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The R-H polymorphism of Fcγ receptor IIa as a risk factor for systemic lupus erythematosus is independent of single-nucleotide polymorphisms in the interleukin-10 gene promoter.

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To the Editor:

Genome scans have indicated the relevance of genes on chromosome 1 in the development of systemic lupus erythematosus (SLE) (1–3). Of interest are potential susceptibility loci at 1q23 and 1q31, because these include the candidate polymorphic genes for Fcγ receptors (FcγR) and interleukin-10 (IL-10) (4,5). A number of association studies have shown that polymorphisms of FcγRIIa and FcγRIIIa influence the development of SLE and lupus nephritis (6).

Indeed, bi-allelic variants of these receptors alter their capacity to interact with human IgG and influence the clearance of immune complexes (6,7). Single-nucleotide polymorphisms (SNPs) in the IL-10 gene promoter have also been associated with lupus nephritis, as well as with neuropsychiatric SLE and the production of autoantibodies (8,9). Because these SNPs are within putative transcription factor binding sites and regulatory regions, they are believed to affect innate IL-10 production at the transcriptional level (10).

The physical distance between FcγR and IL-10 loci on chromosome 1 is probably too large for these genes to be in linkage disequilibrium in a control population. However, the functional implications of FcγR and IL-10 genes in SLE suggest that selection pressure might act on these 2 loci in patients. Selective coevolution may, indeed, lead to loss of independence between FcγR and IL-10 genes, as observed among first-degree relatives of patients with meningococcal disease (11). To test this hypothesis in SLE, we genotyped 180 Caucasian patients and 163 Caucasian controls (described in refs. 7, 9, and 12) for the R/H polymorphism of FcγRIIa, the V/F polymorphism of FcγRIIIa, and SNPs at positions - 1082, -819, and -592 in the IL-10 gene (methods described in refs. 7, 9, and 12). Seventy-seven patients (43%) had developed (symptoms of) nephritis between the time of diagnosis and the current study (7,9,12). In our analysis, we focused primarily on FcγRIIa-R/H131 and IL-10 -1082, because these 2 polymorphic sites appear to be functionally most relevant in SLE (6–9).

As shown in Table 1, FcγRIIa and IL-10 -1082 genotype combinations were randomly distributed in controls and patients with SLE ($X^2 = 7.84$, $P = 0.098$, and $X^2 = 3.20$, $P = 0.53$, respectively). In accordance with previous studies (6,7), we found a trend toward enrichment of the homozygous FcγRIIa-R/R131 genotype in patients compared with controls (55 of 180 versus 36 of 163, respectively; odds ratio [OR] 1.55, 95% confidence interval [95% CI] 0.95–2.53, $P = 0.076$). In contrast, we did not observe an association between any of the IL-10 -1082 genotypes and susceptibility to SLE. Notably, the observed trend toward skewing of the homozygous FcγRIIa-R/R131 genotype in patients could still be observed after correction for IL-10 _1082 genotypes (adjusted OR 1.54, 95% CI 0.94–2.50, P = 0.085). There was neither a correlation nor a synergistic effect between any of the other FcγR or IL-10 promoter genotypes and susceptibility to SLE. In a

separate analysis on the development of lupus nephritis, we found no additional associations (data not shown).

[table 1]

Our findings confirm that the R/H polymorphism of FcγRIIa is a minor determinant in susceptibility to SLE, as described previously in a partly overlapping study population (7). Moreover, we demonstrate that this genetic predisposition is not influenced by SNPs in the IL-10 gene promoter. Several other association studies have previously indicated the relevance of the low-binding FcγRIIa-R131 allele in the development of SLE (6). Indeed, one study showed that patients homozygous for this allele had less capability to interact with immune complexes in vivo, as demonstrated by a prolonged half-life of IgG-coated erythrocytes in the blood (7). Our study shows SNPs in the IL-10 gene promoter to be less relevant for the development of SLE and lupus nephritis. This finding is in accordance with a recent study of a large group of Caucasian patients with SLE (13). However, heritability for IL-10 production is estimated to be 75% (14), and production of IL-10 is increased in healthy relatives of patients with SLE compared with unrelated controls (12,15). These findings support the notion that other regulatory elements in the IL-10 gene influence IL-10 production, and possibly have relevance in SLE (16). Whether there are synergistic effects between such elements and FcγR polymorphisms remains to be determined.

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TABLES

Table 1. Distribution of FcγRIIa and IL-10 −1082 genotypes in Caucasian patients with SLE and Caucasian controls*

	FcγRIIa			
	R/R131	R/H131	H/H131	Total
Controls				
IL-10 −1082				
AA	9 (6)	22 (13)	10 (6)	41 (25)
GA	18 (11)	40 (25)	14 (9)	72 (44)
GG	9 (6)	20 (12)	21 (13)	50 (31)
Total	36 (22)	82 (50)	45 (28)	163 (100)
SLE patients				
IL-10 −1082				
AA	17 (9)	21 (12)	6 (3)	44 (24)
GA	26 (14)	46 (26)	22 (12)	94 (52)
GG	12 (7)	23 (13)	7 (4)	42 (23)
Total	55 (31)	90 (50)	35 (19)	180 (100)

* Values are the no. (%) of patients. FcγR = Fcγ receptor; IL-10 = interleukin-10; SLE = systemic lupus erythematosus.