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The association of polymorphisms in DNA base excision repair genes *XRCC1*, *OGG1* and *MUTYH* with the risk of childhood acute lymphoblastic leukemia

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Abstract The aim of this study was to evaluate the association of polymorphisms in genes encoding three key proteins of DNA base excision repair (BER): the *OGG1* Ser326Cys, the *MUTYH* Tyr165Cys and the *XRCC1* Arg399Gln with the risk of childhood acute lymphoblastic leukemia (ALL). Our study included 97 children patients with ALL (mean age 5.4 ± 2.5) and 131 healthy children (mean age 6.2 ± 2.8) used as controls. Genetic polymorphisms in BER pathway genes were examined using PCR and restriction fragment length polymorphism (RFLP). We have demonstrated that the *OGG1* Cys/Cys genotype increases the risk of ALL (OR 5.36) whereas the Ser/Ser genotype variant strongly reduces the risk of this cancer among Polish children (OR 0.45). Although we did not observe the differences in single nucleotide polymorphisms (SNPs) in *MUTYH* and *XRCC1* genes between control group and children with ALL, we have shown that the combined genotypes of examined genes can modulate the risk of childhood ALL in Polish population. We found that the combined genotype Arg/Gln–Cys/Cys of *XRCC1*/*OGG1* (OR 3.83) as well as the Cys/Cys–Tyr/Tyr of *OGG1*/*MUTYH* (OR 6.75) increases the risk of ALL. In contrast, the combined genotype Arg/Arg–Ser/Ser of *XRCC1*/*OGG1* (OR 0.40) as well as the Ser/Ser–Tyr/Tyr of *OGG1*/*MUTYH* (OR 0.43) played a protective role against this malignant disease. In conclusion, we suggest that polymorphisms of BER genes may be used as an important predictive factor for acute lymphoblastic leukemia in children.

Keywords Childhood acute lymphoblastic leukemia · Base excision repair · Gene polymorphism · XRCC1 · OGG1 · MUTYH

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Introduction

Acute lymphoblastic leukemia (ALL) is neoplastic disease characterized by the blockage of the lymphoid progenitor cells development and their accumulation in the bone marrow and peripheral blood [1–3]. It is the most common childhood cancer with a peak at 2 ± 5 years of age [4]. Although in the last decades, treatment of childhood ALL has remarkably improved with a cure rate of nearly 80% in the developed countries, still a certain number of patients can develop resistance or adverse drug effects hampering the efficacy of treatment or require drug dose reduction [5].

Defective DNA repair is associated with an increased risk of various cancers including hematologic malignancies—leukemia and lymphoma [6, 7]. The main repair system for removal of small, helix non-distorting base lesions is base excision repair (BER). This pathway is initiated by DNA glycosylases that remove the damaged bases and thus create an abasic or AP site in double-stranded DNA [8]. Apurinic/apyrimidinic endonuclease (APE) cleaves 5′ to the abasic site, resulting in a break in

the phosphodiester backbone that is repaired by sequential actions of a phosphodiesterase, DNA polymerase β and DNA ligase [9]. The activity of proteins that are involved in BER system depends on gene polymorphisms, interactions between BER system components and post-translational modifications [10]. The critical enzyme for BER is XRCC1 protein encoded by X-ray repair crosscomplementing group 1 (*XRCC1*) gene [11, 12]. Although several genetic variants in the *XRCC1* gene have been described, the most common are amino acid changes at codons 194 (Arg/Trp), 280 (Arg/His) and 399 (Arg/Gln), respectively [13, 14]. Genetic polymorphisms in *XRCC1* gene can alternate the protein structure thereby influencing the functions of enzymes associated with BER pathway [15].

The main DNA damage used as a key biomarker of oxidative stress is 7,8-dihydro-8-oxoguanine (8-oxoG) [16]. 8-oxoG in DNA template may pair with adenine, inducing G:C to T:A transversions which leads to mutations and can initiate carcinogenesis [17]. The oxidized guanine is removed from DNA by 8-oxoguanine-DNA glycosylase (OGG1) and MUTYH glycosylase, the primary mammalian enzymes of BER pathway [18–20]. OGG1 protein preferentially excises 8-oxoG from damaged DNA via the short-patch BER [20]. Although several validated sequences variant of *OGG1* gene have been described, the most commonly studied polymorphism is an amino acid change from serine to cysteine at codon 326 (Ser326Cys) [16]. Numerous studies have reported that Ser326Cys polymorphism in *OGG1* gene may increase susceptibility to cancer development [21, 22]. MUTYH (Mut Y homolog) removes adenine paired with 8-oxo-G or 1,2-dihydro-2-oxoadenine (2-OH-A) paired with guanine [23]. The association of human MUTYH with proteins of BER pathway such as apurinic/apyrimidinic endonuclease (APE1), proliferating cell nuclear antigen (PCNA), and replication protein A (RPA) indicates that MUTYH is involved in long-patch BER [24, 25].

In our study, we evaluated the effect of genetic polymorphisms of genes encoding three key proteins of the BER pathway: the *OGG1* Ser326Cys, the *MUTYH/MYH* Tyr165Cys and the *XRCC1* Arg399Gln on the risk of childhood acute lymphoblastic leukemia. Since these proteins are functionally involved in DNA repair by BER, we also examined the combined genotypes interactions.

Materials and methods

Patients

Peripheral blood samples from 97 children (69 males and 28 females, mean age 5.4 ± 2.5) diagnosed during the study periods (2004–2008) at Department of Pediatrics, Medical University of Lodz, were included in the study. Childhood acute lymphoblastic leukemia were diagnosed according to lymphoblast count in bone marrow (more than 30%), age, immunophenotyping and responsiveness to the treatment. The blood samples from ethnicity-matched 131 healthy children (59 males and 72 females, mean age 6.2 ± 2.8) collected during standard medical examination and presented no acute or chronic diseases were used as controls. All patients as well as controls were Caucasian. The study was approved by the Local Ethic Committee and a written consent was obtained from family members of each child patients included in this work.

Genotype determination

Genomic DNA was prepared using the QIAamp DNA Blood Mini Kit for isolation of high-molecular-weight DNA. Restriction fragments length polymorphism PCR was employed to determine the genotypes of the Arg399Gln and Ser326Cys polymorphisms and Multiplex Tetra-Primer Amplification Refractory Mutation System PCR was used to detect the genotypes of the Tyr165Cys polymorphism. Each 20 μl of the PCR reaction contained 10 ng genomic DNA, 1.25 U Taq polymerase (Qiagen, Chatsworth, CA, USA) in 1 × PCR buffer (100 mM Tris–HCl, pH 8.3, 500 mM KCl, 11 mM $MgCl_2$, 0.1% gelatin), 1.5 mM $MgCl_2$, 50 mM dNTPs, and 250 nM each primer. Thermal cycling conditions for the Arg399Gln polymorphism of *XRCC1* gene were as follows: initial denaturation step at 94°C for 5 min, 30 cycles at 94°C for 20 s and 30 s at the 61°C annealing temperature, and at 72°C for 45 s. The final extension was performed at 72°C for 7 min. Thermal cycling conditions for the Ser326Cys polymorphism of *OGG1* gene were as follows: initial denaturation step at 95°C for 5 min, 30 cycles at 94°C for 30 s and 60 s at the 57°C annealing temperature, and at 72°C for 30 s. The final extension was performed at 72°C for 5 min. Thermal cycling conditions for the Tyr165Cys polymorphism of the *MUTYH* gene were as follows: initial denaturation step at 94°C for 3 min, 30 cycles at 94°C for 25 s and 25 s at the 69°C annealing temperature, and at 72°C for 25 s. The final extension was performed at 72°C for 4 min. The PCR was carried out in a MJ Research, INC thermal cycler, model PTC-100 (Waltham, MA, USA). The Arg399Gln polymorphism of *XRCC1* gene was determined using the following primers (Sigma–Aldrich, St. Louis, MO, USA):

sense, 5′-TTGTGCTTTCTCTGTGTCCA-3′;
antisense, 5′-TCCTCCAGCCTTTTCTGATA-3′.

The 615 bp PCR product was digested for 6 h at 37°C with 5 U of the restriction enzyme *Msp*I. The Gln allele was digested into 374 and 221 bp fragments whereas the

Arg variant remained intact (Fig. 1a). The Ser326Cys polymorphism of *OGG1* gene was determined using the following primers:

sense, 5′-GGAAGGTGCTTGGGGAAT-3;
antisense, 5′-ACTGTCACTAGTCTCACCAG-3′.

The 200 bp product was digested for 6 h at 37°C with 5 U of the restriction enzyme *Sat*I. The Cys allele was digested into two 100-bp fragments and the Ser was intact (Fig. 1b). Multiplex Tetra-Primer Amplification Refractory Mutation System PCR was used to detect the genotypes of the Tyr165Cys polymorphism of the *MUTYH* gene

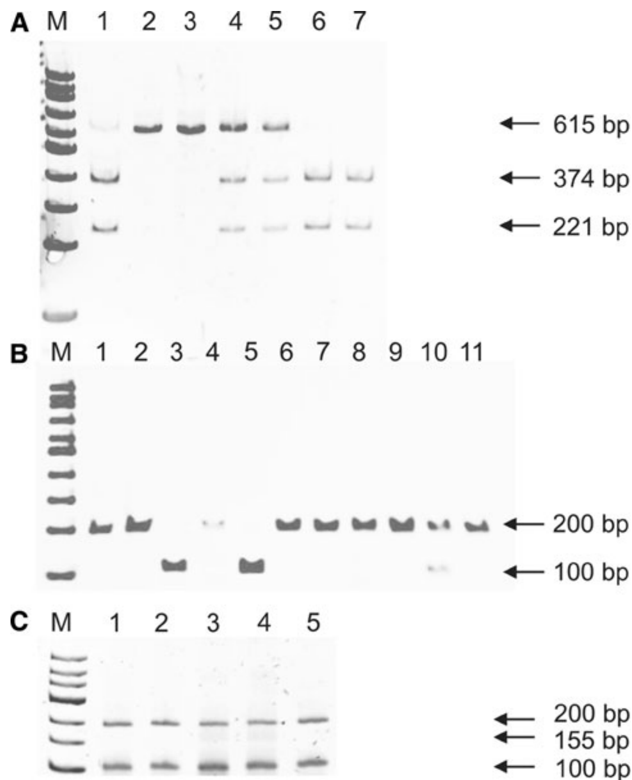

Fig. 1 Representative analyses on 8% polyacrylamide gel containing ethidium bromide. PCR-RELP or T-ARMS-PCR band sizes are indicated on the right panel. **a** PCR-RELP of the Arg399Gln polymorphism of the *XRCC1* gene. *Lane M*: DNA marker Low Range (Fermentas), *lane 2 and 3*: the Gln/Gln homozygote is not cleaved by *Msp*I enzyme and remains the single 615 bp band, *lane 6 and 7*: the Arg/Arg homozygote is cleaved by *Msp*I and yields a 374 and 221 bp bands, *lane 1, 4 and 5*: the Arg/Gln heterozygote contains all 3 bands (615, 374 and 221 bp) following restriction digestion. **b** PCR-RELP of the Ser326Cys polymorphism of the *hOGG1* gene. *Lane M*: DNA marker 100 bp (Fermentas), *lane 1, 2, 4, 6–9 and 11*: the Ser/Ser homozygote is not cleaved by *Sat*I enzyme and remains the single 200 bp band, *lane 3 and 5*: the Cys/Cys homozygote is cleaved by *Sat*I and yields a 100 bp band, *lane 10*: the Ser/Cys heterozygote contains all two bands (200 and 100 bp) following restriction digestion. **c** T-ARMS-PCR for the Tyr165Cys polymorphism of *MUTYH* gene. *Lane M*: DNA marker 100 bp (Fermentas), *lane 1, 2 and 5*: wild-type control 100 bp band, *lane 3 and 4*: Tyr165Cys heterozygote 100 and 155 bp bands. In each line 200 bp product indicate a positive control of PCR

associated with acute lymphoblastic leukemia. T-ARMS-PCR amplified both wild-type and mutant alleles, together with a control fragment, in a single tube PCR reaction. The region flanking the mutation was amplified by 2 common (outer) primers, producing a non-allele-specific control amplicon 200 bp in length:

Fo 5′-GGGACTGACGGGTGATCTCTTTGACCTCTG-3′
Ro 5′-CCTCTACCACCTGATTGGAGTGCAAGACTC-3′

Two allele-specific (inner) primers:

Fi(G) 5′-GGTGAATCAACTCTGGGCTGGCCTGGG*A*TG-3′
Ri(A) 5′-CTGCAGCCGCCGGCCACGAGAAT*C*GT-3′

were designed in opposite orientation and, in combination with the common primers, simultaneously amplified both the wild-type and the mutant amplicons 100 and 155 bp in length, respectively (Fig. 1c). The 2 allele-specific amplicons have different lengths and restriction fragments were separated by 8% polyacrylamide gel electrophoresis. More than 10% of the samples were repeated, and the results were 100% concordant.

Data analysis

Distribution of genotypes and alleles between groups were tested using chi-square tests. Potential linkage between genotype and cancer was assessed by the logistic regression. Analyses were performed using STATISTICA 6.0 package (Statsoft, Tulsa, OK, USA).

Results

Distributions of XRCC1, OGG1 and MUTYH genotypes

The study population consisted of 97 children with acute lymphoblastic leukemia and 131 cancer-free controls. Statistical power of our experiment was 100%. The genotypes of ALL patients and controls were scored according to Arg399Gln polymorphism of the *XRCC1* gene (rs25487), Ser326Cys polymorphism of the *OGG1* gene (rs1052133) and Tyr165Cys polymorphism of the *MUTYH* gene. The genotype and allele distributions of the *XRCC1* Arg399Gln, *OGG1* Ser326Cys and the *MUTYH* Tyr165Cys SNPs in the patients and controls are summarized in Table 1. The observed genotype frequency of *XRCC1*, *OGG1* and *MUTYH* SNPs in the control subjects were not in agreement with HWE ($P < 0.05$; $\chi^2 = 13.84$, $P < 0.001$; $\chi^2 = 71.55$ and $P < 0.001$; $\chi^2 = 125.06$, respectively).

As shown in Table 1, there was no statistically significant difference in the allele and genotype frequencies of the *XRCC1* Arg399Gln and the *MUTYH* Tyr165Cys polymorphisms between the control group and the patients with ALL.

In case of *OGG1* Ser326Cys polymorphism we have shown that the distributions of Cys/Cys and Ser/Ser polymorphic variants of the *OGG1* gene differ significantly between patients and control subjects ($P < 0.001$ and $P < 0.003$, respectively) in contrast to Ser/Cys polymorphic variant of this gene (Table 1). We also demonstrated significant differences in the frequency of the Ser and Cys alleles between patients with ALL and control group ($P < 0.001$ and $P < 0.001$, respectively; Table 1).

Risk estimates for XRCC1, OGG1 and MUTYH polymorphisms

The strong association with childhood ALL and the Ser/Ser as well as Cys/Cys variants of the Ser326Cys—*OGG1* polymorphism was found (Table 1). We have shown that the Cys/Cys variant may increase the risk of acute lymphoblastic leukemia whereas Ser/Ser variant significantly reduces the risk of this cancer among Polish children (OR 5.36; 95% CI 1.90–15.09, OR 0.45; 95% CI 0.26–0.76, respectively). Additionally, we observed the differences in frequency of the Ser and Cys alleles between the group of patients and controls for the Ser326Cys—*OGG1* polymorphism (OR 0.43; 95% CI 0.28–0.65, OR 2.33; 95% CI 1.53–3.55, respectively; Table 1).

Gene–gene combined interactions

The significant association between the combined genotype Arg/Gln–Cys/Cys of *XRCC1*/*OGG1* (OR 3.83; 95% CI 1.00–14.86) and the Cys/Cys–Tyr/Tyr genotype of *OGG1*/*MUTYH* (OR 6.75; 95% CI 2.19–20.77) in childhood ALL was observed (Table 2). These genotype combinations may increase the risk of acute lymphoblastic leukemia. In contrast, the combined genotype Arg/Arg–Ser/Ser of *XRCC1*/*OGG1* (OR 0.40; 95% CI 0.19–0.83) as well as the Ser/Ser–Tyr/Tyr genotype of *OGG1*/*MUTYH* (OR 0.43; 95% CI 0.25–0.73) may play a protective role against this disease (Table 2).

Discussion

The polymorphisms in DNA repair genes may influence the activity of protein involved in the DNA repair and thus play the critical role in genome instability and carcinogenesis. Although many studies have shown that the deficits of DNA repair capacity can be associated with cancer development, there are a few reports showing the influence of polymorphisms in DNA repair genes on the risk of childhood acute lymphoblastic leukemia (ALL).

Since the most important repair system to remove damaged bases is BER, we therefore investigated the genetic polymorphisms of *OGG1*, *MUTYH/MYH*, and *XRCC1* genes encoding a key proteins of this repair

Table 1 The *XRCC1* Arg399Gln, *OGG1*—Ser326Cys and *MUTYH*—Tyr165Cys polymorphisms in childhood acute lymphoblastic leukemia

Polymorphism Genotype or allele	Patients ($n = 97$)	Controls ($n = 131$)	OR (95% CI)	***P***
Arg399Gln				
Arg399Arg	34	50	0.87 (0.50–1.51)	0.629
Arg399Gln	45	57	1.12 (0.66–1.90)	0.665
Gln399Gln	18	24	1.02 (0.52–1.99)	0.963
399Arg	113	157	0.93 (0.64–1.36)	0.718
399Gln	81	105	1.07 (0.73–1.56)	0.718
Ser326Cys				
Ser326Ser	**43**	**84**	**0.45 (0.26–0.76)**	**0.003**
Ser326Cys	37	42	1.31 (0.75–2.26)	0.340
Cys326Cys	**17**	**5**	**5.36 (1.90–15.09)**	**0.001**
326Ser	123	210	0.43 (0.28–0.65)	<0.001
326Cys	**71**	**52**	**2.33 (1.53–3.55)**	**<0.001**
Tyr165Cys				
Tyr165Tyr	96	130	0.74 (0.05–11.96)	0.831
Tyr165Cys	1	1	1.35 (0.08–21.92)	0.831
Cys165Cys	0	0	–	–
165Tyr	193	261	0.74 (0.04–11.89)	0.831
165Cys	1	1	1.32 (0.08–21.76)	0.831

CI confidence interval

Table 2 The distribution of double-combined genotypes of the *XRCC1*—Arg399Gln, *OGG1*—Ser326Cys and *MUTYH*—Tyr165Cys polymorphisms in childhood acute lymphoblastic leukemia

Polymorphism Genotype	Patients ($n = 97$)	Controls ($n = 131$)	OR (95% CI)	*P*
Arg399Gln–Ser326Cys				
Arg/Arg–Ser/Ser	**12**	**34**	**0.40 (0.19–0.83)**	**0.013**
Arg/Arg–Ser/Cys	16	14	1.65 (0.76–3.57)	0.202
Arg/Arg–Cys/Cys	6	2	4.25 (0.84–21.55)	0.080
Arg/Gln–Ser/Ser	21	34	0.79 (0.42–1.47)	0.453
Arg/Gln–Ser/Cys	16	20	1.09 (0.54–2.25)	0.801
Arg/Gln–Cys/Cys	**8**	**3**	**3.83 (1.00–14.86)**	**0.050**
Gln/Gln–Ser/Ser	10	16	0.83 (0.36–1.91)	0.655
Gln/Gln–Ser/Cys	5	8	0.84 (0.26–2.64)	0.759
Gln/Gln–Cys/Cys	3	0	–	-
Arg399Gln–Tyr165Cys				
Arg/Arg–Tyr/Tyr	34	50	0.87 (0.51–1.51)	0.629
Arg/Arg–Tyr/Cys	0	0	–	–
Arg/Arg–Cys/Cys	0	0	–	–
Arg/Gln–Tyr/Tyr	45	57	1.12 (0.66–1.90)	0.665
Arg/Gln–Tyr/Cys	0	0	–	–
Arg/Gln–Cys/Cys	0	0	–	–
Gln/Gln–Tyr/Tyr	17	23	0.99 (0.50–1.99)	0.995
Gln/Gln–Tyr/Cys	1	1	1.35 (0.08–21.92)	0.810
Gln/Gln–Cys/Cys	0	0	–	–
Ser326Cys–Tyr165Cys				
Ser/Ser–Tyr/Tyr	**42**	**84**	**0.43 (0.25–0.73)**	**0.001**
Ser/Ser–Tyr/Cys	1	0	–	–
Ser/Ser–Cys/Cys	0	0	–	–
Ser/Cys–Tyr/Tyr	37	42	1.31 (0.75–2.26)	0.340
Ser/Cys–Tyr/Cys	0	0	–	–
Ser/Cys–Cys/Cys	0	0	–	–
Cys/Cys–Tyr/Tyr	**17**	**4**	**6.75 (2.19–20.77)**	**<0.001**
Cys/Cys–Tyr/Cys	0	1	–	–
Cys/Cys–Cys/Cys	0	0	–	–

CI confidence interval

pathway with regards to the occurrence and progression of childhood acute lymphoblastic leukemia (ALL) in Polish population.

Some reports have demonstrated a positive association of the *MUTYH* gene polymorphisms with various malignant diseases including cancer of the head and neck, lung and colorectal [23, 26, 27]. However, there are no previous results concerning the risk of childhood acute lymphoblastic leukemia (ALL) and the Tyr165Cys polymorphism of the *MUTYH* gene. In this study, we have shown that this polymorphism has no influence on the risk of ALL in Polish population.

The data concerning the association of Ser326Cys polymorphism of the *OGG1* gene and the risk of cancer development are inconsistent. Several studies have suggested that this polymorphism may increase the risk of some cancers such as lung and gallbladder cancer [28, 29] whereas others indicate the lack of its effect on the progression of malignant diseases [30, 31]. In accordance with our knowledge, no results have been published on the association between Ser326Cys polymorphism and the risk of childhood ALL. Our study has demonstrated that Cys/Cys variant of the *OGG1* Ser326Cys polymorphism may increase the risk of ALL (OR 5.36, $P < 0.001$). On the other hand, we have shown that Ser/Ser variant strongly reduces the risk of this cancer in Polish population (OR 0.45, $P < 0.003$). Furthermore, we indicated that the results of combined genotypes interactions are also ambiguous. In our study, the combined genotype Cys/Cys–Tyr/Tyr of *OGG1*/*MUTYH* may increase the risk of childhood ALL among Polish children (OR 6.75; $P < 0.001$) in contrast to the Ser/Ser–Tyr/Tyr genotype that

may play a protective role against this disease (OR 0.43; $P < 0.001$).

Several previous studies provide evidence that polymorphism of the *XRCC1* gene at codon 399 (Arg to Gln) had an effect on the risk of different types of cancers including lung, colon and breast cancer [15, 31]. The results of Pakakasama et al. [11] have demonstrated that the *XRCC1* 399Gln allele and haplotype C were associated with a significantly increased risk of childhood ALL (OR 1.67; 95% CI 1.20–2.33) in Indian population. Moreover, Joseph et al. [7] have shown that the *XRCC1* polymorphism of codon 399 had significant influence on the risk of ALL among males (OR 2.58, 95% CI 1.35–4.94) while this polymorphic variant did not vary significantly among females in Indian population. However, these studies are in contrast with the results of Batar et al. [6] who found out that there was no significant difference as regards the *XRCC1* codon 399 polymorphisms among Turkish patients with childhood ALL. Our findings also suggest that this polymorphism is not associated with the risk of childhood ALL in Polish population. On the other hand, we found out that the combined genotype Arg/Gln–Cys/Cys of *XRCC1*/*OGG1* may increase the risk of ALL (OR 3.83; $P < 0.05$) whereas the Arg/Arg–Ser/Ser genotype of *XRCC1*/*OGG1* may play a protective role against the development of childhood ALL among Polish children (OR 0.40; $P < 0.013$). It is evident that the cancer risk is associated with ethnical differences in allele frequencies that often vary between ethnic groups as well as the number of examined subjects. Some studies have shown that the frequency of 399Gln allele differs significantly between the European, Asian, and African populations [13, 32]. Therefore, the study of common DNA repair gene polymorphisms with regards to cancer progression and prognosis should also enlarge general population though this data is still unclear.

Conclusions

In conclusion, our current study demonstrated that *OGG1* Ser326Cys polymorphism may contribute to individual susceptibility to childhood acute lymphoblastic leukemia. Although we did not observe the differences in single nucleotide polymorphisms (SNPs) in *MUTYH* and *XRCC1* genes between control group and patients with ALL, we have shown that the combined genotypes of the *XRCC1* and *OGG1* genes as well as of the *OGG1* and *MUTYH* genes can modulate the risk of childhood ALL in Polish population.

In accordance with our knowledge, this is the first report showing an association between *OGG1*, *MUTYH* and *XRCC1* gene polymorphisms with susceptibility to childhood ALL among Polish children. Thus, BER genes are suggested to be used as a predictive factor for acute lymphoblastic leukemia in children. However, further studies are needed to evaluate the influence of their polymorphisms on the risk of childhood ALL.

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Conflict of interest statement The authors declare that there are no conflicts of interest.

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