

The contribution of *XRCC3* genotypes to childhood acute lymphoblastic leukemia

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Purpose: A growing body of evidence shows an association between DNA repair protein genotypes and susceptibility to various cancers. However, few studies have assessed the contribution of the genotype of *XRCC3*, a homologous repair gene, to the occurrence or prognosis of childhood acute lymphoblastic leukemia (ALL). In this study, we investigated the contribution of seven *XRCC3* polymorphisms to childhood ALL.

Patients and methods: We recruited 266 patients with childhood ALL and 266 healthy controls. Genomic DNA was isolated from peripheral blood samples. The *XRCC3* rs1799794, rs45603942, rs1799796, rs861530, rs28903081, rs861539, and rs3212057 polymorphic genotypes of each subject were determined through conventional polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis.

Results: Genotypes with the rs861539 polymorphism were significantly associated with the risk of childhood ALL. The allelic distribution analyses suggested a significant association between the T allele at rs861539 with an increased risk of childhood ALL in the Taiwanese population. Polymorphic variants of *XRCC3* at rs3212057 or rs28903081 did not exist in the study population. *XRCC3* rs1799794, rs45603942, rs1799796, and rs861530 were not significantly associated with the risk of childhood ALL in the Taiwanese population.

Conclusion: Our findings suggest that *XRCC3* genotypes with polymorphisms at rs861539 may play a role in determining individual susceptibility to childhood ALL in this Taiwanese population. The polymorphism may be a potential detector and predictor of childhood ALL.

Keywords: acute lymphoblastic leukemia, ALL, childhood, genotype *XRCC3*, polymorphism, Taiwan

Introduction

Leukemia is the most common cancer among children worldwide, and the majority of leukemia cases develop in the absence of any known predisposing factor. However, several germline genetic mutations, which can either be inherited or occur de novo in the patient's germline, are associated with the development of leukemia.¹ The possibility that genetic factors play a crucial role in the development of childhood acute lymphoblastic leukemia (ALL) is supported by the following evidence. First, Down's syndrome and Fanconi anemia, which are both inherited genetic human diseases, are associated with an increased risk of ALL.^{2,3} Second, genetic mutations in several cancer-related genes, such as *p53*, *N-ras*, and *PHF6*, are prevalent in patients with ALL.⁴ Third, only a small fraction of children who have been exposed to relevant environmental factors develop ALL. These findings indicate that genomic predisposition likely has

a greater contribution to the development of childhood ALL than environmental factors.⁵ Discovering useful biomarkers for early detection and prediction of childhood ALL may help improve surveillance guidelines for affected children and their families. In addition, these markers may help deepen our understanding of the genetic polymorphisms related to the etiology of ALL.

XRCC3 encodes the DNA repair protein XRCC3, which is a member of the homologous recombination DNA repair subpathway that removes double-stranded breaks from the human genome.⁶ Subtle polymorphic variations among individuals determine the differences in the human phenotypes. Among all known single-nucleotide polymorphisms (SNPs), the famous rs861539 C/T polymorphism (also called Thr241Met, T241M, C18067T, and C722T) of the *XRCC3* gene is the most commonly studied because of its association with several human diseases, such as cancers.^{7–10} The T variants of *XRCC3* rs861539 are associated with an increased risk of nasopharyngeal carcinoma¹¹ and lung cancer,¹² but are not associated with oral cancer.¹³ The findings for breast cancer are equivocal, as several studies have reported a positive association^{14–16} while others have not.^{17,18} However, the contribution of *XRCC3* to childhood ALL has not been well investigated,^{19–21} and current studies have found no significant association. In 2014, Smolkova et al¹⁹ investigated the contribution of *XRCC3* genotypes together with those of NBN and PPP1R13B to the susceptibility of childhood ALL. They found that no genotype of rs1799794, rs861530, and rs861539 on *XRCC3* individually, or any haplotype or diplotype among them, was associated with altered risk of childhood ALL in a representative population of 460 pediatric ALL cases and 552 healthy controls. They successfully developed a haplotype-based methodology to examine the contribution of a candidate gene to a specific human disease, such as *XRCC3* in childhood ALL in this case. In the current study, we not only evaluated the three SNPs (rs1799794, rs861530, and rs861539) they investigated, but also explored four additional SNPs (rs45603942, rs3212057, rs1799796, and rs28903081). The role of *XRCC3* rs1799794, rs861530, and rs861539 should be validated in many populations with representative samples, and whether other SNPs also contribute to the susceptibility of childhood ALL should also be investigated. Thus, we performed this study to determine whether *XRCC3* genotypes serve as novel biomarkers of childhood ALL in a representative Taiwan population. Specifically, we examined the association between the rs1799794, rs45603942, rs861530, rs3212057, rs1799796,

rs861539, and rs28903081 polymorphisms of *XRCC3* and the risk of childhood ALL.

Materials and methods

Patients and controls

This study protocol was approved by the Institutional Review Board of China Medical University Hospital (DMR103-IRB-153). Written informed consent was obtained from one or both parents of all participants. Briefly, children with ALL <18 years were identified and entered into the study by pediatric clinicians with pathological confirmation, regardless of the age or stage they were diagnosed. Thus, 266 children who had been diagnosed with ALL were recruited from the Department of Pediatrics of China Medical University Hospital (Taichung City) in Taiwan during 2005–2010. All children completed a detailed history taking and provided peripheral blood samples. In addition, an equal number of age- and gender-matched healthy volunteers were recruited as the control group in accordance with the method for initial random sampling established by the Health Examination Cohort during 2005–2010 as published previously.^{22–24} Finally, a total of 457 Taiwanese volunteers aged <18 years were recruited into the study.

XRCC3 genotyping

Genomic DNA from the peripheral blood samples of each participant was extracted, aliquoted, and stored as described previously.^{25–27} Seven polymorphic sites were analyzed. Briefly, the seven polymorphic sites were genotyped through conventional polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) methodology. PCR was performed on the BioRad Mycycler (Bio-Rad Laboratories Inc., Hercules, CA, USA) following the manufacturer's instructions. The PCR conditions for the genotyping experiments consisted of a 5 minutes initial cycle at 94°C, 40 cycles at 94°C for 30 seconds, 55°C for 30 seconds, 72°C for 30 seconds; and a final 10 minutes extension at 72°C. SNP-containing DNA amplicons were digested overnight with specific restriction endonucleases following the manufacturer's instructions as our team published previously.^{28,29} Following digestion, each sample was immediately resolved through 3% agarose gel electrophoresis at 100 V for 20 minutes. All genotypic processing was repeated and performed blindly by at least two independent researchers, and the results were 100% concordant with each other. About 3%–5% of the SNP samples were subject to direct sequencing, and the consistency between PCR-RFLP recognition and direct sequencing was 100%. The success rate of PCR-RFLP was 100%.

Statistical analysis

We evaluated the sample size for the study group; the estimated sample size was 199 in each group with $\alpha = 5\%$, power = 80%, the proportion of homozygous mutants in the case group = 10%, and difference = 10%. This assessment indicates that the sample size for the present study was adequate and sufficient. Pearson's chi-squared test without the Yates' correction or Fisher's exact test was used to compare the distribution of *XRCC3* genotypes between the case and control groups. The association between the *XRCC3* polymorphisms and childhood ALL risk was estimated by computing ORs and 95% CIs through unconditional logistic regression analysis after adjusting for possible confounding factors if needed.

Results

Comparison of the basic demographic characteristics of the childhood ALL cases and controls

The frequency distributions of the demographic characteristics of the 266 childhood ALL cases and 266 controls are summarized and compared in Table 1. Age and gender did not differ between the case and control groups because the case and control groups had been closely matched during subject recruitment ($P > 0.05$) (Table 1).

Analysis of the association between the seven *XRCC3* SNPs and the risk of childhood ALL

With the PCR-RFLP methods introduced in Table 2, the distributions of the frequencies of the *XRCC3* polymorphic genotypes in the childhood ALL cases and controls are summarized and compared in Table 3. First, the *XRCC3* rs3212057 and rs28903081 polymorphisms were not found in the cases or the controls. All subjects were of the same wild-type genotype at these polymorphic sites (Table 3). Second, the crude ORs for individuals with variant CT and TT genotypes at *XRCC3* rs861539 were 2.31 (95%

CI = 1.30–4.12, $P = 0.0037$) and 2.44 (95% CI = 0.91–6.53, $P = 0.0675$) compared with those for individuals carrying the CC wild-type genotype (Table 3). The P -value for the trend analysis was also significant ($P = 0.0039$) (Table 3). The distributions of *XRCC3* rs1799794, rs45603942, rs861530, and rs1799796 in the case and control groups did not differ (Table 3). A representative RFLP electrophoresis analysis of the PCR product for *XRCC3* rs861539 is shown in Figure 1.

Analysis of the association between the *XRCC3* allelic types at the seven SNP sites and the risk of childhood ALL

Supporting the findings in Table 3, the distribution of the *XRCC3* rs861539 allelic frequencies differed significantly between the childhood ALL cases and the control group (Table 4). The crude OR of the subjects carrying the T allele at *XRCC3* rs861539 was 2.25 (95% CI = 1.44–3.51, $P = 0.0003$, Table 4). *XRCC3* rs1799794, rs45603942, rs861530, and rs1799796 were not associated with an increased risk of childhood ALL (Table 4).

Stratification analysis for *XRCC3* rs861539 according to age and gender

We further evaluated the effects of *XRCC3* rs861539 on susceptibility to childhood ALL by stratifying their age

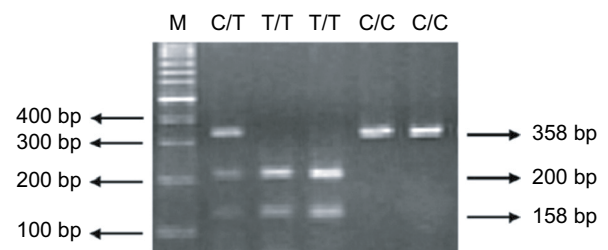


Figure 1 Restriction fragment length polymorphism electrophoresis analysis of the polymerase chain reaction product of *XRCC3* rs861539.

Notes: The CC wild-type genotype is shown in lanes 5 and 6. Lanes 3 and 4 show the TT homovariant genotype, whereas lane 2 shows the C/T heterovariant genotype, respectively. Lane 1 (marked as M) is the DNA 100 bp molecular weight marker.

Table 1 Distribution of selected demographics of the 266 childhood ALL patients and the 266 matched controls

Characteristics	Controls (n=266)			Patients (n=266)			P-value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age at onset (years)			8.3 (4.8)			7.0 (4.4)	0.6483 ^a
Gender							1.0000 ^b
Male	148	55.6		148	55.6		
Female	118	44.4		118	44.4		

Notes: ^aBased on Student's t-test; ^bBased on chi-squared test.

Abbreviation: ALL, acute lymphoblastic leukemia.

Table 2 Summary of the rs numbers, designed primers, amplicon length before and after enzyme digestion, and the specific restriction enzymes according to their allelic genotypes for all the seven *XRCC3* SNPs

rs number	Primer sequence ^a	Restriction enzyme	Amplicon length (bp)	Allelic genotypes and enzymatic fragment sizes
rs1799794	F: 5'-CACACTGCGGTCTTGCAGTG-3' R: 5'-CAGGCTGGGTCTGGATACAA-3'	<i>BtsCI</i>	505	G: 505 bp A: 289+216 bp
rs45603942	F: 5'-GGGATGCAGGTTCAACTGAC-3' R: 5'-AACTTGGACTGTGTCAAGCA-3'	<i>AluI</i>	352	C: 352 bp T: 187+165 bp
rs861530	F: 5'-CCGAGGAACGTGCTGAACTT-3' R: 5'-CTCCCTAACAGCCTCCATGT-3'	<i>FatI</i>	497	G: 497 bp A: 293+204 bp
rs3212057	F: 5'-CCATGACCGCAGGCACTTGT-3' R: 5'-AGAACGCGACAAGGATGGTA-3'	<i>HpyCH4III</i>	455	G: 455 bp A: 235+220 bp
rs1799796	F: 5'-GG AACCAGTTGT GTGAGCCT-3' R: 5'-CCTGGTTGATGCACAGCACA-3'	<i>AluI</i>	430	G: 430 bp A: 226+204 bp
rs861539	F: 5'-GACACCTTGT TGGAGTGTGT-3' R: 5'-GTCTTCTCGATGGTTAGGCA-3'	<i>FatI</i>	358	C: 358 bp T: 200+158 bp
rs28903081	F: 5'-CTGCTTCTGTTTCTCAGGT-3' R: 5'-GCACTGATCGTGTAGGAACA-3'	<i>BstUI</i>	198	A: 198 bp G: 102+96 bp

Notes: ^aF and R indicate forward and reverse primers, respectively.

Abbreviation: SNPs, single-nucleotide polymorphisms.

Table 3 Distribution of *XRCC3* genotypes among the childhood ALL and healthy controls

Genotype	Controls (n=266)	%	Patients (n=266)	%	P-value ^a	OR (95% CI)
rs1799794						
GG	63	23.7	67	25.2		1.00 (ref)
AG	150	56.4	144	54.1	0.6270	0.90 (0.60–1.36)
AA	53	19.9	55	20.7	0.9250	0.98 (0.59–1.63)
<i>P</i> _{trend}					0.8682	
rs45603942						
CC	242	91.0	239	89.9		1.00 (ref)
CT	16	6.0	16	6.0	0.9727	1.01 (0.50–2.07)
TT	8	3.0	11	4.1	0.4829	1.39 (0.55–3.52)
<i>P</i> _{trend}					0.7818	
rs861530						
AA	77	29.0	80	30.1		1.00 (ref)
AG	144	54.1	147	55.2	0.9292	0.98 (0.67–1.45)
GG	45	16.9	39	14.7	0.5030	0.83 (0.49–1.42)
<i>P</i> _{trend}					0.7723	
rs3212057						
GG	266	100.0	266	100.0		1.00 (ref)
AG	0	0.0	0	0.0		
AA	0	0.0	0	0.0		
<i>P</i> _{trend}					1.0000	
rs1799796						
AA	121	45.5	116	43.6		1.00 (ref)
AG	129	48.5	130	48.9	0.7813	1.05 (0.74–1.50)
GG	16	6.0	20	7.5	0.4598	1.30 (0.64–2.64)
<i>P</i> _{trend}					0.7581	
rs861539						
CC	241	90.6	214	80.4		1.00 (ref)
CT	19	7.1	39	14.7	0.0037*	2.31 (1.30–4.12)
TT	6	2.3	13	4.9	0.0675	2.44 (0.91–6.53)
<i>P</i> _{trend}					0.0039*	
rs28903081						
GG	266	100.0	266	100.0		1.00 (ref)
AG	0	0.0	0	0.0		
AA	0	0.0	0	0.0		
<i>P</i> _{trend}					1.0000	

Notes: ^aP-value based on chi-squared test. *Statistically significant.

Abbreviation: ALL, acute lymphoblastic leukemia.

and gender, and the results are presented in Tables 5 and 6, respectively. The association between the *XRCC3* rs861539 genotype and childhood ALL was significant for children aged <3.5 years, but not for those ≥3.5 years (Table 5). The association between the *XRCC3* rs861539 genotype and childhood ALL was slightly significant for boys and girls (Table 6).

Discussion

Adducts or strand breaks induced by DNA-damaging agents are systematically and efficiently removed immediately after they are detected. Removal of damaged DNA sites is the main protective mechanism of living cells against potentially harmful genomic modifications.^{30,31} Hundreds of thousands of DNA adducts and strand breaks are repaired promptly and rapidly or genomic instability intensifies and becomes irreversible, resulting in cell death or carcino-

genesis. Several studies since 2000³² have investigated the contribution of DNA repair gene polymorphisms to childhood ALL and identified useful biomarkers, such as *XRCC1* codon 194,^{33,34} *XRCC1* codon 399,^{33,35} *human 8-oxoG DNA glycosylase 1* codon 326,³⁶ and *NBN* codon 185,²¹ for early detection and prediction of childhood ALL susceptibility. We have also investigated the association among several DNA repair genes in Taiwan^{37–39} and first revealed that the *XRCC4* G-1394T (rs6869366) and intron 3 DIP (rs28360071) genotypes were associated with an increased risk for childhood ALL.³⁹ Several combined predictors, such as *XRCC1* codon 399 plus *OGGI* codon 326,⁴⁰ and *OGGI* codon 326 plus *MUTYH* codon 165, have also been proposed.⁴⁰ These findings are inconclusive; thus, further multi-population and multi-institutional investigations should be conducted. The contribution of other DNA repair genes, such as *XRCC3*, has yet to be investigated.

Table 4 Distribution of *XRCC3* alleles among the childhood ALL patients and healthy controls

Allele	Controls	%	Patients	%	P-value ^a	OR (95% CI)
rs1799794						
Allele G	276	51.9	278	52.3	0.9023	1.00 (ref)
Allele A	256	48.1	254	47.7		0.99 (0.77–1.25)
rs45603942						
Allele C	500	94.0	494	92.9	0.4581	1.00 (ref)
Allele T	32	6.0	38	7.1		1.20 (0.74–1.95)
rs861530						
Allele A	298	56.0	307	57.7	0.5775	1.00 (ref)
Allele G	234	44.0	225	42.3		0.93 (0.73–1.19)
rs1799796						
Allele A	371	69.7	362	68.0	0.5512	1.00 (ref)
Allele G	161	30.3	170	32.0		1.08 (0.83–1.40)
rs861539						
Allele C	501	94.2	467	87.8	0.0003*	1.00 (ref)
Allele T	31	5.8	65	12.2		2.25 (1.44–3.51)

Note: ^aP-value based on chi-squared test. *Statistically significant.

Abbreviation: ALL, acute lymphoblastic leukemia.

Table 5 ORs for *XRCC3* rs861539 genotype and childhood ALL after stratification by age

Genotype	<3.5 years old, n		OR (95% CI) ^a	aOR (95% CI) ^b	P-value ^c	≥3.5 years old, n		OR (95% CI) ^a	aOR (95% CI) ^b	P-value
	Controls	Cases				Controls	Cases			
AA	121	99	1.00 (ref)	1.00 (ref)	0.0030*	120	115	1.00 (ref)	1.00 (ref)	0.2929
AG	9	24	3.26 (1.45–7.33)	3.14 (1.59–6.78)		10	15	1.57 (0.68–3.63)	1.49 (0.63–3.27)	
GG	3	10	4.07 (1.09–15.21)	3.98 (1.14–11.94)	0.0025*	3	3	1.04 (0.21–5.28)	1.16 (0.33–6.48)	0.9589
<i>P</i> _{trend}					0.0017*					0.5751

Notes: ^aMultivariate logistic regression analysis; ^bMultivariate logistic regression analysis after adjusted of gender; ^cP-value based on chi-squared test. *Statistically significant.

Abbreviation: ALL, acute lymphoblastic leukemia.

Table 6 ORs for *XRCC3* rs861539 genotype and childhood ALL after stratification by gender

Genotype	Males, n		OR (95% CI) ^a	aOR (95% CI) ^b	P-value ^c	Females, n		OR (95% CI) ^a	aOR (95% CI) ^b	P-value
	Controls	Cases				Controls	Cases			
AA	135	114	1.00 (ref)	1.00 (ref)		106	100	1.00 (ref)	1.00 (ref)	
AG	9	25	3.29 (1.48–7.33)	3.07 (1.63–6.59)	0.0024*	10	14	1.48 (0.63–3.49)	1.54 (0.61–3.67)	0.3640
GG	4	9	2.66 (0.80–8.88)	2.25 (0.58–9.47)	0.0987	2	4	2.12 (0.38–11.83)	2.23 (0.51–13.38)	0.3814
<i>P</i> _{trend}					0.1492					0.0012*

Notes: ^aMultivariate logistic regression analysis; ^bMultivariate logistic regression analysis after adjusted of age; ^cP-value based on chi-squared test. *Statistically significant.

Abbreviation: ALL, acute lymphoblastic leukemia.

XRCC3 is involved in the homologous recombination repair of double-stranded DNA and chromosomal fragmentation, translocations, and deletions.⁴¹ In 2003, Hinz et al reported that the hamster cell line *irs1SF* cannot produce normal cell-cycle checkpoint responses to double-strand break-induced programmed cell death because it is deficient in the homologous recombination repair gene *XRCC3*.⁴² However, the contribution of *XRCC3* genotypes to cancer susceptibility remains largely unknown, and few researchers have investigated their role in childhood leukemia.^{20,21} In 2012, Erculj et al reported that carriers of the G allele at *XRCC3* rs1799794 are at a lower risk for secondary neoplastic development than patients with the AA wild-type genotype.²⁰ In 2014, Smolkova et al examined the genotype, haplotype, and diplotype of *XRCC3* rs1799794, rs861530, and rs861539 but found no positive association.¹⁹ In 2015, Goricar et al reported that *XRCC3* rs1799794 genotypes are not associated with the risk of childhood leukemia.²¹ We also did not find an association between SNP *XRCC3* rs1799794 and susceptibility to childhood ALL (Tables 3 and 4). Previous studies have failed to detect a positive association between *XRCC3* rs861539 and childhood ALL. Interestingly, we determined that *XRCC3* rs861539 was significantly associated with the risk of childhood leukemia (Tables 3 and 4). The inconsistencies among the findings may lie in several factors. First, different populations were investigated, and the previous studies were investigating Caucasians, whereas we studied a Chinese population. Second, different sampling methods were used, so sampling bias may exist. We calculated sample size based on sampling and analyzing power >80%, which indicated that our samples are representative. In addition, the cases and controls were all Taiwanese, who have a very conservative genetic and geographic background.

Among the *XRCC3* SNPs we investigated, rs1799794 and rs45603942 are promoter SNPs, rs861530 and rs1799796

are intronic SNPs, whereas rs3212057, rs861539, and rs28903081 are exonic SNPs. One of the highlights of the current study is that the *XRCC3* rs861539 genotype was significantly associated with the risk of childhood ALL. *XRCC3* rs861539 occurred in response to the polymorphism at amino acid 241, which was changed from threonine to methionine (or the nucleotide from C to T), resulting in impaired DNA repair function via a defect in the function of *XRCC3* by removing the phosphorylation site.⁴³ The *XRCC3* homozygous Met/Met genotype has been identified with higher DNA double-strand break adducts after the same level of DNA damage challenges in the lymphocytes of investigated healthy subjects,⁷ while modifying the *XRCC3* levels of the Thr241Met variant cells alters their DNA repair capacity.⁴⁴ In addition, the *XRCC3* heterozygous Thr241Met carriers who were exposed to ionizing radiation are associated with an increased number of micronuclei in their lymphocytes.⁴⁵ In sum, DNA repair defects caused by *XRCC3* rs861539 may affect DNA repair capacity and genomic stability, leading to variant susceptibilities to all types of cancers, including childhood ALL. All of the children with ALL investigated here may be at higher risk of recurrence and other types of cancers during their life, particularly those with the *XRCC3* rs861539 variant genotypes.

Some limitations of this study should be discussed. First, phenotypic data, including the *XRCC3* mRNA or protein expression levels are not currently available for further analysis. Second, DNA repair capacity measured with the patients' blood sample according to their *XRCC3* rs861539 different genotypes was also not available. In the future, the complete correlation among patient status, cell type, genetic type, and phenotype will help provide further insight into the role of *XRCC3* in the initiation and development of childhood ALL.

In conclusion, this study investigated the contribution of *XRCC3* genotypes with up to seven different SNPs to child-

hood ALL. In contrast to previous reports, our study showed that the XRCC3 rs861539 genotypes were significantly associated with increased susceptibility to childhood ALL in a Taiwanese population. Additional studies that elucidate the contribution of the genotypes of other DNA repair enzymes to the development of childhood ALL may promote early detection of childhood ALL. In addition, the XRCC3 genotype–phenotype correlation will further our understanding of the etiology of childhood ALL.

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Disclosure

The authors report no conflicts of interest in this work.

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