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The EPHX1 rs1051740 Polymorphism Is Associated with Childhood Acute Lymphoblastic Leukemia in a Korean Population

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Abstract

Microsomal epoxide hydrolase (EPHX1) is involved in the activation and detoxification of exogenous chemicals. Genetic polymorphisms in *EPHX*1 have been associated with the development of leukemia. To investigate an association between single-nucleotide polymorphisms (SNPs) of *EPHX*1 and risk factors for childhood acute lymphoblastic leukemia (ALL) in Korean children, we genotyped two SNPs, Tyr113His (rs1051740) and His139Arg (rs2234922) in 185 childhood ALL cases and 536 healthy controls. Genotyping for these two SNPs was performed by simplex pyrosequencing assay and high-resolution melt analysis, respectively. We found that the Tyr113His genotype was associated with a decreased risk of childhood ALL (odds ratio, OR = 0.64, 95% confidence interval, CI = 0.43 - 0.93; p = 0.02). There was no association between His139Arg and the combined genotypes and the risk of childhood ALL. These results suggest that the *EPHX*1 113TyrHis genotype may protect against leukemogenesis in childhood.

Keywords

***EPHX*1, Polymorphism, Association, Childhood ALL**

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1. Introduction

Childhood acute lymphoblastic leukemia (ALL) is the most common type of cancer in children, representing nearly one-third of all pediatric cancers [1]. Childhood ALL is caused by multiple factors, including genetic disorders, exposure to radiation, and immune dysfunction [2] [3]. Environmental factors, such as pesticides, household chemical exposure, and parental smoking and alcohol use, have also been associated with childhood cancers, including childhood ALL [3]-[5]. These factors are detoxified by drug-metabolizing enzymes, through phase I and II metabolism.

Many studies have suggested that genetic polymorphisms in the drug-metabolizing enzymes play a role in susceptibility to childhood ALL [6]-[9]. Recent studies have suggested that the interaction between these genes and environmental factors may also affect the susceptibility to leukemia [10]-[12]. Microsomal epoxide hydrolase (EPHX1), along with CYP, another family of xenobiotic-metabolizing enzymes, plays an important role in both the detoxification and activation of procarcinogens [13] [14] and is considered to be a protective enzyme [15]. Two polymorphisms in *EPHX*1, Tyr113 His in exon 3 (rs1051740) and His139Arg in exon 4 (rs2234922), have been identified to affect enzyme activity. The 113His allele in exon 3 decreases enzyme activity by 40% and is called the "slow" allele, whereas the 139Arg allele in exon 4 increases enzyme activity *in vitro* by 25% and is referred to as the "fast" allele [16].

Previous studies have reported inconsistent findings regarding an association between *EPHX*1 polymorphisms and cancer risk [17]-[20]. To our knowledge, only three reported studies have analyzed these polymorphisms in childhood ALL [7] [11] [21], with the results being variable. Additionally, no research on an Asian population has been published. Thus, the aim of this study was to investigate the association of these two polymorphisms and their haplotypes in *EPHX*1 with the risk of childhood ALL in Korean children.

2. Materials and Methods

2.1. Study Population

All childhood ALL less than 18 years of age were consecutively enrolled at Chonnam National University Hwasun Hospital between October 2001 and August 2012. The 185 ALL cases consisted of 105 males and 80 females, with a mean age of 6.2 ± 4.2 years (range, 3 months to 17 years).

The control group consisted of 536 unrelated individuals (267 males, 269 females) with a mean age of 7.5 ± 4.0 years (range, 1 month to 17 years) with no previous history of malignancy. The controls were selected randomly from local residents during the same time period.

At the time of peripheral blood collection, the parents of all cases and control subjects provided informed consent to participate in this study. Childhood ALL cases for this study were provided by the Chonnam National University Hwasun Hospital National Biobank of Korea, a member of the National Biobank of Korea, supported by the Ministry of Health, Welfare, and Family Affairs. This study was approved by the Chonnam National University Hwasun Hospital Institutional Review Board, Hwasun, Korea.

2.2. Genotyping

Genomic DNA was extracted from peripheral blood using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA), according to the manufacturer's protocol. Genotyping for the Tyr113His polymorphism was performed by a simplex pyrosequencing assay as described previously (**Figure 1**) [22]. The specific primers designed using the Pyrosequencing SNP primer design software (ver. 1.0.6) were as follows: F: 5'-ACTGGAAGAAGCAGGTGGAGATT-3' and R: 5'-ACTGGAAGAAGCAGGTGGAGATT-3'. PCR was performed in a 20 μL reaction volume containing 200 nM PCR primer, 0.5 U f-Taq polymerase (Solgent, Daejeon, Korea), and 40 ng of genomic DNA. The cycling conditions were started with denaturation at 95˚C for 5 min, followed by 35 cycles of 94˚C for 20 s, 62˚C for 30 s and 72˚C for 30 s. Genotyping for His139Arg was performed by high-resolution melt analysis (HRM), as described previously (**Figure 2**) [23]. The primer pair for this polymorphism was F: 5'-GGCTGGACATCCACTTCATC-3' and R: 5'-GTTCTTGGGGTCAGTCAGGA-3'. The reaction mixture for HRM included 200 nM PCR primer, 1 μM SYTO 9 fluorescent dye (Invitrogen, Carlsbad, CA, USA), 0.5 U f-Taq polymerase (Solgent, Daejeon, Korea), and 40 ng of genomic DNA in 10 μL reaction volumes. The cycling conditions included an initial 5-min hold at 95˚C, followed by 40 cycles at 94˚C for 30 s, 62˚C for 30 s, and 72˚C for 30 s and melting increasing from 85˚C to 91˚C at 0.1˚C per second.

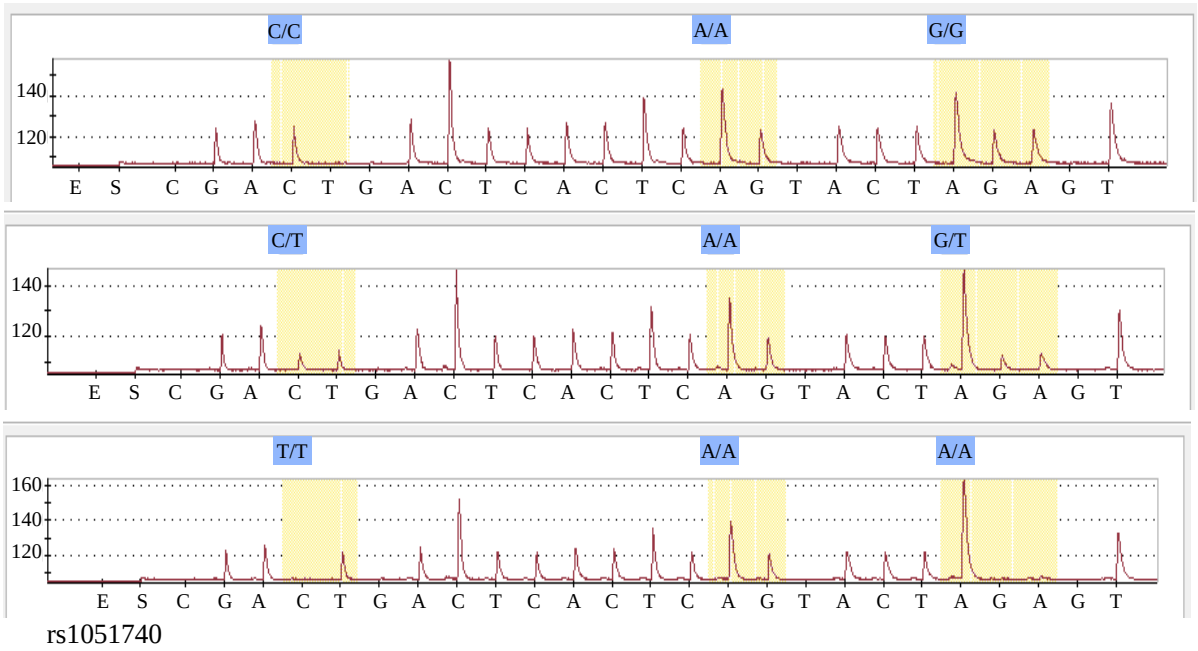

Figure 1. Typical pyrosequencing results for Tyr113His polymorphism. Upper: CC homozygotes; Middle: CT heterozygotes; Bottom: TT homozygotes.

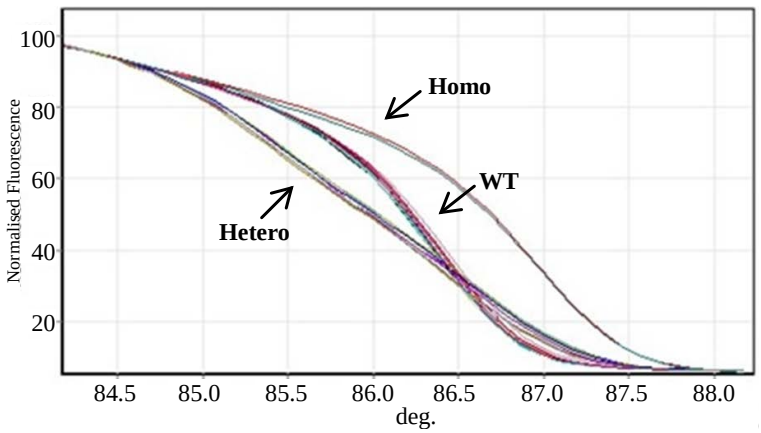

Figure 2. Typical HRM results for His139Arg polymorphism. WT: AA homozygotes; Hetero: AG heterozygotes; Homo: GG homozygotes.

2.3. Statistical Analysis

The expected frequency of control genotypes was evaluated using the Hardy-Weinberg equilibrium test. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression models, adjusting for age and gender, to estimate the association between each genotype and childhood ALL. Subjects with wild-type genotypes were considered to represent the baseline risk. Statistical analyses were performed using the SPSS software version 21.0 (SPSS, Inc., an IBM Company, Chicago, IL, USA).

3. Results

The distributions of polymorphisms in *EPHX*1 among the childhood ALL cases and the controls are shown in **Table 1**. Two major polymorphisms, Tyr113His in exon 3 and His139Arg in exon 4, were analyzed. The control genotype frequencies were within Hardy-Weinberg equilibrium and did not differ significantly between males and females (data not shown). *EPHX*1 113Tyr/His and the combined Tyr/His and His/His genotypes were asso-

ciated with a decreased risk for childhood ALL (OR_{TC} = 0.64, p = 0.02; OR_{TC+CC} = 0.68, p = 0.03). No association was found between the His139Arg polymorphism and the risk of childhood ALL.

The distribution of the combined genotypes of *EPHX*1 Tyr113His and His139Arg polymorphisms with the imputed phenotypes [16] between the cases and controls are shown in **Table 2**. Eight genotype combinations, the exceptions being 113 His/His and 139Arg/Arg, are listed. No association was found between the combined genotypes with imputed phenotypes and the risk of childhood ALL compared with normal *EPHX*1 enzyme activity.

4. Discussion

In the present study, we investigated whether two polymorphisms in *EPHX*1 genes were associated with a risk of developing childhood ALL in a Korean population. The Tyr113His genotype was associated with a decreased risk of childhood ALL. There was no association between the His139Arg polymorphism and the combined genotypes and the risk of childhood ALL.

*EPHX*1 is an important metabolizing enzyme that is involved in detoxification by catalyzing the hydrolysis of arene and aliphatic epoxides from PAHs and activation by generating carcinogenic compounds from epoxides [13] [14]. Two major polymorphisms, the 113 His allele in exon 3 (rs1051740) and the 139 Arg allele in exon 4

Table 1. Association between polymorphisms in *EPHX*1 and risk of childhood ALL.

SNP	Genotype	Control, *n* (%)	Case, *n* (%)	OR (95% CI)	*p*
*EPHX*1	T/T	156 (29.1)	71 (38.4)	1	
Y113H	T/C	277 (51.7)	78 (42.2)	**0.64 (0.43 - 0.93)**	0.02
rs1051740	C/C	103 (19.2)	36 (19.5)	0.79 (0.49 - 1.27)	0.32
	T/C-C/C	380 (70.9)	114 (61.6)	**0.68 (0.48 - 0.96)**	0.03
	T allele	589 (54.9)	220 (59.5)	1	
	C allele	483 (45.1)	150 (40.5)	0.84 (0.66 - 1.07)	0.17
*EPHX*1	A/A	399 (74.4)	125 (67.6)	1	
H139R	A/G	123 (22.9)	56 (30.3)	1.43 (0.98 - 2.09)	0.07
rs2234922	G/G	14 (2.6)	4 (2.2)	0.90 (0.29 - 2.81)	0.85
	A/G-G/G	137 (25.6)	60 (32.4)	1.37 (0.95 - 1.99)	0.09
	A allele	921 (85.9)	306 (82.7)	1	
	G allele	151 (14.1)	64 (17.3)	1.26 (0.91 - 1.74)	0.17

Table 2. Association between the combined *EPHX*1 Tyr113His and His139Arg polymorphism genotypes and risk of childhood ALL.

Genotype	Imputed phenotype	Control, *n* (%)	Case, *n* (%)	OR (95% CI)	*p*
113Tyr/Tyr and 139His/His	Normal	110 (20.5)	43 (23.2)	1	
113Tyr/His and 139His/Arg	Normal	75 (14.0)	22 (11.9)	0.76 (0.42 - 1.37)	0.36
113Tyr/Tyr and 139His/Arg	Fast	37 (6.9)	26 (14.1)	1.79 (0.96 - 3.23)	0.07
113Tyr/Tyr and 139Arg/Arg	Fast	9 (1.7)	2 (1.1)	0.54 (0.11 - 2.65)	0.45
113Tyr/His and 139His/His	Slow	197 (36.8)	54 (29.2)	0.72(0.45 - 1.15)	0.17
113Tyr/His and 139Arg/Arg	Slow	5 (0.9)	2 (1.1)	1.11 (0.20 - 6.07)	0.90
113His/His and 139His/His	Very slow	92 (17.2)	28 (15.1)	0.80(0.46 - 1.39)	0.43
113His/His and 139His/Arg	Very slow	8 (1.5)	19 (10.3)	1.84 (0.69 - 4.96)	0.23

(rs2234922), are known to reduce and increase enzyme activity, respectively [16]. To date, these two polymorphisms were considered to be associated with cancer risk. However, the many studies that have investigated this have produced inconsistent findings. The Tyr113His polymorphism has been associated with, in most studies, an increased risk for various cancers, such as lung [20] [24] [25], ovarian [26], esophageal [27], breast [28], and bladder [29] cancer and, in a few studies, a decreased risk of childhood ALL [7] and lung cancer [30]. In contrast, the His139Arg polymorphism has no association with many cancers [11] [27] [29] [31]. These results suggest that the decreased enzyme activity of the His allele in the Tyr113His polymorphism affects the risk of cancer to a greater degree than the increased enzyme activity due to the Tyr allele in the Tyr113His polymorphism.

In the present study, the 113Tyr/His and the combined Tyr/His and His/His genotypes were associated with a decreased risk of childhood ALL, while the His139Arg polymorphism had no effect. Three studies of childhood ALL risk have also reported no association with His139Arg, while Tyr113His showed a decreased risk [7] in Brazil, an increase [21] in Turkey, and no association [11] in France. Our results are similar to those of Silveira Vda *et al*. [7].

The conflicting results for the associations between the polymorphisms and the risk for ALL may be due to differing genotype frequencies, ethnicities, and environmental factors. In the four studies, including ours, the frequencies of the 113 His/His genotype in the control groups ranged from 2% to 18.4%. However, the frequencies of the 139 Arg/Arg genotype in the control groups were less diverse, ranging from 2.1% to 4.4%.

Correlations between *EPHX*1 enzymatic activity and different combinations of the two variants were reported by Hasset *et al*. [16], and activity was suggested to be a cancer risk factor. Tumer *et al*. reported that only the very low activity of the 113 His/His and 139 His/His combinations significantly increased the risk of childhood ALL [21]. However, in our study, no associations were found between these combinations and childhood ALL.

Our study had several limitations. First, we did not evaluate gene-environment interactions. Zhou *et al*. reported that lung cancer risk decreased as cumulative smoking increased and suggested that smoking plays an important role in the association of the His/His genotype with lung cancer [32]. Several studies have suggested that the interaction between drug-metabolizing genes and parental smoking and alcohol might affect childhood leukemia [11] [12] [33]. Thus, additional studies with stratification according to chemical exposure and with larger sample sizes in local areas should be conducted to further explore the associations between *EPHX*1 polymorphisms and childhood leukemogenesis. Second, it is possible that the null association between His139Arg and childhood ALL may have been due to the small sample size.

5. Conclusion

In conclusion, the *EPHX*1 113 Arg/His genotype was associated with a decreased risk of childhood ALL in Korean children. These results suggest that Arg113His polymorphism may have some protective function against leukemogenesis in childhood.

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Declaration of Interest

The authors declare that they have no competing interests.

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