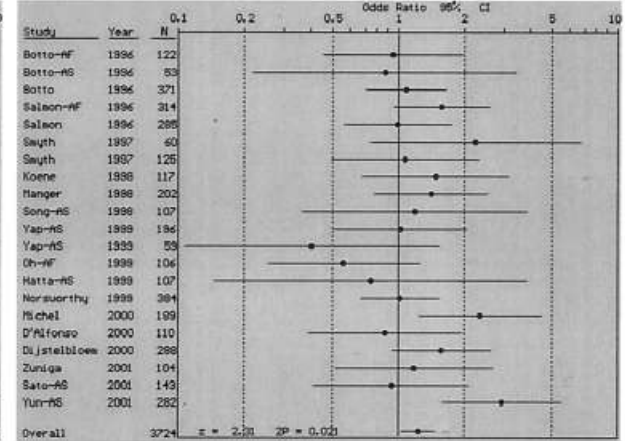
RR vs RH + HH



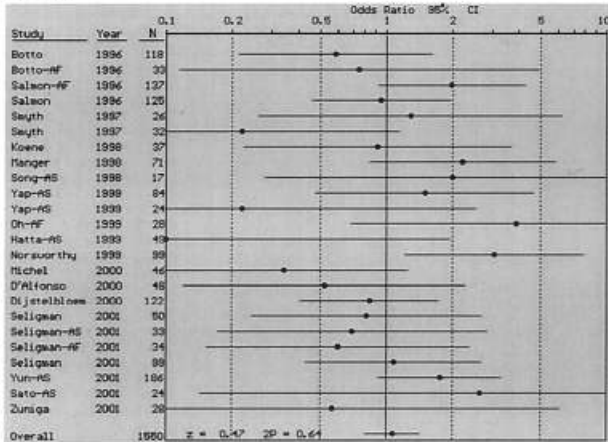
RR vs RH



RR vs RH



RR vs HH



RR vs HH

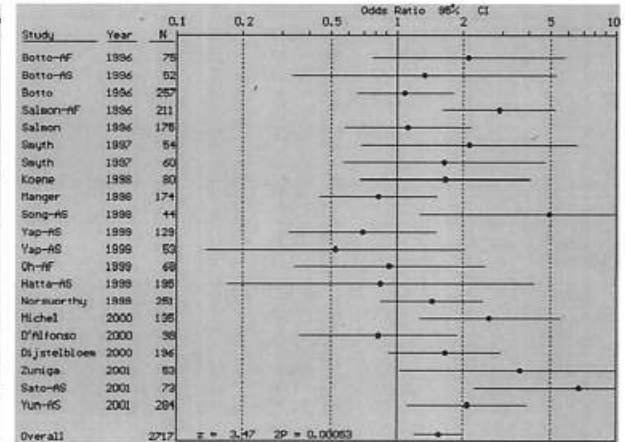


Figure 1. Meta-analysis for effects of Fcγ receptor IIa-R/H131 polymorphism on the risk of lupus nephritis (left) and systemic lupus erythematosus (SLE; right). Comparisons from individual studies are shown. AF signifies African descent, AS signifies Asian descent; all other comparisons are for subjects of European descent. For each comparison, a point estimate of the odds ratio (OR) and the accompanying 95% confidence intervals (95% CIs) are presented. Also shown are the summary random effects estimates for each comparison along with the respective 95% CIs as well as final Z scores and the respective 2-tailed P values for the summary ORs. Values >1 denote an increased risk.

a more typical escalation of risk with the RR compared with the RH genotype. An escalation of risk was less clear in subjects of African or Asian descent, although there was no statistically significant heterogeneity between the 3 racial subgroups for any of the examined contrasts (Table 2). However, there was considerable between-study heterogeneity within some of the comparisons involving subjects of African and Asian descent. In particular, among subjects of African descent, between-study heterogeneity was only moderate and involved mainly the RR genotype relative to RH and HH combined ($P = 0.05$). The RR versus HH contrast showed an SLE susceptibility effect for RR homozygotes without any between-study heterogeneity (Table 2). Likewise, RH heterozygosity conferred a much higher risk for SLE than did HH homozygosity (OR 1.87, 95% CI 1.24–2.83), without any between-study heterogeneity. No escalation of risk with RR versus RH was seen.

In subjects of Asian descent, both RR and RH were associated with a trend toward increased susceptibility to SLE as contrasted with HH, but between-study heterogeneity was significant. The 2 comparisons reported by Yap et al (17), which demonstrated OR <1 , contrasted sharply with the study by Sato et al (32), which showed a very strong predisposition for SLE among Japanese patients with this polymorphism. Yap et al may have made some error in genotyping, because they also reported a very low prevalence of the H131 allele compared with the prevalence reported in all other studies of subjects of Asian descent, and their method of genotyping had not been validated.

Other bias diagnostics. In both cumulative meta-analysis and recursive cumulative meta-analysis, no evidence was found that early studies in the field had overestimated the magnitude of the effect of the polymorphism on SLE susceptibility, with the exception of the very first preliminary study (5), which had shown a very large odds ratio. Otherwise, the magnitude of the effect had been stable over time. Similarly, inverted funnel plots showed no evidence of bias differentiating the magnitude of the observed effect between small and large studies.

Attributable fraction. The random effects relative risk for RR versus HH and for RH versus HH was 1.38 and 1.12, respectively, in subjects of European descent, 1.95 and 1.87, respectively, in subjects of African descent, and 1.64 and 1.58, respectively, in subjects of Asian descent. The estimated attributable fraction for the R131 allele was 13%, 40%, and 24% in the 3 racial subgroups, respectively.

DISCUSSION

This meta-analysis documents that common genetic variants of Fc γ R that alter IgG binding capacity are important determinants of susceptibility to SLE. Overall homozygosity for R131, the low-binding allele of the *Fc γ RIIA* gene, was associated with a 1.30-fold greater risk for the development of SLE compared with both other genotypes combined. The effect of the R131 allele on the risk for lupus seemed also to have a dose–response character, at least in subjects of European descent. Our results do not support a role for this polymorphism as far as susceptibility to lupus nephritis is concerned. The evidence is most conclusive among subjects of European descent, but data from subjects of African and Asian descent are also consistent with this interpretation.

Predisposition to complex autoimmune diseases such as SLE is probably affected by a variety of genetic and environmental factors (35). The identification of susceptibility alleles remains difficult because of extensive heterogeneity and possible epistatic interaction among the multiple genes required for disease development. Both linkage studies (36) and association studies require careful replication. This meta-analysis documents a consistent role for the Fc γ RIIa-R/H131 polymorphism in predisposition to SLE. Even though the summary OR estimates suggest only a modest genetic effect, the relevance of this effect may be appreciable at the population level, considering that R131 is a common variant. The proportion of SLE cases attributed to this polymorphism is estimated at 13% for subjects of European descent. The estimated proportions of SLE cases among subjects of African and Asian descent are even greater; however, because of the limited data, the 95% CIs of the relative risks (that are used to calculate attributable fractions) do not exclude the possibility of no effect at all.

For a randomly selected individual, the absolute (additive) risk for SLE that is conferred by the R131 allele is small. Assuming that the average risk for developing SLE is ~ 1 in 2,000, a 30% increase corresponds to an absolute risk increase of 3 in 20,000. However, the overall effect of this polymorphism at the population level is considerable. Although the vast majority of individuals with the R131 allele will not develop SLE, a clinically meaningful proportion of SLE cases may be attributed to this polymorphism. The importance of the Fc γ RIIa-R/H131 polymorphism for susceptibility to SLE at the population level may also be viewed against traditional genetic factors identified in the past

(37). When compared with extremely rare genetic markers, common markers are more important at the population level, even if they exert only modest effects on disease susceptibility. For example, ~50% of Caucasian SLE patients have HLA-DR3, compared with 25% of the general population (38). This corresponds to an attributable fraction of ~33% at the population level. Conversely, hereditary homozygous deficiencies of early complement components are strongly associated with SLE (39), but they are extremely rare. The most common C2 homozygous deficiency occurs in 1 of every 10,000–40,000 individuals (40) and ~1 of every 10 affected persons develops SLE (39); thus, the attributable fraction is <1%.

One potential mechanism by which the R131 allele confers risk for SLE could be impaired binding of IgG2-containing ICs, defective clearance of these circulating ICs, increased tissue deposition, and accelerated organ damage (3). However, if this mechanism is the most important one involved, a maximal effect on lupus nephritis—an IC-mediated manifestation—might be expected (41). Nevertheless, the major IgG subclasses in immune deposits of proliferative glomerulonephritis are IgG1 and IgG3 rather than IgG2 (42,43), which may explain the lack of a stronger association between lupus nephritis and the Fc γ RIIa-R/H131 polymorphism.

Alternative pathogenetic pathways may be involved as well. Some evidence (44,45) suggests that on phagocytic cells, Fc γ RIIa may be the major receptor for C-reactive protein (CRP) and one of the receptors for the serum amyloid P (SAP) component. Because these 2 molecules may function as opsonins for nuclear antigens (44,45), the handling of nucleosomes that are bound to either CRP or SAP may also be influenced by allelic polymorphisms (46). This theory has been challenged: an intact Fc region of the antibody used for detection of CRP binding to Fc γ RIIa on phagocytic cells may be important for this binding (47). However, further evidence seems to support the theory (48).

The effect of the Fc γ RIIa-R/H131 polymorphism on the risk of SLE may have a dose–response character, with an escalation of SLE risk between RR homozygotes and RH heterozygotes. A dose–response effect is consistent with *in vitro* experiments showing that RR homozygotes have poor phagocytosis of IgG2 model ICs, RH heterozygotes have intermediate phagocytic capacity, and optimal IgG2 handling occurs only in HH homozygotes (4).

Some limitations of this study should be discussed. First, although we found no association with lupus nephritis, the meta-analysis pertains only to sus-

ceptibility for this manifestation and does not exclude the possibility that the Fc γ RIIa-R/H131 polymorphism may influence the clinical course of nephritis (6,10), other disease manifestations (9,10), or even the course of SLE (10,11). More data are needed to clarify these issues. Second, bias is possible in a meta-analysis. However, formal bias diagnostics did not suggest such problems. Some studies used modified genotyping methods without reporting full validation; however, similar results were obtained when such studies were excluded. The meta-analysis should also help sensitize investigators conducting research in the burgeoning field of SLE genetics to methodologic issues. For example, it is important to ensure that blinding procedures are used in such assessments and to avoid bias by carefully defining selection criteria and then making sure that all selected patients are genotyped. Overall, although it is unlikely that bias would have affected our conclusions, attention to subtle study design and study reporting issues (49) may be important in future research in the field.

In fact, there is accumulating evidence that besides the Fc γ RIIa-R/H131 polymorphism, other functional Fc γ R polymorphisms may be important for SLE susceptibility or disease phenotype. For example, the Fc γ RIIIa-F/V158 has been studied recently (8,11,14–16,18,33,50) for its potential influence on disease expression, because the F158 isoform binds IgG1 and IgG3 with lower affinity than does the V158 isoform (50,51). However, the relative importance of interactions among alleles and the potential role of linkage disequilibrium between Fc γ R genes on chromosome 1q21–24 are not well known. Future association studies should simultaneously analyze Fc γ R haplotypes, along with other candidate genes, to define a genetic risk profile for the disease. Genetic variants in totally different genes may also be at least as relevant as Fc γ R variants.

The meta-analysis approach offers a powerful method to organize and synthesize information on subtle yet clinically important genetic effects (52,53). In individual studies, ORs in the range of 1.2–1.5 are very difficult to detect or confirm unless thousands of subjects are genotyped. A consortium approach (20,54), with synthesis of the accumulated data through a comprehensive meta-analysis, may be useful for clarifying the role of additional polymorphisms in SLE genetics.

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