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The *NBS1* Genetic Polymorphisms and the Risk of the Systemic Lupus Erythematosus in Taiwanese Patients

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Abstract
Introduction Systemic lupus erythematosus (SLE), a multisystemic autoimmune disease, is characterized by the production of a range of autoantibodies against nuclear constituents and other self-antigens. The studies in DNA repair deficiencies in SLE patients have been recently investigated.

Aims Few studies have been conducted on DNA repair gene polymorphisms and their role in autoimmune diseases. Our study purpose was to examine and compare *NBS1* genotype distributions in a group of Taiwanese SLE patients and controls in Taiwan.

Patients and Methods Participants were Taiwanese SLE patients and healthy controls. We studied associations among *NBS1* polymorphisms—rs1061302, rs709816, and rs1805794—considering clinical features for the entire group and stratified subgroups. No statistically significant differences between the patients and controls were noted. However, we observed significant decreases in Ht1-GGG, Ht2-AAC, and Ht3-AGC in the SLE patients (Ht1-GGG, OR=0.26, 95% CI: 0.16–0.41; Ht2-AAC, OR=0.30, 95% CI: 0.17–0.53; Ht3-AGC, OR=0.35, 95% CI: 0.19–0.71) and significant increases in Ht4-AAG, Ht5-AGG, and Ht8-GGC among the SLE patients. Combined, these results suggest an association between *NBS1* genetic polymorphisms and Taiwanese SLE patients.

Keywords Systemic lupus erythematosus · *NBS1* · genetic polymorphism

Ying-Ju Lin and Yu-Ching Lan made equal contributions to this work.

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Introduction

Systemic lupus erythematosus (SLE), a multisystemic autoimmune disease, is characterized by the production of a range of autoantibodies against nuclear constituents and other self-antigens [1–3]. Since SLE is a multifactorial disease, complex interactions among genetic, hormonal, and environmental factors play important roles in determining its induction and development [4, 5]. The immune complex damages multiple organ systems and presents numerous clinical manifestations [6–9]. Arthritis, serum

autoantibodies, glomerulonephritis, joint pain, skin rash, and vasculitis commonly develop in combination with one or more symptoms observed in SLE patients [10].

An important clinical factor is autoimmunity to double-stranded DNA and nucleosomes that present diagnostic and pathogenic impacts. Although DNA is poorly immunogenic, antigenicity may be induced by reactive oxygen species, drugs, and exposure to UV light [11–14]. These environmental factors may trigger altered DNA conformation or damage to/breaks in DNA bases, resulting in apoptotic bodies. Once produced, damaged DNA is normally recognized and repaired by complex mechanisms [15, 16]. DNA repair system deficiencies have been investigated in SLE patients [17–23], and among other findings researchers have reported that (a) their peripheral blood neutrophils display increased DNA damage [17], (b) DNA damage repair is delayed by ionizing radiation or oxidative damage in cells [18, 19], and (c) DNA repair pathway genes are downregulated in peripheral blood lymphocytes [20, 21].

The *NBS1* gene contains 16 exons and is located on chromosome band 8q21.3 [24, 25]. One *NBS1* gene product, nibrin (p95, NBS1), is a key regulator of the MRE11/RAD50/nibrin (M/R/N) protein complex that is involved in DNA double-strand break repair, telomere maintenance, immunoglobulin class switching, meiotic recombination, and DNA damage response [26, 27]. Nibrin directs the M/R/N complex to DNA damage sites and promotes DNA binding and nuclease activity. In addition, nibrin is required for ataxia telangiectasia mutated (ATM) kinase activation and the related downstream ATM phosphorylation of targets that are critical to the cell cycle [28, 29].

To date, few studies have been conducted on DNA repair gene polymorphisms and their role in autoimmune diseases [30–33]. Our study purpose was to examine and compare *NBS1* genotype distributions in a group of Taiwanese SLE patients and controls in Taiwan. It is interesting to carry out an association study for a better understanding of the role of *NBS1* in SLE.

Patients and Methods

Patients The study sample consisted of 164 SLE patients and 176 healthy individuals recruited from China Medical University Hospital in Taichung, Taiwan. All of the patients met American Rheumatism Association criteria for SLE classification [10]. Data collection was partly determined by patient availability, diagnoses of inactive or active disease, and whether or not they were undergoing treatment with steroids. All samples for genomic DNA isolation were collected by venipuncture. Members of the control group were identified through routine health examinations. All participants signed informed consent forms. The study

Table I PCR Primer and Probe Sequences of *NBS1* Genetic Polymorphisms that Were Used in this Study

Gene Name	Polymorphisms	Exon/Intron	Location in the Protein	SNP Database ID	Nucleotide Change	Reporter 1 Dye	Allele	Reporter 1 Quencher	Reporter 2 Dye	Allele	Reporter 2 Quencher	Context Sequence
NBS1	Glu185Gln	5	BRCT domain	rs1805794	C/G	VIC	C	NFQ	FAM	G	NFQ	AATTTGTGGAGGCTGCTTCTTGGACT[**C/G**]AACTGCTTTCAGGAATTCAGTAAAA
	Asp399Asp	10	central region	rs709816	A/G	VIC	A	NFQ	FAM	G	NFQ	TGCAGGACTCCTTTACAGTGGGTGC[**A/G**]TCTTGTGAAAGCATTCTGAATTTTT
	Pro672Pro	13	MRE11 binding domain	rs1061302	A/G	VIC	A	NFQ	FAM	G	NFQ	ATTAAAAACTCTACTTCCAGAAATCC[**A/G**]TCTGGCATAAATGATGATTATGGTC

The genotyping method was designed by TaqMan® Genotyping Assays (Applied Biosystems)
BRCT breast cancer C-terminal

design was approved by the Human Subjects Committee of the Institutional Review Board of China Medical University Hospital.

Genomic DNA Extraction and Genotyping Genomic DNA was extracted from peripheral blood leukocytes according to standard protocols (Genomic DNA Kit, Qiagen). Biallelic *NBS1* genetic polymorphisms were detected using TaqMan(R) Genotyping Assays (Applied Biosystems; Table I).

Statistical Analysis Genotype and allelic frequency distributions for the targeted polymorphisms in both SLE patients and controls were analyzed using a chi-squared test. Allelic frequencies are expressed as percentages of total alleles. Odds ratios (OR) were calculated for genotype and allelic frequencies (95% confidence interval [CI]). Haplotypes were inferred from unphased genotype data using the Bayesian statistical method in the Phase 2.1 software program [34, 35]. All statistical tests were performed using SPSS 12.0 for Windows XP (SPSS, Inc., Chicago, IL, USA). The p values were adjusted by using Bonferroni's correction. Statistical significance was considered as p value <0.016 for allele and genotype frequency analysis data. Statistical significance was considered as p value <0.00625 for haplotype analysis data.

Results

The genotypes of *NBS1* (rs1061302), *NBS1* Asp399Asp (rs709816), and *NBS1* Glu185Gln (rs1805794) were identified by probe hybridization with corresponding primers (Table I). Allele and genotype frequencies are presented in Table II. As shown, genotype distributions were consistent with the Hardy–Weinberg equilibrium. Statistically significant differences in allele and genotype frequencies were not observed between the patients and controls.

Haplotype frequencies were estimated using the three genetic polymorphisms (allele frequency >5%; Fig. 1 and Table III). Of the eight observed haplotypes, six were present in both SLE patients and control individuals. The frequency of the most common haplotype (Ht1-GGG) in the control group was 51.98%, compared to 21.75% for the SLE patients (Table III). According to results from a haplotype-specific analysis, Ht1-GGG, Ht2-AAC, and Ht3-AGC were identified as "protective" (Ht1-GGG, $p<0.001$, OR=0.26, 95% CI: 0.16–0.41; Ht2-AAC, $p<0.001$, OR=0.30, 95% CI: 0.17–0.53; Ht3-AGC, $p<0.001$, OR=0.35, 95% CI: 0.19–0.71). Ht4-AAG, Ht5-AGG, and Ht8-GGC were presented as "at-risk" (Ht4-AAG, $p<0.001$, OR=104.06, 95% CI: 6.42–1,685.70; Ht5-AGG, $p<0.001$, OR=2524.06, 95% CI: 7.96×10^{-6}–8×10^{11}; Ht8-GGC, $p<0.001$). Results from our analysis of associations between SLE patient clinical feature profiles and various haplotypes suggested that there were no significant associations (not shown).

Discussion

In this study, our findings suggest that (a) Taiwanese individuals with the *NBS1* haplotypes Ht1-GGG, Ht2-AAC, and Ht3-AGC are at lower risk of developing SLE and (b)

Table II Allele and Genotype Frequencies of *NBS1* Gene Polymorphisms in Taiwanese SLE Patients and Controls

Polymorphisms		SLE Number (%)	Controls Number (%)	p value	Odds ratio (95% CI)
NBS1 Pro672Pro (rs709816)	A	149 (54.4)	169 (48.0)	0.114	1.29 (0.94–177)
	G	125 (45.6)	183 (52.0)		1
	AA	41 (29.9)	35 (19.9)	0.121	1.70 (0.88–3.26)
	AG	67 (48.9)	99 (56.3)		0.98 (0.56–1.73)
	GG	29 (21.2)	42 (23.9)		1
NBS1 Asp399Asp (rs709816)	A	105 (38.3)	109 (31.0)	0.054	1.39 (0.99–1.93)
	G	169 (61.7)	243 (69.0)		1
	AA	16 (11.7)	18 (10.2)	0.060	1.57 (0.74–3.37)
	AG	73 (53.3)	73 (41.5)		1.77 (1.10–2.86)
	GG	48 (35.0)	85 (48.3)		1
NBS1 Glul85Gln (rs1805794)	C	135 (41.2)	163 (47.9)	0.078	0.76 (0.56–1.03)
	G	193 (58.8)	177 (52.1)		1
	CC	24 (14.6)	34 (20.0)	0.174	0.55 (0.28–1.06)
	CG	87 (53.0)	95 (55.9)		0.71 (0.43–1.17)
	GG	53 (32.3)	41 (24.1)		1

Allele frequency was compared between SLE and controls by 2×2 χ^2 tests. Genotype frequency was compared between SLE and controls by 3×2 χ^2 tests. The p values were adjusted by using Bonferroni's correction. Statistical significance was considered as p value <0.016 (0.053)

CI confidence interval

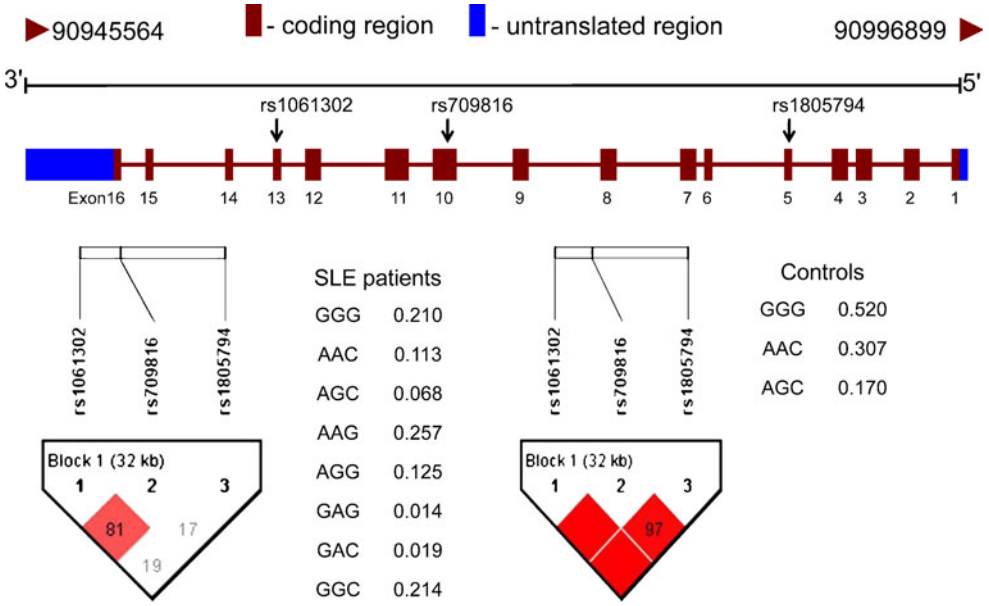

Fig. 1 Results of SNP association study of the *NBS1* genetic polymorphisms on chromosome 8q21.3. *Upper schematic* showing the *NBS1* gene which contains 16 exons (from chromosome 8: 90,945,564 to 90,996,899) were used for genotyping in 164 Taiwanese SLE patients and the 176 individuals from the general population of Taiwan with Han Chinese ethnic background for SNP association. *Lower schematic* showing haplotype blocks for control and SLE patients. The *blocks* were constructed based on the confidence interval approach using the HAPLOVIEW software [50]. The *red* denotes the haplotype blocks and the *white* represents evidence of recombination

individuals with the *NBS1* haplotypes Ht4-AAG, Ht5-AGG, and Ht8-GGC are at higher risk of developing SLE. Combined, these results suggest an association between *NBS1* genetic polymorphisms and Taiwanese SLE patients.

To date, few studies have been conducted on DNA repair gene polymorphisms and their role in autoimmune diseases [30–33]. In the present study, we found an association between SLE and *NBS1* haplotypes. Interpreting these results is limited by the lack of research on links between *NBS1* genetic variants, autoimmune diseases, and related clinical manifestations. However, a possible explanation for our results is that insufficient DNA damage repair may contribute to SLE immune dysfunction. More detailed studies are required to determine which molecular mechanisms are controlled by *NBS1* genetic variants.

The genetic variants from DNA repair genes have been investigated in cancers [30, 32, 36–38]. These genetic polymorphisms commonly found in DNA repair genes have been suggested for altering protein function and deficits in repair capacity, resulting in genetic instability and failure to maintain normal cell proliferation. SNPs in *NBS1* are

Table III Haplotype Frequencies of *NBS1* Gene Between SLE Patients and Controls

Haplotype	rs1061302	rs709816	rs1805794	SLE (%)	Control (%)	*p* value	Odds ratio (95% CI)
Ht1	G	G	G	21.75%	51.98%	<0.001	0.26 (0.16–0.41)
Ht2	A	A	C	11.79%	30.67%	<0.001	0.30 (0.17–0.53)
Ht3	A	G	C	6.63%	17.05%	<0.001	0.35 (0.19–0.71)
Ht4	A	A	G	23.04%	0.29%	<0.001	104.06 (6.42–1,685.70)
Ht5	A	G	G	12.58%	0.01%	<0.001	2,524.06 (7.96×10^{-6}–8×10^{11})
Ht6	G	A	G	1.50%	0.01%	0.106	178.71 (1.87×10^{-5}–1.71×10^{9})
Ht7	G	A	C	1.78%	0.00%	0.075	—
Ht8	G	G	C	20.93%	0.00%	<0.001	—

—indicates not applicable, *CI* confidence interval

Order of SNPs comprising the *NBS1* haplotypes: rs1061302, rs709816, and rs1805794. Percentages may not add to 100% because of the presence of rare haplotypes not presented in this table. The *p* values were adjusted by using Bonferroni's correction. Statistical significance was considered as *p* value <0.00625 (0.05/8)

associated with certain types of cancer. For example, *Glu185Gln* (rs1805794) is associated with increased risks for lung cancer, breast cancer, and leukemia [39–44]. The functional relevance of this polymorphism is unknown. However, its location within the breast cancer C-terminal domain may be related to some effect on protein function [27]. Lu and colleagues suggested that the homozygous CC genotype and heterozygous GC genotype may contribute to sporadic breast cancer in young non-Hispanic white women [43]. The heterozygous GC genotype carriers had an increased risk of lung cancer in China [44]. In addition, no significant difference of this polymorphism but some specific haplotypes of the *NBS1* gene was observed in leukemia [42]. Few studies have been conducted so far to study the association of *NBS1* haplotypes with SLE. Our analysis on the *NBS1* haplotype provided additional information on these polymorphisms as markers of genetic susceptibility and a more efficient method for assessing the genetic susceptibility of a candidate gene than any of the polymorphisms. Individuals with SLE are known to have increased susceptibility to lung cancer, breast cancer, and hematological malignancies [45–47]. Our findings suggest that SLE and certain types of cancer share similar pathogenic pathways during disease development (e.g., DNA repair system deficiencies caused by genetic variants of functional SNPs in DNA repair genes). Furthermore, DNA repair mechanisms are central to genetic recombination during lymphocyte maturation [48, 49]. Further studies are required to determine the role of DNA repair genes in the relationship between SLE and cancer. It is our hope that these findings will assist in that effort.

In summary, to our knowledge, this is the first evidence of an association between common *NBS1* genetic variants and SLE. According to our results, haplotypes containing variant alleles from the three studied *NBS1* polymorphisms may cause increased susceptibility to SLE.

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