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HOGG1 rs1052133 Genotypes and Risk of Childhood Acute Lymphoblastic Leukemia in a Taiwanese Population

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Abstract. *Background/Aim: Cells suffer from oxidative DNA damage which leads to the accumulation of 8-oxoguanine (8-oxoG) adducts in our genome that can become carcinogenic. The human 8-oxoG DNA glycosylase 1 (hOGG1) plays a central role in repairing these 8-oxoGs via the base excision repair pathway. Mounting evidence has suggested that hOGG1 polymorphisms may affect the activity of hOGG1 and serve as genomic markers for the prediction of personal susceptibility to several cancers. To determine whether the commonly examined hOGG1 rs1052133 (Ser326Cys) polymorphism is associated with the risk of childhood acute lymphoblastic leukemia (ALL) among Taiwanese children, we genotyped the hOGG1 rs1052133 (Ser326Cys) in 266 cases and 266 controls. Results: The distributions of the GG, CG and CC genotypes at the hOGG1 rs1052133 were 49.2, 39.1 and 11.7% in the control group and 48.1, 36.1 and 15.8% in the case group (p=0.3656). The combined genotypes CG+CC were not associated with increased risk of childhood ALL (odds ratio [OR]=1.05, 95% confidence interval [CI]=0.74-1.47, p=0.7947). Conclusion: The hOGG1 rs1052133 polymorphism is not associated with susceptibility to childhood ALL in the Taiwanese population.*

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Leukemia is the most common cancer among children worldwide, and acute lymphoblastic leukemia (ALL) is a clonal disease of a lymphoblast and the most frequent malignancy in children, accounting for approximately 25% of all pediatric malignancies (1). Studies of developed countries have reported that cancer incidence among children has risen steadily from the 1950s to 2010s, with 38 new cases per million occurring every year (2, 3). Like other cancers, mounting evidence has shown that childhood ALL is generally believed to be caused by the interaction of genomic susceptibility factors and environmental factors (2, 4-9). It is believed that DNA adducts formed on the genome of hematopoietic precursor cells are essential for the development of leukemia (10, 11), and are estimated to occur at a rate of about 10,000 lesions per cell per day (12). In order to maintain genomic stability, several gatekeepers, the DNA repair systems including base excision repair (BER), mismatch repair and nucleotide excision repair have evolved to prevent cells from undergoing carcinogenesis (13-15).

The most abundant oxidative DNA adduct 8-oxoguanine (8-oxoG), mainly produced by reactive oxygen species,

causes oxidative damage leading to a transversion from G:C→T:A leading to carcinogenesis (16, 17). The human 8-oxoG DNA glycosylase 1 (hOGG1) is the pilot enzyme in the BER pathway used for the detection and recognition of 8-oxoG in our genome (13, 18). Functional studies have shown that the genotypes rs1052133 (Ser326Cys) in exon 7 of the *hOGG1* gene might determine the activity of the glycosylase (19, 20), and may serve as a genomic predictor of an individual's susceptibility to various types of cancer (21-26). In 2011, Stanczyk and his colleagues reported that the Cys/Cys genotype at *hOGG1* rs1052133 increased the risk of childhood ALL in a Polish population (27). Almost at the same time in a Chinese population, Li and his colleagues reported that the combined genotypes Ser/Ser and Ser/Cys at the same *hOGG1* rs1052133 polymorphic site were associated with a statistically significant decrease in the risk of childhood ALL (28). There has been no investigation on the *hOGG1* rs1052133 polymorphism and the risk of childhood ALL in the Taiwanese population till now. Therefore, in this study, we aimed to determine whether the *hOGG1* rs1052133 polymorphism is associated with susceptibility to childhood ALL in a Taiwanese population and its interactions with age and gender.

Materials and Methods

Childhood ALL patients and control subjects. The research design and the detailed procedures of the current study were approved by the Institutional Review Board of China Medical University Hospital (Approval No. DMR103-IRB-153). Written informed consent was obtained from one or both parents of all participants. Briefly, cases with pathologic confirmed childhood leukemia were identified and ascertained into the study by pediatricians, regardless of the patient's age and stage at diagnosis. In brief, a total of 266 patients who had been diagnosed with childhood ALL were recruited from the general surgery outpatient clinics of the pediatric departments of China Medical University Hospital and the National Taiwan University Hospital, Taiwan, Republic of China during the period of 2005 to 2010. All basic and clinical characteristics of the recruited children, including their histological details, were identified by expert surgeons in the two hospitals. All investigated subjects voluntarily participated in this study, completed a questionnaire form with the help of their parents or guardians, and provided 5 ml of their peripheral blood samples without any uncomfortable feelings. An equal number of age-matched healthy subjects were recruited as the control group in accordance with the method for initial random sampling established by the Health Examination Cohort between 2005 to 2010 as previously described (29-31). Most of the healthy subjects underwent health examinations every 5 to 6 months. A total of 457 volunteers aged under 18 years were recruited in the study and were diagnosed as cancer-free in accordance with the criteria set by the International Classification of Disease (ninth revision, defined by World Health Organization). At last, 266 participants were included in the analysis to match the population structure (number, age, and gender) of our case population. All the participants were Taiwanese and the overall agreement rate in the study exceeded 85%. As shown in Table I, we have provided a concise summary and comparison of the selected recorded characteristics of the case and control groups.

Genotyping. Genomic DNA from peripheral blood samples was extracted, aliquoted, and stored. The polymerase chain reaction plus restriction fragment length polymorphism (PCR-RFLP) cycling conditions were: one cycle at 94˚C for 5 min; 35 cycles at 94˚C for 30 sec, 55˚C for 30 sec, and 72˚C for 30 sec, and a final extension at 72˚C for 10 min. The sequences of forward and reverse primers for *hOGG1* rs1052133 genotypes were 5'-ACTGTCACTAGTCTCACCAG-3' and 5'-GGAAGGTGGGAAGGTG-3', respectively. PCR amplicons were digested by the specific restriction enzyme *Fnu4H I* for 2 h, and enzyme-digestion products were subjected to 3% DNA gel electrophoresis.

Statistical analysis. The Student's *t*-test was used to test the differences in the age between the case and control groups. The Pearson's χ-square test without Yates' correction or Fisher's exact test (when any cell number is less than 5) was used to compare the distribution of *hOGG1* rs1052133 genotypes between case and control groups or any other two sub-groups. The associations between the *hOGG1* rs1052133 genotypes and the risk of childhood ALL were estimated *via* computing odds ratios (ORs) and 95% confidence intervals (CIs) through unconditional logistic regression analysis with adjustment for possible confounding factors whenever needed.

Results

Comparison of the basic demographic characteristics of the investigated cases and controls. The basic demographic characteristics of 266 childhood ALL cases and 266 cancer-free controls are presented in Table I. Overall, there was no significant difference between the cases and controls in the distribution of age and gender status (both $p>0.05$) (Table I).

Analysis of the association between hOGG1 rs1052133 genotypes and childhood ALL risk. The observed genotypic and allelic frequencies of *hOGG1* rs1052133 among cases and controls and their associations with the risk of childhood ALL are presented in Table II. The *hOGG1* rs1052133 genotypes of the control subjects were in agreement with the Hardy–Weinberg equilibrium ($p=0.1451$). There was no significant difference in the distribution of genotypes of *hOGG1* rs1052133 between the control and case groups (p for trend=0.3656). In detail, the *hOGG1* rs1052133 CG and CC variant genotypes were present in 39.1 and 11.7%, respectively, in the control group, and in 36.1 and 15.8%, respectively, in the case group (Table II, top part). Multiple logistic regression analysis indicated that the *hOGG1* rs1052133 CG and CC variant genotypes were not associated with altered risk of childhood ALL (the OR=0.94 and 1.39, 95%CI=0.65-1.37 and 0.82-2.34, $p=0.7627$ and 0.2206 for *hOGG1* rs1052133 CG heterozygotes and CC homozygotes, respectively)

Table I. *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
Gender							1.0000
Male	148	55.6%		148	55.6%		
Female	118	44.4%		118	44.4%		

ALL: Acute lymphoblastic leukemia; SD: standard deviation. [a]Analyzed by the Student's *t*-test; [b]analyzed by the Chi-square test.

Table II. *Analysis of the association between the hOGG1 rs1052133 genotype and risk of acute lymphoblastic leukemia.*

rs1052133	Controls		Patients		*p*-Value[a]	OR (95%CI)
	Number	%	Number	%		
Genetic frequency						
GG	131	49.2%	128	48.1%		Reference (1.00)
CG	104	39.1%	96	36.1%	0.7627	0.94 (0.65-1.37)
CC	31	11.7%	42	15.8%	0.2206	1.39 (0.82-2.34)
P_{trend}					0.3656	
CG+CC	135	50.8%	138	51.9%	0.7947	1.05 (0.74-1.47)
P_{HWE}					0.1451	
Allelic frequency						
Allele G	366	68.8%	352	66.2%		Reference (1.00)
Allele C	166	31.2%	180	33.8%	0.3596	1.13 (0.87-1.46)

OR: Odds ratio; CI: confidence interval; HWE: Hardy-Weinberg Equation. [a]Analyzed by the Chi-square test without Yates' correction.

(Table II, top part). We subsequently combined the *hOGG1* rs1052133 CG and CC genotypes to construct a dominant genetic model, but there was still no significant association between the combined genotypes and the risk of childhood ALL (Table II, middle part). Allelic frequencies of *hOGG1* rs1052133 among cases and controls were also analyzed, but no association was found between the *hOGG1* rs1052133 allelic frequency distribution and an altered risk of childhood ALL in Taiwan.

Discussion

The *hOGG1* gene encodes a glycosylase responsible for recognizing the most common oxidative DNA adducts, 8-oxoGs, so as to be removed from our genome by the BER machinery (16, 17). In the first step, the hOGG1 enzyme not only recognizes the 8-oxoGs but also cleaves the glycosylic bond between the modified base and the sugar moiety, leaving a basic apurinic/apyrimidinic site for further action of DNA polymerase β and DNA ligase I and III (13). Among leukemia cell lines, the activity of hOGG1 plays an important role in determining their sensitivities to environmental exposures such as radiation and 8-hydroxydeoxyguanosine-induced apoptosis (32, 33). The most famous polymorphic site of hOGG1 is *hOGG1* rs1052133 (Ser326Cys, C to G) and several functional studies have shown that the glycosylase activity of the "G" variant of the hOGG1 enzyme is more sensitive to inactivation by oxidizing agents than that of the "C" wild-type, and that cells carrying the "G" allele accumulate mutations more readily under oxidative stress (19, 34, 35).

As mentioned above, two groups have reported that the GG genotype at *hOGG1* rs1052133 may be a risk factor for childhood ALL in Polish and Chinese populations (27, 28). This is not in accordance with our results which showed no association between the genotypes at the rs1052133 polymorphic site of *hOGG1* and childhood ALL in a Taiwanese population. In 2009, two genome-wide association studies also reported that there was no association between *hOGG1* rs1052133 polymorphism and childhood ALL risk (36, 37). Noticeably, these studies are all valuable since they provide genomic information from

different populations. At the same time, it is important to know that the sample sizes of Stanczyk's, Li's and ours are at more representative levels than those of Trevino's and Papaemmanuil's, who studied a smaller number of children. Additional studies with larger sample sizes and different populations are necessary to validate these results. To the best of our knowledge, this is the first study to show an association between the *hOGG1* rs1052133 polymorphism and childhood ALL risk in a Taiwanese population.

As for other solid tumors, the genotypes of CG and/or GG at *hOGG1* rs1052133 have been reported to be associated with increased risk of various types of cancer, including oral cancer (26), lung adenocarcinoma (22), breast cancer (38), larynx cancer (39), esophageal cancer (40), colorectal cancer (21), gallbladder cancer (23) and prostate cancer (41, 42). At the same time, there are lots of negative findings showing no association between *hOGG1* rs1052133 genotypes and specific types of cancer (43, 44). Importantly, it has been shown that the G allele may cause reduced glycosylase hOGG1 activity leading to an overall down-regulated BER capacity (19, 20). Possible explanations for these inconsistencies may be due to differences in the genetic background between different populations, sampling methodology and small sample size.

In conclusion, our data suggest that the *hOGG1* rs1052133 genotypes are not associated with childhood ALL risk among Taiwanese children. More functional examinations will benefit this genotype–phenotype correlation investigation, and a larger sample size with more information regarding exposure to environmental factors for precise stratification analysis will be helpful to reveal the etiology of childhood ALL.

Conflicts of Interest

The Authors have no conflict of interest to declare regarding this study.

Authors' Contributions

Research Design: Hsu PC, Chen CC and Tzeng HE; Patient and Questionnaire Summarize: Hsu YN, Kuo CC and Pei JS; Experiment Performance: Wang YC and Chang WS; Statistical Analysis: Lin ML and Pei JS; Manuscript Writing: Tsai CW and Bau DT; Reviewing and Revising: Bau DT, Chang WS and Tsai CW.

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