Association Between *XRCC3* Thr241Met SNP and Systemic Lupus Erythematosus in Han Chinese Patients in Taiwan, and a Meta-Analysis of Healthy Populations

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Background: X-ray repair cross-complementing group 3 (*XRCC3*) plays a crucial role in mammalian DNA repair processes. The polymorphism of *XRCC3*, rs861539 (Thr > Met at codon 241), is common in populations worldwide. This study analyzed the relationship between this functional single nucleotide polymorphism and systemic lupus erythematosus (SLE) in the Han Chinese population in Taiwan (HC-TW). **Methods:** Genotyping was performed using polymerase chain reaction restriction fragment length polymorphism on 163 SLE patients and 191 healthy participants in the control group. **Results:** The data showed that the genotype frequency at codon 241 did not differ significantly between the SLE patients and the healthy participants in the control group; however, the allele frequency

analysis indicated a significant difference between these groups. In addition, we used the genotype and allele frequencies of 191 healthy HC-TW participants for comparison with HapMap populations. The results indicated a significant difference of *XRCC3* Thr241Met allele and genotype frequencies between the HC-TW population and HapMap populations, except for the other Han Chinese populations. A prior study showed that Thr241 > Met substitution in *XRCC3* protein was positive as damaging and functional consequences as well. **Conclusion:** This is the first study to demonstrate the difference of *XRCC3* Thr241 > Met variant between the HC-TW population and HapMap population. J. Clin. Lab. Anal. 28:118–123, 2014. © 2014 Wiley Periodicals, Inc.

Key words: systemic lupus erythematosus (SLE); X-ray repair cross-complementing group 3 (*XRCC3*); single nucleotide polymorphisms (SNPs); genotype; haplotype

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex multifactorial autoimmune disease that is characterized by B-cell hyperactivity and autoantigen production against nuclear constituents and other self-antigens (1, 2). SLE may be induced by genetic, hormonal, environmental factors, viral infection (3, 4). Exposure to ultraviolet (UV) light is considered crucial environmental factors (5). Defective immune regulatory mechanisms induced by genetic mutations can result in the dysregulation of inflammatory cytokine production and insufficient clearance of apoptotic cells or immune complexes, which activate antiseif-immune responses (6–9). Single nucleotide

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polymorphism (SNP) typing can be used to determine the potential molecular mechanisms in whole genomes (10, 11); the interactions between environmental factors and genetic variants in SLE remain unclear.

Hypersensitivity to UV irradiation is frequently diagnosed in patients with SLE. Recently, deficiencies in the ability to repair DNA damage and the consequent abnormal levels of apoptotic bodies have been identified as causative factors for SLE. Clinical studies have further demonstrated that a number of SLE patients are highly deficient in DNA repair (12–14), suggesting that genetic variations in the genes encoding DNA repair proteins contribute to the susceptibility to SLE. Among the genes involved in the DNA repair pathways, the X-ray repair cross-complementing (*XRCC*) gene family can protect mammalian cells from DNA damage caused by ionizing radiation (15, 16). Consistent with this observation, previous studies have indicated that the *XRCC* 4, 5, 7, and 9 proteins function at DNA break sites to trigger the development of autoimmune diseases (17–20). A prior study indicated that *XRCC1* is the genetic factor that interacts with environmental factors, such as UV irradiation, to promote the pathogenesis of SLE in the Han Chinese population in Taiwan (HC-TW) population (21). DNA polymorphisms in the *XRCC1* and *XRCC3* have been an area of intense current investigation (22).

XRCC3 is an X-ray repair cross-complementing gene family that can protect mammalian cells from DNA damage induced by ionizing radiation (15, 16). Cells lacking *XRCC3* are unable to form Rad51 foci after radiation damage, and demonstrate genetic instability and increased sensitivity to DNA damaging agents (23, 24). The SNP within *XRCC3* have been identified at codon 241, which is located in exons 7 (25). Molecular epidemiological studies have linked *XRCC3* polymorphism to increased risk of breast cancer (26), lung cancer (27), skin cancer (28), and colorectal cancer (29). The results have been inconsistent (30). The SNP at codon 241 is also linked to reduced DNA repair activity (31). Typically, the allele frequencies of genes often differ substantially between populations, and thus, ethnic-specific association studies are required to confirm genetic association in different populations. In this present study, we investigated whether the *XRCC3* rs861539 SNP contributes to SLE susceptibility in HC-TW populations and confirm genetic association in different populations using a meta-analysis approach.

MATERIALS AND METHODS

Patients and Sample Collection

A total of 163 SLE patients and 191 healthy controls were recruited from the China Medical University Hospital in Taiwan. All SLE patients met the criteria for

SLE as defined by the American Rheumatism Association. People who underwent health examinations at the same hospital were recruited for the healthy control group. Informed consent was obtained from all participants, and was approved by the institutional review board at the China Medical University.

Genomic DNA Extraction and Genotyping

All blood samples were collected using venipuncture for genomic DNA isolation. Genomic DNA was extracted from peripheral blood leukocytes according to standard protocols (Genomic DNA kit; Qiagen, Valencia, CA). We used the following primers: Forward: 5'-GCT CGCCTGGTGGTCATC-3' and reverse: 5'-CTTCCG CATCCTGGCTAAAAA-3'. The polymerase chain reaction (PCR) products were amplified with an initial denaturation at 95°C for 5 min, followed by 40 cycles of 95°C for 10 s, 56°C for 10 s, 72°C for 20 s, and one additional cycle of 72°C for 5 min. DNA fragments containing the polymorphism were detected using PCR restriction fragment length polymorphism (PCR-RFLP), and *CviA* II digestion was used to detect codon 722 C/T.

Identification of Eligible Studies and Data Extraction

A literature search was conducted for studies that examined associations between the *XRCC3* Thr241Met polymorphism and SLE. We utilized the MEDLINE citation index to identify articles in which the *XRCC3* Thr241Met polymorphism was determined in SLE patients and controls (until December 2012). In addition, all references mentioned in identified articles were reviewed to identify additional studies not indexed by MEDLINE. The following information was extracted for each study: author, year of publication, ethnicity of the study population, demographics, numbers of cases and controls.

Meta-Analysis

Population data were selected using a population data source (www.hapmap.org) for meta-analysis. The HapMap database was used to identify the allele and genotype frequencies of *XRCC3* Thr241Met polymorphisms in various ethnic populations. The populations were as follows: Tunisian (TUN), Utah residents with Northern and Western European ancestry from the CEPH collection (CEU), Tuscan in Italy (TSI), Luhya in Webuye, Kenya (LWK), Maasai in Kinyawa, Kenya (MKK), Mexican ancestry in Los Angeles, California (MEX), Gujarati Indians in Houston (GIH), Yoruban in Ibadan, Nigeria (YRI), African ancestry in Southwest USA (ASW), Japanese in Tokyo, Japan (JPT), Han Chinese in

Beijing China (HCB), Chinese in Metropolitan Denver, Colorado, Texas (CHD), and Han Chinese in Taiwan (HC-TW).

Statistical Analysis

The allelic and genotype frequency distributions for the polymorphism of SLE were determined through χ^2 analysis using SPSS software (version 10.0, SPSS Inc., Chicago, IL). A *P* value of less than 0.05 was considered statistically significant. Allelic and genotype frequencies were expressed as percentages of the total number of alleles and genotypes. Odds ratios were calculated from allelic and genotype frequencies with a 95% confidence interval (95% CI). Haplotypes were determined using the Bayesian statistical method, which was available in the program Phase 2.1.32. Adherence to the Hardy–Weinberg equilibrium constant was tested using a χ^2 test with one degree of freedom. Pairwise chi-square (χ^2) tests were also performed between HC-TW and HapMap populations using the allele frequencies in a 2×2 contingency table to determine whether the HC-TW population significantly differed from other populations.

RESULT

The SNP rs861539: C > T at exon 7 causes threonine to methionine substitution at codon 241 of *XRCC3* protein (Thr241>Met). PCR-RFLP product for rs861539 showed in Figure 1. Table 1 shows the genotype distribution values of *XRCC3* Thr241Met polymorphism in SLE patients and the healthy control. No statistically significant difference was observed in the genotype frequency of *XRCC3* Thr241Met polymorphisms between the SLE patients and the healthy control. However, a statistically significant difference was observed in allele frequency of *XRCC3* Thr241Met polymorphism between the SLE patients and the healthy control (*P* < 0.05).

Furthermore, we determined the association among *XRCC3* SNP and clinical and biochemical manifestations

Fig. 1. Electrophoresis of PCR-RFLP product for rs861539. The sizes of PCR amplified products were 214 base pair (bp), after CviA II digestion, line 1 is CC genotype (214 bp). Line 2 was CT genotype, the fragments were 214, 112, and 102 bp. Line 3 was TT genotype, fragments were 112 and 102 bp.

in SLE patients. The results showed that no significant difference occurred between the clinical and biochemical manifestations of SLE patients with *XRCC3* genotype and allele distribution (Table 2).

We compared the *XRCC3* Thr241Met polymorphism of healthy females and males in the HC-TW population, and the results indicated that no significant difference occurred between females and males in this population (Table 3). The *XRCC3* Thr241Met T/T genotype was not observed in the healthy HC-TW population.

We compared the *XRCC3* Thr241Met between the healthy HC-TW population and the healthy HapMap population. The meta-analysis results, based on 13 studies, indicated that the genotype of *XRCC3* Thr241Met polymorphism differed significantly between the HC-TW population and HapMap populations worldwide (Table 4). The Thr/Thr (CC), Thr/Met (CT), and Met/Met (TT) genotype frequencies in the HC-TW population were 0.922, 0.078, and 0, respectively (Table 4). The wild-type (C) and variant (T) alleles frequencies were 0.961 and 0.039, respectively. For HapMap

TABLE 1. Allelic and Genotype Frequencies of *XRCC3* Polymorphisms Among the Han Chinese SLE Patients in Taiwan and the Healthy Control Group

Polymorphisms		SLE <i>N</i> (%) <i>N</i> = 163	Control <i>N</i> (%) <i>N</i> = 191	<i>P</i> -value ^a	^c OR (95% CI)
<i>XRCC3</i> 241 (rs861539)	TT	1 (0.6)	0 (0)	0.06	-
	TC	24 (14.7)	15 (7.9)		2.04 (1.03–4.04)
	CC	138 (84.7)	176 (92.1)		1
	T	26 (8.0)	15 (3.9)	0.02 ^b	2.12 (1.10–4.08)
	C	300 (92.0)	367 (96.1)		1

^aGenotype and allelic frequencies were compared between SLE patients and normal controls by χ^2 tests.

^bStatistical significance.

^cOR, odds ratio.

TABLE 2. Comparison of Clinical and Biochemical Manifestations of SLE Patients With XRCC3 Genotype and Allele Distribution

Clinical features	Genotype				Allele		
	CC	CT	TT	<i>P</i> -value ^a	C	T	<i>P</i> -value ^a
ANA	110	20	1	1.000	240	22	1.000
Immunologic	91	15	1	0.645	197	17	0.782
Hematologic	58	10	0	1.000	126	10	0.824
CNS	14	1	0	0.728	29	1	0.486
Renal	49	7	0	0.885	105	7	0.495
Serositis	25	2	0	0.490	52	2	0.267
Arthritis	60	13	1	0.265	133	15	0.116
Mucosal ulcer	30	7	1	0.184	67	9	0.133
Photosensitivity	52	8	1	0.792	112	10	0.824
Discoid lupus	16	2	0	1.000	24	2	1.000
Malar rash	61	8	1	0.459	130	10	0.821

^aWhen compared with normal controls by χ^2 tests.

ANA, antinuclear antibody; CNS, central nervous system; SLE, systemic lupus erythematosus.

populations, the variant allele frequency was 0.041 among the CHD population, and 0.474 among the TUN population (Table 4). The HC-TW population differed significantly from all HapMap populations ($P < 0.01$), except for Chinese populations, such as the HCB and CHD ($P > 0.05$).

DISCUSSION

UV irradiation is a powerful inducer of SLE, and genetic variation determines the susceptibility of a person to the development of SLE. We previously reported that SLE patients were associated with DNA repair gene *XRCC1* polymorphism in the HC-TW population (21). Patients with SLE are commonly observed in RA patients. Previously report found that genetic polymorphisms of the DNA repair gene uracil-DNA glycosylase (*UNG*), 8-oxoguanine glycosylase 1 (*OGG1*), and N-methylpurine-DNA glycosylase (*MPG*) are associated with the susceptibility of RA in Taiwan population (32–34). We attempted to determine whether the functional SNP of *XRCC3* Thr241Met is the genetic factor

that reduces protection from DNA damage induced by UV exposure in SLE patients. The genetic polymorphism of DNA repair gene *XRCC3* was significantly associated with SLE in the HC-TW population. The results suggest that the HC-TW population with genotype T/C at codon 241 of *XRCC3* have a higher risk of developing SLE. No association between *XRCC1* Arg399Gln, *XRCC3* Thr241Met polymorphism and SLE patients was observed in Brazilian populations (35). *XRCC3* is one of the DNA repair genes, and encodes for a protein participating in the homologous recombination repair (HRR) of DNA double-strand breaks and cross-links (31, 36, 37). It is a member of an emerging family of Rad-51-related proteins that may participate in HRR to maintain chromosome stability and repair DNA damage (24). These phenotypes are a result of failure to initiate HRR and aberrant processing of HRR intermediates (31). Our results indicated that *XRCC3* Thr241Met SNP associated with SLE disease in the HC-TW population and the distribution profile of the SNP is significant different compared with other non-Han-Chinese populations.

The variant T allele frequencies were 0.039 in HC-TW, 0.041 in CHD, and 0.062 in HCB populations. However, the variant T allele frequencies were 0.116 in JPT, 0.429 in CEU, 0.461 in TSI, and 0.474 in TUN populations. The results of meta-analysis, based on 13 studies, indicated that the genotype and allele frequencies of the *XRCC3* Thr241Met polymorphism differed significantly between the HC-TW population and HapMap populations, except for the Han Chinese populations. The *XRCC3* systematic function remains unclear. Walker Boxes A and B are two potential ATP-binding domains (38), and suggest that the transition from hydrophilic threonine to a hydrophobic methionine can affect ATP-binding and DNA repair efficiency (31, 39). A recent study indicated that the variant allele of TUN differed significantly from all HapMap populations, except the CEU and TSI populations (38). We found that the variant allele of the HC-TW population differed significantly from all HapMap non-Han-Chinese populations. These results indicate that *XRCC3* Thr241Met SNP differs among populations worldwide.

TABLE 3. Genotype Distributions and Allele Frequencies of XRCC3 SNP Among the HC-TW Population

Genotype	Total (<i>N</i> = 191)		Woman (<i>N</i> = 157)		Man (<i>N</i> = 34)		Allele frequency		HWE <i>P</i> -value ^a
	<i>N</i>	Freq	<i>N</i>	Freq	<i>N</i>	Freq	Wild type	Variant	
rs861539: C > T (p.Thr241 > Met)									
C/C	176	0.922	143	0.911	33	0.971			
C/T	15	0.078	14	0.089	1	0.029	(C)0.961	(T)0.039	0.571
T/T	0	0	0	0	0	0			

^aWhen compared with normal controls by χ^2 tests.

TABLE 4. Genotype and Allele Frequencies of *XRCC3* p.Thr241>Met in HapMap and HC-TW Population

Population	Genotype frequency						Allele frequency		Pairwise <i>P</i> -value between HC-TW and other populations	
							Wild-type allele (C)	Variant allele (T)		
	Geno.	Freq.	Geno.	Freq.	Geno.	Freq.	Genotype	Allele		
<i>XRCC3</i> C > T (p.Thr241 > Met)										
TUN (<i>n</i> = 154)	C/C	0.312	C/T	0.428	T/T	0.260	0.526	0.474	9.19×10^{-32}	4.45×10^{-41}
CEU (<i>n</i> = 226)	C/C	0.310	C/T	0.522	T/T	0.168	0.571	0.429	7.94×10^{-36}	2.45×10^{-38}
TSI (<i>n</i> = 204)	C/C	0.324	C/T	0.431	T/T	0.245	0.539	0.461	1.28×10^{-33}	7.98×10^{-42}
LWK (<i>n</i> = 220)	C/C	0.582	C/T	0.364	T/T	0.055	0.764	0.236	2.94×10^{-14}	1.15×10^{-15}
MKK (<i>n</i> = 310)	C/C	0.645	C/T	0.310	T/T	0.045	0.800	0.200	2.13×10^{-11}	8.73×10^{-13}
MEX (<i>n</i> = 114)	C/C	0.719	C/T	0.246	T/T	0.035	0.842	0.158	5.32×10^{-6}	3.04×10^{-7}
GIH (<i>n</i> = 202)	C/C	0.574	C/T	0.356	T/T	0.069	0.752	0.248	1.70×10^{-14}	1.49×10^{-16}
YRI (<i>n</i> = 288)	C/C	0.660	C/T	0.319	T/T	0.021	0.819	0.181	2.64×10^{-10}	8.47×10^{-11}
ASW (<i>n</i> = 114)	C/C	0.684	C/T	0.281	T/T	0.035	0.825	0.175	2.43×10^{-7}	1.34×10^{-8}
JPT (<i>n</i> = 224)	C/C	0.777	C/T	0.214	T/T	0.009	0.884	0.116	2.00×10^{-4}	5.15×10^{-5}
HCB (<i>n</i> = 274)	C/C	0.876	C/T	0.124	T/T	0.000	0.938	0.062	0.116	0.126
CHD (<i>n</i> = 218)	C/C	0.917	C/T	0.083	T/T	0.000	0.959	0.041	0.881	0.884
HC-TW (<i>n</i> = 191)	C/C	0.922	C/T	0.078	T/T	0.000	0.961	0.039		

Population data source: (www.hapmap.org).

n, number of individuals

TUN, Tunisian; CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; TSI, Tuscan in Italy; LWK, Luhya in Webuye, Kenya; MKK, Maasai in Kinyawa, Kenya; MEX, Mexican ancestry in Los Angeles, California; GIH, Gujarati Indians in Houston; YRI, Yoruban in Ibadan, Nigeria; ASW, African ancestry in Southwest USA; JPT, Japanese in Tokyo, Japan; HCB, Han Chinese in Beijing, China; CHD, Chinese in Metropolitan Denver, Colorado, Texas; HC-TW, Han Chinese in Taiwan.

P < 0.05, a significant difference between HC-TW and other populations.

P > 0.05, no significant difference between HC-TW and other populations.

This study identified the polymorphism in the DNA repair gene *XRCC3* Thr241Met and its associations with SLE risk in the HC-TW population. The meta-analysis of *XRCC3* Thr241Met polymorphism showed a significant difference between the HC-TW population and the HapMap populations.

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