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Association of Polymorphisms in DNA Repair Gene *XRCC3* with Asthma in Taiwan

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Abstract. *Aim: Accumulating evidence suggests that DNA damage and repair play a role in asthma etiology, however, little is known about the contribution of genotypes of DNA repair genes to asthma susceptibility. This study aimed to examine the contribution of genotypes of DNA double-strand break repair gene X-ray repair cross complementing protein 3 (XRCC3) and its polymorphisms to asthma risk in the Taiwanese. Materials and Methods: Associations of seven XRCC3 genotypes, namely rs1799794, rs45603942, rs861530, rs3212057, rs1799796, rs861539 and rs28903081, with the risk of asthma were investigated among 198 patients with asthma and 453 non-asthma controls by polymerase chain reaction-restriction fragment length polymorphism genotyping methodology. Results: Unlike Caucasian populations, no polymorphic genotypes at XRCC3 rs3212057 or rs28903081 were found among the Taiwanese. For the genotypes of XRCC3 rs1799794, rs45603942, rs861530, rs1799796 and rs861539, the percentages of hetero-and homo-variant genotypes were not differentially represented between the asthma patient and the non-asthma control groups. In addition, there was no differential distribution of allelic frequencies for these XRCC3 polymorphic sites between the two groups. No interaction of these genotypes with gender or age were found. Conclusion: Although XRCC3 plays a role in asthma etiology, the variant XRCC3 genotypes do not serve as practicable predictive markers for asthma risk in Taiwanese.*

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Asthma, characterized by reversible airflow obstruction, airway inflammation, remodeling, and hyper-responsiveness, is a complex disease with variable phenotype and aberrant T-helper (Th) 2 cytokine profile (1, 2). Frequently, asthma is divided into two subtypes: allergic and non-allergic (3). Allergic asthmatic patients are, in general, younger and have a better response to conventional therapy. Non-allergic asthmatic patients are often those with adult onset; it is associated with non-allergic co-morbidities, such as rhinosinusitis and gastroesophageal reflux, and is less responsive to conventional therapy (3). Over the past three decades, there has been a significant increase in the number of patients diagnosed with asthma (4), reportedly comprising more than 300 million people around the world (5). Etiologically, asthma is determined by the interaction of genetic and environmental components; the contribution of heritability to the susceptibility to asthma was estimated to vary between 36-79% (6, 7). The fact that genetic factors play a role in the pathogenesis of asthma has been recognized for more than 100 years (4). The mechanism of asthma etiology is still poorly understood and asthma progresses with various unidentifiable causes. Although continuously studied, like for cancer, difficulty remains in identifying specific causal genes and determining whether ethnic disparities should be attributed to the genetic control of certain genes for asthma. In recent

years, more than 200 asthma candidate genes have been proposed by different approaches, such as human association and positional cloning (8, 9).

The X-ray repair cross-complementing group 3 (*XRCC3*) encodes for the DNA repair protein XRCC3. It is a member of RAD51 recombinase-related protein family that plays a role in homologous recombination to repair double-strand breaks (DSB) induced by exogenous and endogenous DNA insults and maintain the overall integrity of the human genome (10). In literature, several studies were performed to evaluate the relationship between rs861539 C/T polymorphism (also named Thr241Met, T241M, C18067T and C722T) of the *XRCC3* gene and cancer risk, making it the most commonly studied polymorphism of the *XRCC3* gene (11-14). In literature, the studies investigating the contribution of *XRCC3* rs861539 polymorphism to cancer report controversial findings. Some of them (15-20), but not others (21-23) have identified T variants of *XRCC3* rs861539 to be associated with increased risk for cancer. However, none of the previous literature has discussed its contribution to asthma. The lack of analysis for asthma may be due to the limited sample size and lack of early detection and predictive markers for asthma.

However, there is no study to date to have examined the association between *XRCC3* genotypes and the risk of asthma, and the contribution of *XRCC3* genotypes and phenotype to asthma is largely unknown. Thus, in the current study, we aimed to determine whether *XRCC3* genotypes can serve as novel genomic biomarker of asthma for a Taiwanese population, which has a high prevalence of asthma. To fulfill the purpose, the rs1799794, rs45603942, rs861530, rs3212057, rs1799796, rs861539 and rs28903081 polymorphisms of *XRCC3* were determined to investigate whether these polymorphisms were associated with the risk of asthma in Taiwanese.

Materials and Methods

Study population. A total of 198 patients with asthma were recruited at the China Medical University Hospital. The medical history was reviewed, and the data were entered into the database. At the same time, 453 healthy individuals, who had been matched with the patients by age (±5 years), admitted to the same hospital for health checkup (similar residential areas) and who had no previous diagnosis of neoplastic disease or other malignancy were enrolled as matched controls. All the participants enrolled provided their informed consent to use of than tissue and data, and Human Research Committees approved this study (CMUH106-REC1-004). After binge interviewed, 5 ml of venous blood sample was collected from each participant and used for DNA extraction and further genotyping assays as described below. The selective demographic information for the participants is summarized in Table I.

Genotyping conditions. Genomic DNA from the peripheral blood leucocytes of each patient and matched control was prepared using the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed as per our previous articles (24, 25).

Table I. *Distributions of age and gender of the 198 patients with asthma and the 453 matched controls.*

Characteristic	Controls (n=453)		Patients (n=198)		*p*-Value[a]
	n	%	n	%	
Age (years)					
25-40	285	63.4%	133	67.2%	
>40	168	36.6%	65	32.8%	0.2972
Gender					
Male	190	41.9%	83	41.9%	
Female	263	58.1%	115	58.1%	0.9956

[a]Based on chi-square without Yate's correction test.

In this study, a total of seven polymorphic sites were analyzed for all the participants in both the control and asthma patient groups. In brief, the seven polymorphic sites were genotyped by typical polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodologies. PCR was performed on a BioRad Mycycler (BioRad, Hercules, CA, USA) following the normal manufacturer's instructions. Each PCR reaction consisted of 5 min initial cycle at 94˚C for 5 min; 40 cycles of 94˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s; and a final extension at 72˚C for 10 min. Then the SNP-containing DNA amplicons were subjected to individual overnight digestion by restriction endonucleases following the manufacturer's instructions (see Table II for details). Following digestion, each sample was immediately analyzed by agarose gel electrophoresis. The agarose gel was 3% and the electrophoresis conditions were 100 V for 20 min. The genotype analysis was performed by three researchers independently and blindly.

Statistical analyses. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotypic frequencies of *XRCC3* SNPs in the controls from those expected under the Hardy–Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's chi-square test was performed to compare the distributions of the *XRCC3* genotypes between the two groups. The associations between the *XRCC3* genotypes and asthma were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs). Differences with values of $p<0.05$ were considered statistically significant.

Results

As we matched all the controls and cases by age and gender, there was no difference between the two groups in these aspects ($p=0.2972$ and 0.9956, respectively) (Table I).

The distributions of genotypic frequencies of the seven *XRCC3* SNPs examined are summarized and shown in Table III. Firstly, we found the genotypes at rs3212057 and rs28903081 of *XRCC3* were the same for all members of this Taiwanese population (Table III). Secondly, the distributions of the genotypes at *XRCC3* rs1799794, rs45603942, rs861530, rs1799796 or rs861539 did not significantly differ between the

Table II. *Summary of the rs numbers, designed primers, restriction enzymes used and amplicon length before and after enzyme digestion for all the seven X-ray repair cross complementing protein 3 (XRCC3) single nucleotide polymorphisms.*

rs number	Primer sequence	Restriction enzyme	Amplicon length	Allele: enzymatic fragment size
rs1799794	F: 5'-CACACTGCGGTCTTGCAGTG-3'	*Bts*CI	505 bp	G: 505 bp
	R: 5'-CAGGCTGGGTCTGGATACAA-3'			A: 289 + 216 bp
rs45603942	F: 5'-GGGATGCAGGTTCAACTGAC-3'	*Alu*I	352 bp	C: 352 bp
	R: 5'-AACTTGGACTGTGTCAAGCA-3'			T: 187 + 165 bp
rs861530	F: 5'-CCGAGGAACGTGCTGAACTT-3'	*Fat*I	497 bp	G: 497 bp
	R: 5'-CTCCCTAACAGCCTCCATGT-3'			A: 293 + 204 bp
rs3212057	F: 5'-CCATGACCGCAGGCACTTGT-3'	*HpyCH4*III	455 bp	G: 455 bp
	R: 5'-AGAACGCGACAAGGATGGTA-3'			A: 235 + 220 bp
rs1799796	F:5'-GG AACCAGTTGT GTGAGCCT-3'	*Alu*I	430 bp	G: 430 bp
	R: 5'-CCTGGTTGATGCACAGCACA-3'			A: 226 + 204 bp
rs861539	F: 5'-GACACCTTGT TGGAGTGTGT-3'	*Fat*I	358 bp	C: 358 bp
	R: 5'-GTCTTCTCGATGGTTAGGCA-3'			T: 200 + 158 bp
rs28903081	F: 5'-CTGCTTCCTGTTTCTCAGGT-3'	*Bst*UI	198 bp	A: 198 bp
	R: 5'-GCACTGATCGTGTAGGAACA-3'			G: 102 + 96 bp

case and control groups (Table III). For instance, the frequencies of the heterozygous variant AG and homozygous variant AA of *XRCC3* rs1799794 were 53.5 and 21.2% in asthma cases and 56.0 and 19.9% in controls, respectively. The AG (OR=0.91, 95% CI=0.61-1.36), and AA (OR=1.02, 95% CI=0.62-1.67) genotype at *XRCC3* rs1799794 seemed not to be a risk factor for asthma in Taiwan (Table III). The findings for *XRCC3* rs45603942, rs861530, rs1799796 and rs861539 were similar to those of *XRCC3* rs1799794 (Table III). Overall, there was no significant difference in the distribution of these *XRCC3* genotypes between the cases and controls (p for trend all >0.05) (Table III).

The distributions of allelic frequencies of the five *XRCC3* SNPs found to have different genotypes among Taiwanese in Table III are summarized in Table IV. Supporting the findings in Table III, none of the variants were associated with increased risk of asthma (Table IV).

Since age and gender may play a role in asthma, we are also interested in the interaction of the genotypes with the age and gender of the participants. The analysis of age and gender stratifications showed that the genotypic distributions of these variant genotypes of *XRCC3* were not significantly different among all the subgroups (data not shown).

Discussion

Asthma is well characterized by chronic inflammation in the conducting airways which leads to bronchial obstruction and airway hyper-responsiveness (26). Immune cells of patients with asthma generate many genotoxic reactive oxygen and nitrogen species (RONS), that can be measured in peripheral blood, induced sputum, and bronchoalveolar lavage fluid from the lungs of the patients with asthma (27, 28). RONS can damage lipids, proteins and nucleic acids (29), and very

Table III. *Distribution of X-ray repair cross complementing protein 3 (XRCC3) genotypes among patients with asthma and healthy controls.*

	Controls (n=453)		Patients (n=198)			
Genotype	n	%	n	%	p-Value[a]	Odds ratio (95% CI)
rs1799794					0.8340	
GG	109	24.1%	50	25.3%		1.00 (Reference)
AG	254	56.0%	106	53.5%	0.6465	0.91 (0.61-1.36)
AA	90	19.9%	42	21.2%	0.9459	1.02 (0.62-1.67)
rs45603942					0.9440	
CC	422	93.1%	183	92.4%		1.00 (Reference)
CT	25	5.5%	12	6.1%	0.7791	1.11 (0.54-2.25)
TT	6	1.5%	3	1.5%	>0.9999	1.15 (0.29-4.66)
rs861530					0.7873	
AA	131	28.8%	60	30.3%		1.00 (Reference)
AG	248	54.5%	109	55.1%	0.8314	0.96 (0.66-1.40)
GG	76	16.7%	29	14.6%	0.4958	0.83 (0.49-1.41)
rs3212057					>0.9999	
GG	453	100.0%	198	100.0%		-
AG	0	0.0%	0	0.0%		-
AA	0	0.0%	0	0.0%		-
rs1799796					0.5751	
AA	207	45.7%	86	43.4%		1.00 (Reference)
AG	221	48.8%	97	49.0%	0.7562	1.06 (0.75-1.49)
GG	25	5.5%	15	7.6%	0.2930	1.44 (0.73-2.87)
rs861539					0.4489	
CC	412	91.0%	174	87.9%		1.00 (Reference)
CT	34	7.5%	19	9.6%	0.3499	1.32 (0.73-2.38)
TT	7	1.5%	5	2.5%	0.3699	1.69 (0.53-5.40)
rs28903081					>0.9999	
GG	453	100.0%	198	100.0%		-
AG	0	0.0%	0	0.0%		-
AA	0	0.0%	0	0.0%		-

CI: Confidence interval. [a]Based on chi-square test without Yates' correction (all numbers of 5 or more) or Fisher's exact test (for numbers of less than 5).

Table IV. *Distribution of X-ray repair cross complementing protein 3 (XRCC3) alleles among the patients with asthma and healthy controls.*

Allele	Controls		Patients		*p*-Value[a]	Odds ratio (95% CI)
	n	%	n	%		
rs1799794						
Allele G	472	52.1%	206	52.1%	0.9796	1.00 (Reference)
Allele A	434	47.9%	190	47.9%		1.00 (0.79-1.27)
rs45603942						
Allele C	869	95.9%	378	95.5%	0.7033	1.00 (Reference)
Allele T	37	4.1%	18	4.5%		1.12 (0.63-1.99)
rs861530						
Allele A	510	56.3%	229	57.8%	0.6066	1.00 (Reference)
Allele G	396	43.7%	167	42.2%		0.94 (0.74-1.93)
rs1799796						
Allele A	635	70.1%	269	67.9%	0.4366	1.00 (Reference)
Allele G	271	29.9%	127	32.1%		1.11 (0.86-1.43)
rs861539						
Allele C	858	94.7%	367	92.7%	0. 1541	1.00 (Reference)
Allele T	48	5.3%	29	7.3%		1.41 (0.88-2.28)

CI: Confidence interval. [a]Based on Chi-square test.

possibly contribute to increased asthma severity (28). Among the typical types of DNA lesions, DNA DSBs are the most cytotoxic forms of damage, and if they are not properly and timely repaired, they can lead to genomic rearrangements and cell death (30). The house dust mite, one of most common allergens implicated in asthma, affecting 50 to 85% of patients (31), was reported to cause airway inflammation, oxidative DNA damage and cell death in the airway (32). In addition, direct exposure of bronchial epithelial cells to dust mites may induce DNA damage and RONS production (32). Furthermore, increased levels of DSB repair proteins were found in the lung tissues from humans and dust mite-induced asthmatic mice, and inhibiting the DSB repair protein expression in bronchial epithelial cells can further increase the levels of proinflammatory cytokine production and cell apoptosis (32). All these findings point to a potential role of the DSB repair system in asthma pathophysiology.

Following the concept that XRCC3 plays an important role in the DSB repair system, we firstly examined the genotypes of *XRCC3* rs1799794, rs45603942, rs861530, rs3212057, rs1799796, rs861539 and rs28903081 in Taiwanese patients with asthma and investigated their associations with risk of asthma in Taiwan. The sample size is very representative including198 patients with asthma and 453 age-and gender-matched healthy individuals (Table I). We found that two sites, rs3212057 and rs28903081, were not polymorphic among this Taiwanese group, and the others (rs1799794, rs45603942, rs861530, rs1799796 and rs861539) did not fit the criteria to serve as novel genomic determinants for the risk of asthma in practice (Tables III and IV). Regard the interaction analysis between *XRCC3* genotype and age or gender, we have found that none of them was associated with elevated asthma risk among those of younger age (25-40 years old), older (more than 40 years old), male or female patients (data not shown).

Although the findings are all negative, the current study helps to shed light on the potential role of functional polymorphisms in *XRCC3* in asthma in Taiwanese. In the past decade, scientists have paid less attention to the genotypic or phenotypic role of XRCC3 in asthma, thus the related investigations are very few. The team of Chan has provided some interesting evidence showing that the DSB repair system is worthy of further investigation (32) and the studies of Ghonim *et al.* (33) and Mishra *et al.* (34) demonstrated that long-term inhibition of DNA-dependent protein kinase (DNAPK) has beneficial effects on asthma. Ghonim and his colleagues showed that DNAPK inhibition reduced airway inflammation and airway hyper-responsiveness (33). Furthermore, Mishra and colleagues showed that DNAPK inhibition in dendritic cells reduced airway inflammation (34). In the near future, we hope to reveal the contribution of other DSB repair members to asthma pathophysiology, and their role as novel biomarkers in prediction of asthma risk.

In conclusion, we found that although XRCC3 may play a role in the asthma initiation and progression, its genotypes do not serve as good predictive or preventive biomarkers in the Taiwanese.

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