Response to Intravenous Cyclophosphamide Treatment for Lupus Nephritis Associated with Polymorphisms in the *FCGR2B-FCRLA* Locus

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ABSTRACT. Objective. Cyclophosphamide (CYC) is an immunosuppressant drug widely used to treat various diseases including lupus nephritis, but its efficacy highly varies from individual to individual. This pharmacogenomics association study searched for genetic variations associated with CYC efficacy.
Methods. Genome-wide association scan was performed for 109 Korean patients with systemic lupus erythematosus with lupus nephritis (classes III–V) who received intravenous CYC induction therapy. Genetic differences between responders and nonresponders were examined using Cochran–Armitage trend tests, and genotype imputation was used for defining the association locus.
Results. Genetic polymorphisms in the Fcγ receptor gene (*FCGR*) cluster at human chromosome 1q23, previously associated with lupus nephritis susceptibility, were associated with the response to CYC treatment for lupus nephritis. Significant response association was found for 3 perfectly correlated ($r^2 = 1$) single-nucleotide polymorphisms (SNP): rs6697139, rs10917686, and rs10917688, located between the *FCGR2B* and *FCRLA* genes ($p = 3.4 \times 10^{-8}$). Carriage of the minor alleles in these SNP was found only in nonresponders (31%) and none in responders (0%).
Conclusion. This first genome-wide association approach for CYC response yielded a robust profile of genetic associations including large-effect SNP in the *FCGR2B-FCRLA* locus, which may provide better insights to CYC metabolism and efficacy. (First Release March 15 2016; J Rheumatol 2016;43:1045–9; doi:10.3899/jrheum.150665)

Key Indexing Terms:
LUPUS NEPHRITIS   CYCLOPHOSPHAMIDE   GENETIC STUDIES

Systemic lupus erythematosus (SLE; Online Mendelian Inheritance in Man 152700) is an autoimmune disease affecting various vital organs by chronic inflammation. The kidney is one of the most vulnerable organs in SLE[1]. Lupus nephritis affects 43% to 55% in Asian, 51% in African, 43%

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in Hispanic, and 14% in white patients with SLE, and results in renal failure and death[2,3].

Cyclophosphamide (CYC) has been frequently used to improve the renal outcomes of patients with lupus nephritis[4]. Active metabolites of the pro-drug CYC induce DNA damage in genomic DNA by alkylating G bases and lead to death of well-dividing cells such as stimulated lymphocytes and cancer cells[5]. Interestingly, response to CYC administration varies much among individuals, but causal factors have remained unclear.

There were several association studies of candidate gene approach on metabolic enzymes for CYC (e.g., hepatic cytochrome P450 isozymes, GSTA1, GSTM1, GSTP1, GSTT1, ALDH1A1, and ALDH3A1) to investigate their genetic effects on response, adverse events, or both[6]. A few genetic variations have been identified, but with moderate statistical significance[6].

We conducted for the first time, to our knowledge, a genome-wide association study (GWAS) testing half a million single-nucleotide polymorphisms (SNP) in a hypothesis-free manner and identified genetic polymorphisms at 1q23 associated with response to intravenous (IV) CYC therapy in Korean patients with SLE with lupus nephritis.

MATERIALS AND METHODS

Subjects. A total of 109 Korean patients with SLE with lupus nephritis were recruited from the BAE SLE cohort of Hanyang University Hospital for Rheumatic Diseases in Seoul, Korea, with approval from the institutional review board. Written informed consent was obtained from all participants. The patients satisfying the American College of Rheumatology (ACR) criteria for SLE with lupus nephritis and > 500 mg/day proteinuria were included in our study. Among the patients, 14 without renal biopsy showed high SLE activity and either proteinuria of > 2 g/day or 4+ in a dipstick urinalysis. They did not receive any nonsteroidal antiinflammatory drugs (NSAID) that might induce nephritis.

CYC treatment and response assessment. Baseline characteristics and clinical outcomes at 6 months after initiation of IV CYC therapy were assessed for 109 patients with SLE with lupus nephritis. All subjects received IV CYC induction therapy with either low-dose CYC (0.5 g, 6 pulses, every 2 weeks) based on the Euro-Lupus regimen[7] or high-dose CYC (0.5–1.0 g per body surface area m^2, 6 pulses, monthly) based on the US National Institutes of Health regimen[8]. All subjects received additional high-dose oral glucocorticoid therapy starting at 1 mg/kg per day.

At 6 months after initiation of IV CYC therapy, renal response of the subjects was evaluated by the ACR renal response criteria[9] demonstrating 3 major outcomes: renal function, urinary protein, and urinary sediment. The subjects were divided into 3 groups, according to their response to the CYC therapy: complete, partial, and no response. Complete response was defined as a decrease in proteinuria to < 200 mg/day, normal estimated glomerular filtration rate (GFR), and disappearance of hematuria and cellular casts, and partial response as > 50% improvement in proteinuria (200–2000 mg/day) and 25% increase above GFR baseline (if the baseline was abnormal) from pretreatment values. Patients who did not fulfill the complete or partial response criteria were classified as nonresponders.

Genotyping and data analysis. To examine the response-associated polymorphisms, we obtained genome-wide SNP data of the study subjects by Illumina Human 610-Quad BeadChip. A total of 491,617 SNP showed call rate per SNP of ≥ 90%, minor allele frequency of ≥ 1%, and expected genotype distribution (p for Hardy-Weinberg disequilibrium < 1×10^{-6}), and were used in association testing. Genetic homogeneity of the study participants were assessed by principal component analysis using Eigenstrat software and quantile-quantile plots for association results using R program. Statistical significance of associations between drug response and SNP was computed using Cochran-Armitage trend tests assuming additive effects of the minor allele dosages. The genetic markers within a 1 Mb flanking region from the most significant SNP were imputed using IMPUTE2 program with a multiethnic long-range haplotype reference derived from the 1000 Genomes Project.

RESULTS

Among 109 Korean patients with SLE with lupus nephritis, 93 patients (85%) showed improved renal outcomes at 6 months after initiation of IV CYC therapy based on the ACR response criteria. This responder group consisted of 67 with partial response and 26 with complete response. In the non-responder group, 16 patients (15%) showed no improved response.

Demographic and clinical characteristics including baseline proteinuria level and the total dose of CYC were not significantly different between the nonresponder and responder groups (p > 0.05; Table 1). Additionally, the drug dose at a single CYC pulse was not significantly associated with response to the therapy (p = 0.26). Euro-Lupus treatment regimen using low-dose CYC pulse was applied to 14% of responders (n = 13) and 25% of nonresponders (n = 4).

The GWAS dataset was filtered by general quality control criteria. The final genotyping call rate per individual was ≥ 99.95%, and 491,617 polymorphic SNP were analyzed in our study. The Korean CYC cohort was genetically homogeneous as East Asians and there was no evidence of genetic stratification related to the response status (p > 0.05 for difference of the first 2 principal components; Supplementary Figure 1 is available from the authors on request).

In comparison between the responder and nonresponder groups, genotyped SNP rs6697139 (marked with † in Table 2) in human chromosome 1q23 was significantly associated with response to CYC therapy ($p_{trend} = 3.4 \times 10^{-8}$), passing a generally accepted significance threshold for GWAS ($\alpha = 5 \times 10^{-8}$; Table 2; Supplementary Figure 2 is available from the authors on request), passing a generally accepted significance threshold for GWAS ($p = 5 \times 10^{-8}$). This SNP rs6697139 is located between *FCGR2B* [Fc fragment of immunoglobulin G (IgG), low affinity IIb, receptor (CD32)] and *FCRLA* (Fc receptor-like A). Its minor allele A was found in the non-responder group (5 among 16, 31%) but not in the responder group, with either partial or complete response (0 among 93; Table 2).

Additionally, another genotyped SNP, rs17411858 (marked with † in Table 2), located between *FCGR2B* and *FCGR3B* [Fc fragment of IgG, low affinity IIIb, receptor (CD16b)] at ~40 kb upstream of rs6697139, showed a suggestive association with the response status ($p_{trend} = 3.6 \times 10^{-6}$), not passing the GWAS significance threshold. However, carriage of the minor allele in the SNP rs17411858 was found only in the nonresponder group (4 out of 16, 25%), similar to rs6697139 (Table 2).

Quantile-quantile plot for the genome-wide Cochran-Armitage trend tests showed little inflation and minimal population substructure ($\lambda = 1.02$). However, there was evidence of genetic contribution in the response induction, showing associations of 339 SNP including rs6697139 and rs17411858 lifted off the expected association signals (Supplementary Figure 3 is available from the authors on request). Supplementary Table 1 (available from the authors on request) provides detailed information about the association results of the 339 SNP and their nearest genes (e.g., *SCARB1*, *EPHA5*, *CAMK1D*, *BARX2*, *MIR5580*, *ATG4C*, *LOC285577*, *SRRM4*, *LOC286370*, and *HIPK2*).

To further define the associated region near rs6697139, we imputed genotypes of all SNP in the *FCGR* (Fcγ receptor) cluster region around the 2 associated SNP. A total of 11 SNP (2 genotyped and 9 imputed) showed p_{trend} values of 3.6×10^{-6} or lower, and were all located in a region harboring 3 protein-coding genes: *FCGR3B*, *FCGR2B*, and *FCRLA*, and a pseudogene *RPL31P11* (Table 2 and Figure 1).

Three of the 11 SNP listed in Table 2 (including the genotyped rs6697139 and imputed rs10917686 and rs10917688) were significantly associated with the response ($p_{trend} = 3.4 \times 10^{-8}$), passing the GWAS significance

Table 1. Demographic and clinical characteristics of the study subjects. Data are median (IQR) unless otherwise indicated.

Characteristics	Nonresponders	Responders	p*	Partial Responders	Complete Responders
Total, n (female %)	16 (100)	93 (100)		67 (100)	26 (100)
Age, yrs	23.5 (21.0–28.5)	29.0 (24.0–36.0)	0.06	28. 0 (22.0–35.0)	32.5 (27.0–43.0)
Height, cm	159 (151–165)	160 (156–164)	0.90	160 (156–164)	160 (156–163)
Weight, kg	58.5 (48.5–64.3)	53.0 (49.0–59.0)	0.42	54.0 (50.0–59.0)	50.0 (46.0–59.0)
BMI, kg/m^2	22.2 (19.8–24.4)	20.8 (19.0–23.0)	0.42	21.3 (19.7–23.1)	19.7 (18.8–21.3)
SLE duration, yrs	3.50 (1.68–6.28)	2.40 (0.74–5.50)	0.16	3.10 (0.69–6.39)	1.86 (0.74–4.18)
Class of lupus nephritis, n (%)			0.37		
Class III	0 (0.0)	11 (11.8)		6 (9.0)	5 (19.2)
Class IV	9 (56.3)	43 (46.2)		33 (49.3)	10 (38.5)
Class V	1 (6.3)	5 (5.4)		3 (4.5)	2 (7.7)
Class III + V	1 (6.3)	9 (9.7)		5 (7.5)	4 (15.4)
Class IV + V	1 (6.3)	15 (16.1)		12 (17.9)	3 (11.5)
Not biopsied	4 (25.0)	10 (10.8)		8 (11.9)	2 (7.7)
Proteinuria, mg/day	2483 (1976–7088)	3364 (1750–6500)	0.44	4290 (2180–7150)	1932 (1386–2833)
Serum creatinine, mg/dl	0.80 (0.60–1.15)	0.80 (0.70–0.90)	0.56	0.80 (0.70–0.90)	0.80 (0.70–0.90)
Serum C3, mg/dl	55.2 (44.5–77.5)	59.8 (44.9–82.9)	0.79	61.5 (44.0–84.8)	57.5 (49.2–76.1)
Serum C4, mg/dl	13.3 (9.7–27.0)	11.7 (7.7–17.6)	0.96	11.6 (7.3–16.7)	12.3 (9.2–17.8)
Positive anti-dsDNA antibody, n (%)	10 (66.7)	52 (58.4)	0.55	41 (64.1)	11 (44.0)
Cyclophosphamide total dose, mg	4200 (3000–5250)	4440 (3125–4800)	0.97	4480 (3125–4797)	4225 (3172–4800)

* P values for the difference between the nonresponder and responder groups were obtained using median tests or chi-square tests. IQR: interquartile range; BMI: body mass index; SLE: systemic lupus erythematosus; C3: complement factor 3; C4: complement factor 4.
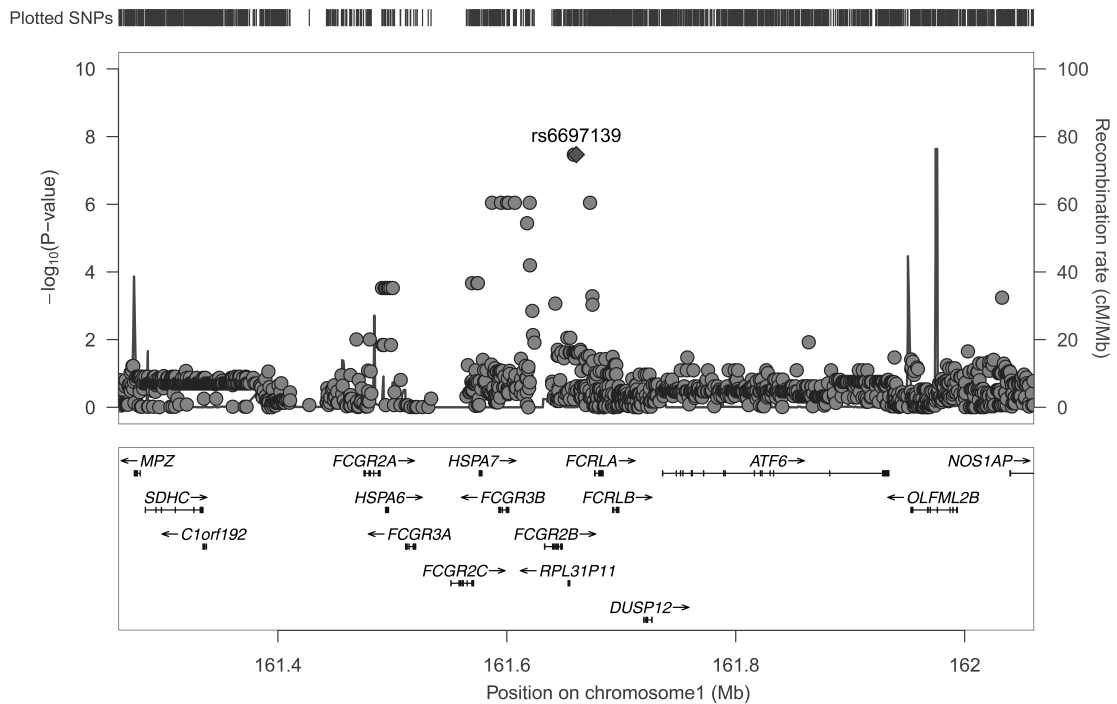

Figure 1. Cyclophosphamide response association plot for SNP in a region of human chromosome 1q23. The significance levels (Y axis) at all genotyped and imputed SNP were calculated using Cochran–Armitage trend tests and plotted against their chromosomal positions based on hg19 (X axis). The most significant association was observed at the genotyped rs6697139 (p = 3.41 × 10^{-8}). SNP: single-nucleotide polymorphism.

threshold. These 3 SNP were perfectly correlated (r^2 = 1) with each other and they were located next to one another in the intergenic region between *FCGR2B* and *FCRLA*. Among these 3 response-associated SNP, rs10917688 was enriched with several annotations for regulatory characteristics such as histone marks and DNase hypersensitivity for myeloid and

Table 2. Genotyped and imputed SNP at 1q23 associated with response to cyclophosphamide treatment for lupus nephritis.

SNP	Position	Location	1 > 2*	Nonresponders, n = 16		Responders, n = 93		p_{trend}
				11/12/22*	MAF	11/12/22*	MAF	
rs180978155	161587016	6 kb 3' of *FCGR3B*	G > A	12/4/0	0.13	93/0/0	0.00	9.0×10^{-7}
rs66963969	161594822	Intron of *FCGR3B*	A > –	12/4/0	0.13	93/0/0	0.00	9.0×10^{-7}
rs149686267	161600109	Intron of *FCGR3B*	C > T	12/4/0	0.13	93/0/0	0.00	9.0×10^{-7}
rs34907291	161601539	0.4 kb 5' of *FCGR3B*	G > C	12/4/0	0.13	93/0/0	0.00	9.0×10^{-7}
rs12756398	161606926	6 kb 5' of *FCGR3B*	T > A	12/4/0	0.13	93/0/0	0.00	9.0×10^{-7}
rs17411858[†]	161617516	13 kb 5' of *FCGR2B*	A > G	12/3/1	0.16	93/0/0	0.00	3.6×10^{-6}
rs1771568	161619874	13 kb 5' of *FCGR2B*	T > G	12/4/0	0.13	93/0/0	0.00	9.0×10^{-7}
rs10917686	161658490	10 kb 3' of *FCGR2B*	C > T	11/5/0	0.16	93/0/0	0.00	3.4×10^{-8}
rs10917688	161658780	10 kb 3' of *FCGR2B*	C > T	11/5/0	0.16	93/0/0	0.00	3.4×10^{-8}
rs6697139[†]	161660696	12 kb 3' of *FCGR2B*	G > T	11/5/0	0.16	93/0/0	0.00	3.4×10^{-8}
rs113053770	161672474	4 kb 5' of *FCRLA*	C > T	12/4/0	0.13	93/0/0	0.00	9.0×10^{-7}

* Major and minor alleles are denoted as 1 and 2, respectively. [†] These 2 SNP were genotyped and the others were imputed among the 11 SNP showing $p_{trend} < 1 \times 10^{-5}$. SNP: single-nucleotide polymorphism; MAF: minor allele frequency.

lymphoid cells, and transcription factor GATA1-binding according to the ENCODE data analysis[10]. Consistently, another SNP rs6697139 was identified as an expression quantitative trait loci (eQTL) associated with *FCGR2B* expression in the ImmVar eQTL analysis[11] using monocytes of whites (p = 5.0×10^{-6}) where the minor allele frequency was much higher (23% in the Utah residents with Northern and Western European ancestry) than in Koreans (2%).

DISCUSSION

The European League Against Rheumatism and ACR guidelines for management of lupus nephritis published in 2012 recommended both CYC and mycophenolate mofetil for the initial management of lupus nephritis[12,13]. Predicting the response to CYC for lupus nephritis is a clinically important part of choosing between the 2 drugs for timely treatment, because the degree of response cannot be determined until several months after initiation of induction therapy[12,13], and failure in response to therapy might result in outcomes that significantly worsen a patient's quality of life and even threaten that life.

Patients with lupus nephritis carrying nonresponse-associated alleles can choose other drugs to avoid the most common but possibly ineffective CYC therapy, although efficacy of alternative drugs is not yet predictable. For better therapeutic decisions, especially for nonresponders to CYC therapy, further pharmacogenomics studies for other immunosuppressant drugs are needed.

This first GWAS provided evidence of significant genetic contribution to CYC response across the human genome, including the significant single-locus association in the *FCGR* cluster region that has been associated with susceptibility to SLE, lupus nephritis, and other renal diseases both genetically and biologically[14,15,16]. This *FCGR* locus is characterized by highly polymorphic copy number variations and sequence similarity within the segmental duplication near

the associated SNP[17]. It would be worth testing for association of the copy number variations with the response in future.

Fcγ receptor, low affinity receptor for the Fc region of γ immunoglobulins (IgG), binds to IgG-containing immune complexes that are the major component deposited in renal tissues of patients with lupus nephritis to induce antibody-mediated phagocytosis and antibody-dependent cell-mediated cytotoxicity. Interestingly, CYC enhances the 2 FcγR-mediated functions by enhancing expression of *FCGR*[18]. Considering this along with our finding that the *FCGR* SNP are associated with both *FCGR* expression and CYC response, it is plausible that the response to CYC treatment for lupus nephritis is affected by *FCGR* expression, which may be affected by the response-associated SNP.

There was histological heterogeneity (proliferative or membranous lupus nephritis) in the 109 study subjects, which may have confounded our GWAS results, although patients who received NSAID were not included in our study because they could have had NSAID-induced nephritis. Six patients (5.5%) had pure membranous nephritis (lupus nephritis class V), and 14 patients (12.8%) were not biopsied because of their severe conditions. Nevertheless, these 14 patients not biopsied were included in our study because they showed proteinuria of > 2 g/day or 4+ in a dipstick urinalysis and had typical characteristics of proliferative nephritis including hematuria, low C3 (complement factor 3), and high titer of anti-dsDNA antibodies.

Even after excluding the 6 subjects with membranous nephritis, the association of the identified SNP remained virtually the same ($p_{trend} = 2.82 \times 10^{-8}$ at rs6697139). Additionally, the same analysis using only 89 patients with biopsy-proven proliferative lupus nephritis (excluding 6 patients with membranous nephritis and 14 patients without biopsy data) also showed a similar association result ($p_{trend} = 5.05 \times 10^{-8}$ at rs6697139).

Our study has 2 major limitations: the low number of subjects in the GWAS and the absence of a replication study. Genomic DNA samples of patients with lupus nephritis with well-defined CYC response information have not been common. Two previous studies investigated candidate genetic markers for associations with CYC efficacy in lupus nephritis, but used smaller sample sizes[19,20].

In addition to the low statistical power because of the small sample size, the popular statistical methods using a large sample approximation (e.g., Cochran-Armitage trend and chi-square tests) could be inaccurate in testing small-size sets. For example, p values at rs6697139 ($p_{trend} = 3.4 \times 10^{-8}$ or $p_{chi\text{-}square} = 4.9 \times 10^{-8}$) become weaker in exact tests ($p_{Fisher} = 5.1 \times 10^{-5}$) or permutation tests ($p_{permutation} = 3.9 \times 10^{-5}$), which gave us underpowered results ($\lambda = 0.97$) without a GWAS-level significance. Further, logistic regression with adjustment for genetic and clinical covariates was not suitable for calculation of trait effect size at rs6697139 in which 0 allele appears in the responder group, although principal components and other characteristics were not different between the responder and nonresponder groups. Thus, our findings need to be confirmed in replication studies.

Our pilot GWAS on CYC response in lupus nephritis identified the association of genetic variants in the *FCGR* locus, suggesting a useful genetic marker to predict CYC nonresponders before treatment. This finding provided new hypothesis on the link of *FCGR* with CYC efficacy.

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