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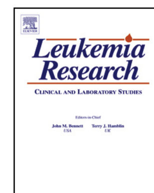

# Amerindian genetic ancestry and INDEL polymorphisms associated with susceptibility of childhood B-cell Leukemia in an admixed population from the Brazilian Amazon

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## ABSTRACT

Acute lymphoblastic leukemia (ALL) is a malignant tumor common in children. Studies of genetic susceptibility to cancer using biallelic insertion/deletion (INDEL) type polymorphisms associated with cancer development pathways may help to clarify etymology of ALL. In this study, we investigate the role of eight functional INDEL polymorphisms and influence of genetic ancestry to B-cell ALL susceptibility in children of Brazilian Amazon population, which has a high degree of inter-ethnic admixture. Ancestry analysis was estimated using a panel of 48 autosomal ancestry informative markers. 130 B-cell ALL patients and 125 healthy controls were included in this study. The odds ratios and 95% confidence intervals were adjusted for confounders. The results indicated an association between the investigated INDEL polymorphisms in *CASP8* (rs3834129), *CYP19A1* (rs11575899) e *XRCC1* (rs3213239) genes in the development of B-cell ALL. The carriers of Insertion/Insertion (Ins/Ins) genotype of the polymorphism in *CASP8* gene presented reduced chances of developing B-cell ALL ($P = 0.001$; OR = 0.353; 95% CI = 0.192–0.651). The Deletion/Deletion (Del/Del) genotype of the polymorphism in *CYP19A1* gene was associated to a lower chance of developing B-cell ALL ($P = 3.35 \times 10^{-6}$; OR = 0.121; 95% CI = 0.050–0.295), while Del/Del genotype of the polymorphism in *XRCC1* gene was associated to a higher chance of developing B-cell ALL ($P = 2.01 \times 10^{-4}$; OR = 6.559; 95% CI = 2.433–17.681). We also found that Amerindian ancestry correlates with the risk of B-cell ALL. For each increase of 10% in the Amerindian ancestry results in 1.4-fold chances of developing B-cell ALL (OR = 1.406; 95% IC = 1.123–1.761), while each increase of 10% in the European ancestry presents a protection effect in the development of B-cell ALL (OR = 0.666; 95% IC = 0.536–0.827). The results suggest that genetic factors influence leukemogenesis and might be explored in the stratification of B-cell ALL risk in admixed populations.

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*Abbreviations:* ALL, acute lymphoblastic leukemia; B-Cell ALL, B-cell acute lymphoblastic leukemia; AIMs, ancestry informative markers; INDEL, insertion/deletion.

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## 1. Introduction

Acute lymphoblastic leukemia (ALL) is a malignant tumor common in children that accounts for more than 30% of all pediatric cancers [1]. Despite many studies, ALL etiology is not well defined. Various studies have suggested that an interaction between exposure to certain environmental agents and genetic susceptibility has an important mechanistic role in the development of this childhood leukemia [2–4]. In this context, studies of genetic susceptibility to cancer using biallelic insertion/deletion (INDEL)-type polymorphisms associated with cancer development pathways may help to clarify the etiology of a certain tumor [5–7]. Polymorphisms of the INDEL type have been related to susceptibility to different cancers, including gastric [8,9], breast [10–12], colorectal [13–15] and others [16,17]. However, studies linking INDEL type polymorphisms and susceptibility to ALL are scarce [18].

To provide a more complete view of ALL etiology, we selected eight polymorphisms in genes (*CYP2E1, CYP19A1, TYMS, XRCC1, TP53, CASP8, NFKβ1* and *IL-1α*) involved in pathways associated to the carcinogenesis of different types of cancer, including B-cell acute lymphoblastic leukemia (B-cell ALL) [19]. These genes encode enzymes of the carcinogens metabolism [20–22], enzymes of the folate metabolism [23–25] and proteins of DNA repair [26–28], apoptosis and immune response [29–31].

Furthermore, it is well reported in the literature that ethnic differences influence in ALL incidence [32–35]. Children with admixed ancestry, such as Hispanic, tend to have a greater risk of developing B-cell ALL in comparison to children from other ethnic groups [35]. This higher incidence in Hispanic children is, at least partially, attributable to genomic variations that are characteristic of Native American genetic ancestry [36]. Therefore, it is conceivable that genomic variations related to ancestry may contribute to ethnic disparities in ALL incidence. This is especially important in admixed populations, such as the Brazilian, which is known for being one of the most heterogeneous populations worldwide, with the main contribution of three parental groups: Amerindian, European and African [37,38]. However, there are no works exploring the influence of genetic ancestry in the risk of developing ALL in Brazilian children.

The goal of this work was to investigate the role of eight functional INDEL polymorphisms and the influence of genetic ancestry in B-cell acute lymphoblastic leukemia susceptibility in children from an Amazon region with high degree of inter-ethnic admixture.

## 2. Materials and methods

### 2.1. Cases and controls

The research participants were chosen based on a case-control study design. The case group was composed of B-cell acute lymphoblastic leukemia patients ($n = 130$) in treatment for childhood cancer in the clinics of the Hospital Ophir Loyola (Pará, Brazil) between the years of 2006 and 2012. Samples from 125 non-related cancer-free individuals from the same geographic area were used as controls.

All patients included in the study were confirmed to have acute lymphoblastic leukemia based on the criteria of the French-American-British (FAB) rating systems. Samples of bone marrow or peripheral blood were obtained at the time of diagnosis. Immunophenotype was determined for ALL cases using flow cytometry profiles, as previously described [39].

### 2.2. Ethical aspects

The protocol used in this study was approved by the Committee for Research Ethics of the Universidade Federal do Pará (UFPA; approval no. 119.649). Consent forms were obtained from all patients and control participants in the study.

### 2.3. DNA extraction and quantification

Genomic DNA was extracted using a commercial kit for DNA extraction (Roche Applied Science DNA Isolation Kit, Penzberg, Germany) and quantified with a NanoDrop 1000 spectrophotometer (Thermo Scientific NanoDrop 1000; NanoDrop Technologies, Wilmington, DE).

### 2.4. Analysis of polymorphisms

Multiplex polymerase chain reaction (PCR) was used to allow the simultaneous amplification of eight investigated markers (Supplemental material, Table A).

Amplification of the markers was performed on an ABI Verity thermocycler (Life Technologies, Foster City, CA, USA). The PCR-based genotyping assay used a QIAGEN Multiplex PCR kit (QIAGEN, Germany) with the following reaction conditions: 5.0 μL of QIAGEN Multiplex PCR Master Mix, 1.0 μL of Q-solution, 1.0 μL of Primer Mix, 2.0 μL of water, and 1.0 μL of DNA. The samples were incubated at 95 °C for 15 min, followed by 35 cycles of 94 °C for 45 s, 60 °C for 90 s and 72 °C for 1 min, with a final extension at 70 °C for 30 min. For fragment analysis using capillary electrophoresis, 1.0 μL of PCR product was added to 8.5 μL of HI-DI deionized formamide (Life Technologies) and 0.5 μL of GeneScan 500 LIZ pattern size standard (Life Technologies). DNA fragments were separated using the ABI PRISM 3130 genetic analyzer (Life Technologies) and analyzed using the GeneMapper ID v.3.2 software (Life Technologies).

### 2.5. Analysis of ancestral populations

The INDEL polymorphisms here investigated that presented genotypic distribution significantly different between cases and controls were investigated in a sample of 703 individuals from different continents, including: 270 European individuals (mainly Portuguese individuals), 211 Sub-Saharan Africans (individuals from Angola, Mozambique, Zaire, Cameroon and the Ivory Coast) and 222 Native American individuals (from indigenous tribes of the Brazilian Amazon region). Details about these populations can be found in [37].

### 2.6. Analysis of genetic ancestry

Ancestry analysis was performed according to Santos et al. [37] using 48 autosomal ancestry informative markers (AIMs). Three multiplex PCR reactions with 16 markers each were performed, and the PCR amplicons were analyzed by electrophoresis using the ABI Prism 3130 sequencer and GeneMapper ID v.3.2 software. The individual proportions of European, African and Amerindian genetic ancestries were estimated using STRUCTURE v.2.3.3 software, assuming three parental populations (European, African and Amerindian).

### 2.7. Statistical analysis

All statistical analyses were performed using SPSS v.20.0 Statistical Program (SPSS, Chicago, IL, USA). Group comparisons for the categorical variables (gender) were tested in pairs by Pearson's Chi-squared test, while Student's *t*-test was used for the analysis of

**Table 1**
Demographic variables for patients with B-cell ALL and the control group.

| Variable | Case | Control | *P*-value |
|---|---|---|---|
| No. | 130 | 125 | |
| Age, years[a] | 5.16 ± 2.79 | 23.09 ± 4.62 | 0.006 |
| Gender (male/female) | 85/45 | 55/70 | 0.001 |
| Genetic ancestry[b] | | | |
| European ancestry | 0.443 ± 0.115 | 0.505 ± 0.131 | $2.42 \times 10^{-5}$ |
| African ancestry | 0.218 ± 0.904 | 0.204 ± 0.790 | 0.291 |
| Amerindian ancestry | 0.339 ± 0.116 | 0.294 ± 0.119 | $2.92 \times 10^{-4}$ |

[a]Values are as expressed as mean (±SD = standard deviation). Significance determined by Student's *t*-test.
[b]Values are as expressed as mean ± SD. Significance determined by Mann–Whitney test.

**Table 2**
Categorical distribution of Amerindian and European ancestry in patients with B-cell ALL in the comparison with the control group.

| Genetic Ancestry (%) | Case no. (%) | Control no. (%) |
|---|---|---|
| Amerindian ancestry | | |
| [5–10] | 1 (1) | 3 (2) |
| [10–20] | 18 (14) | 25 (20) |
| [20–30] | 30 (23) | 47 (38) |
| [30–40] | 44 (34) | 30 (24) |
| [40–50] | 22 (17) | 10 (8) |
| [50–60] | 12 (9) | 10 (8) |
| >60 | 3 (2) | 0 |
| *P*-value | 0.010 | |
| European ancestry | | |
| [5–10] | 1 (1) | 3 (2) |
| [10–20] | 3 (2) | 2 (1) |
| [20–30] | 13 (10) | 7 (6) |
| [30–40] | 30 (23) | 17 (14) |
| [40–50] | 45 (35) | 27 (22) |
| [50–60] | 26 (20) | 38 (30) |
| >60 | 12 (9) | 31 (25) |
| *P*-value | 0.001 | |

quantitative variables (age). For the comparison of ancestry index among the samples, we used Mann-Whitney test. Multiple logistic regression analyses were carried out to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). In these analyses, covariates considered as potential confounders (age, gender and genetic ancestry) were analyzed. All statistical tests were based on a two-tailed probability and *P*-value <0.05 was considered significant. *P*-values were adjusted by Bonferroni correction for multiple testing.

## 3. Results

### 3.1. Demographic

We analyzed 130 patients with B-cell ALL and 125 healthy individuals. Table 1 shows the demographic features of these groups. The case group was predominately male, while the control group had a higher proportion of females. The results showed statistically significant differences between the cases and controls in the following variables: age ($P = 0.006$), gender ($P = 0.001$), European ancestry ($P = 2.42 \times 10^{-5}$) and Amerindian ancestry ($P = 2.92 \times 10^{-4}$).

Regarding genomic ancestry, the ethnic composition of the case group was 44% European, 22% African and 34% Amerindian, while the control group was 50% European, 20% African and 30% Amerindian. The results revealed an increased Amerindian ancestry and a reduced European ancestry in B-cell ALL patients compared with the control group.

Using 10% increments, we compared the categorical distribution of the estimated Amerindian and European ancestries in the studied population (Table 2), and we found different distributions of these ancestries between the case and control groups. To determine the influence of ancestry in the susceptibility to B-cell ALL, we performed a logistic regression (Table 3). According to the adopted model, for each increase of 10% in the Amerindian ancestry there are 1.4-times higher chances of developing B-cell ALL (OR = 1.406; 95% CI = 1.123–1.761), while each increase of 10% in the European ancestry results in reduced chances of developing B-cell ALL (OR = 0.666; 95% CI = 0.536–0.827).

### 3.2. Distribution of genotypes associated with susceptibility to ALL

The genotypic distributions of *CYP2E1, CYP19A1, TYMS, XRCC1, TP53, CASP8, NFKβ1* and *IL-1α* markers in the case group compared with the control group are described in Table 4. Analyses were performed multivariate regression (adjusted for age, gender and for European and Amerindian ethnicities). Through Bonferroni correction, *P*-values were corrected for eight INDEL, which was the number of performed tests ($P_{limit} = 0.00625$).

The polymorphisms in *TP53*, *NFKβ1*, *TYMS*, *CYP2E1* and *IL-1α* genes had no significant effect in the analysis after adjustment using multiple logistic regression.

In relation to the polymorphism in *CASP8* (rs3834129) gene, the carriers of Insertion/Insertion (Ins/Ins) genotype present diminished chances ($P = 0.001$; OR = 0.353; 95% CI = 0.192–0.651) in the development of B-cell ALL. Analyses also revealed reduced chances of developing B-cell ALL for the carriers of deletion/deletion (Del/Del) genotype in *CYP19A1* (rs11575899) gene ($P = 3.35 \times 10^{-6}$; OR = 0.121; 95% CI = 0.050–0.295).

In the *XRCC1* gene, a significant risk association was found for the Del/Del genotype (rs3213239) ($P = 2.01 \times 10^{-4}$; OR = 6.559; 95% CI = 2.433–17.681). Therefore, individuals homozygous for this deletion in the *XRCC1* gene have an approximately 7-fold increased risk of ALL development over those with other genotypes.

## 4. Discussion

B-cell ALL is the most common neoplasm in children [1]. The association of the investigated polymorphisms with the risk of developing this type of leukemia was studied, and demographic factors such as gender and ancestry were used to control for possible confounding effects. ALL incidence is approximately 20% higher in males than in females [40]. Similarly, males were predominant among the B-cell ALL patients studied herein.

Our results show that genetic ancestry influences the risk of developing B-cell ALL. Amerindian ancestry correlated with the risk of developing B-cell ALL, while European ancestry had a protective effect on the development of this childhood leukemia in the studied population (Table 3).

Our study found genetic ancestry differences in the incidence of ALL [36,41–44]. Our results corroborate with those of Walsh et al. [36], in which Native American ancestry is associated with an increased risk of B-cell ALL in Hispanic children. In that work, each 20% increase in the proportion of an individual's genome that is of Native American origin conferred a 1.20-fold increased risk of B-cell ALL. Whereas Hispanics are an admixed population between European, African and Native American ancestries, the authors suggested that the observed high incidence of B-cell ALL in Hispanic children might be partially attributed to genetic risk factors associated with Amerindian ancestry [36]. We employed a statistical approach similar to the work of Walsh et al. [36] and found that an increment of 10% in the Amerindian ancestry corresponds to an increment of 1.4-times the risk of developing B-cell ALL in the investigated Brazilian population. Therefore, our results are promising because they can help to clarify leukemogenesis and

**Table 3**
Odds ratio (OR) and 95% confidence intervals (CIs) of logistic regression model of Amerindian and European ethnicity.

| Genetic ancestry | Case mean | Control mean | OR[a] | 95% CI[a] | *P*-value[a] |
|---|---|---|---|---|---|
| Amerindian ancestry | 0.339 ± 0.116 | 0.294 ± 0.119 | 1.406 | 1.123–1.761 | 0.003 |
| European ancestry | 0.443 ± 0.115 | 0.505 ± 0.131 | 0.666 | 0.536–0.827 | $2 \times 10^{-4}$ |

Logistic regression adjusted for confounders.
[a] Odds-ratio of 10% ethnicity increase.

**Table 4**
Genotype distribution of the investigated polymorphisms in patients with B-cell ALL in comparison with the control group.

| Genotype | No. (%) Case | No. (%) Control | *P*-value[a] | OR (95% IC)[a] |
|---|---|---|---|---|
| ***CASP8*** | 130 | 125 | | |
| INS/INS | 23 (17.7) | 47 (37.6) | **0.001** | INS/INS vs. others: 0.353 (0.192–0.651) |
| INS/DEL | 81 (62.3) | 53 (42.4) | | |
| DEL/DEL | 26 (20) | 25 (20) | | |
| *Allele INS* | 0.488 | 0.588 | | |
| *Allele DEL* | 0.512 | 0.412 | | |
| ***TYMS*** | 130 | 125 | | |
| INS/INS | 33 (25.4) | 53 (42.4) | 0.005 | INS/INS vs. others: 0.438 (0.247–0.775) |
| INS/DEL | 84 (64.6) | 56 (44.8) | | |
| DEL/DEL | 13 (10) | 16 (12.8) | | |
| *Allele INS* | 0.577 | 0.648 | | |
| *Allele DEL* | 0.423 | 0.352 | | |
| ***CYP19A1*** | 130 | 121 | | |
| INS/INS | 41 (31.5) | 25 (20.7) | | |
| INS/DEL | 82 (63.1) | 56 (46.3) | | |
| DEL/DEL | 7 (5.4) | 40 (33) | $\mathbf{3.35 \times 10^{-6}}$ | DEL/DEL vs. others: 0.121 (0.050–0.295) |
| *Allele INS* | 0.631 | 0.438 | | |
| *Allele DEL* | 0.369 | 0.562 | | |
| ***TP53*** | 130 | 125 | | |
| INS/INS | 2 (1.5) | 6 (4.8) | | |
| INS/DEL | 54 (41.5) | 33 (26.4) | | |
| DEL/DEL | 74 (57) | 86 (68.8) | 0.097 | DEL/DEL vs. others: 0.630 (0.364–1.088) |
| *Allele INS* | 0.223 | 0.180 | | |
| *Allele DEL* | 0.777 | 0.820 | | |
| **NFKβ1** | 130 | 123 | | |
| INS/INS | 17 (13.1) | 28 (22.8) | | |
| INS/DEL | 74 (56.9) | 49 (39.8) | | |
| DEL/DEL | 39 (30) | 46 (37.4) | 0.202 | DEL/DEL vs. others: 0.692 (0.394–1.218) |
| *Allele INS* | 0.415 | 0.427 | | |
| *Allele DEL* | 0.585 | 0.573 | | |
| ***XRCC1*** | 122 | 123 | | |
| INS/INS | 64 (52.4) | 65 (52.8) | | |
| INS/DEL | 34 (27.9) | 51 (41.5) | | |
| DEL/DEL | 24 (19.7) | 7 (5.7) | $\mathbf{2.01 \times 10^{-4}}$ | DEL/DEL vs. others:6.559 (2.433–17.681) |
| *Allele INS* | 0.664 | 0.736 | | |
| *Allele DEL* | 0.336 | 0.264 | | |
| ***CYP2E1*** | 105 | 123 | | |
| INS/INS | 4 (3.8) | 2 (1.6) | | |
| INS/DEL | 8 (7.6) | 12 (9.8) | | |
| DEL/DEL | 93 (88.6) | 109 (88.6) | 0.681 | DEL/DEL vs. others: 1.204 (0.496–2.921) |
| *Allele INS* | 0.076 | 0.065 | | |
| *Allele DEL* | 0.924 | 0.935 | | |
| **IL-1α** | 130 | 125 | | |
| INS/INS | 46 (35.4) | 45 (36) | | |
| INS/DEL | 69 (53.1) | 55 (44) | | |
| DEL/DEL | 15 (11.5) | 25 (20) | 0.05 | DEL/DEL vs. others: 0.478 (0.229–0.995) |
| *Allele INS* | 0.619 | 0.580 | | |
| *Allele DEL* | 0.381 | 0.420 | | |

[a] Logistic regression adjusted for confounders

to find biomarkers that might be of interest in the stratification of B-cell ALL risk in admixed populations.

In the present work, we found significant associations between three investigated INDEL polymorphisms and the development of B-cell ALL. Data suggest that Ins/Ins genotype of the polymorphism in *CASP8* (rs3834129) gene and Del/Del genotype of the polymorphism in *CYP19A1* (rs11575899) gene are associated to a lower chance of developing B-cell ALL, while Del/Del genotype of the polymorphism in *XRCC1* (rs3213239) gene is associated to a higher risk of developing B-cell ALL.

CASP8 is a key-regulator of apoptosis, which is a defense mechanism that is fundamental against tumor development [5]. The deletion of 6 bp (CTTACT), at −652 in promoter region of CASP8 gene (rs3834129) suppresses linkage site Sp1, which acts as a transcription factor of the gene. Notably, this polymorphism has been associated with the development of many types of cancer, includ-

**Table 5**
Genotype distribution of the polymorphisms in the *CASP8*, *CYP19A1* and *XRCC1* genes in patients with B-cell ALL compared with the control group and parental populations (European, Amerindian and African).

| Genotype | No. (%) | | | | |
|---|---|---|---|---|---|
| | Case | Control | European | African | Amerindian |
| *CASP8* (rs3834129) | **130** | **125** | **268** | **211** | **222** |
| INS/INS | 23 (17.7) | 47 (37.6) | 81 (30) | 49 (18.1) | 142 (52.6) |
| INS/DEL | 81 (62.3) | 53 (42.4) | 123 (45.6) | 113 (41.9) | 59 (21.9) |
| DEL/DEL | 26 (20) | 25 (20) | 64 (23.7) | 49 (18.1) | 21 (7.8) |
| *Allele INS* | 0.488 | 0.588 | 0.532 | 0.5 | 0.773 |
| *Allele DEL* | 0.512 | 0.412 | 0.468 | 0.5 | 0.227 |
| ***CYP19A1*** (rs11575899) | **130** | **121** | **270** | **211** | **222** |
| INS/INS | 41 (31.5) | 25 (20.7) | 85 (31.5) | 95(45) | 92 (41.44) |
| INS/DEL | 82 (63.1) | 56 (46.3) | 145 (53.7) | 97(46) | 98 (44.14) |
| DEL/DEL | 7 (5.4) | 40 (33) | 40 (14.8) | 19 (9) | 32 (14.4) |
| *Allele INS* | 0.631 | 0.438 | 0.5833 | 0.6801 | 0.6351 |
| *Allele DEL* | 0.369 | 0.562 | 0.4167 | 0.3199 | 0.3649 |
| ***XRCC1*** (rs3213239) | **122** | **123** | **261** | **211** | **222** |
| INS/INS | 64 (52.4) | 65 (52.8) | 117(44.8) | 85 (40.3) | 215 (96.8) |
| INS/DEL | 34 (27.9) | 51 (41.5) | 116 (44.4) | 95 (45) | 5 (2.3) |
| DEL/DEL | 24 (19.7) | 7 (5.7) | 28 (10.7) | 31 (14.7) | 2 (0.9) |
| *Allele INS* | 0.664 | 0.736 | 0.6705 | 0.628 | 0.9797 |
| *Allele DEL* | 0.336 | 0.264 | 0.3295 | 0.372 | 0.0203 |

ing in lung, breast, stomach, colon/rectum, pancreas, among others [5,17]. However, there is no information over the influence of this polymorphism to the risk of developing childhood B-cell ALL.

The *CYP19A1* gene encodes the aromatase enzyme, which is responsible for the final phase of estrogen biosynthesis. Thus, mutations in this gene may affect the levels of aromatase enzyme activity as well as cellular differentiation and growth [45]. Polymorphisms in this gene have been associated with an increased risk of breast cancer [10,46] and gastric cancer [47]. However, little is known about the relationship between *CYP19A1* variants and B-cell ALL susceptibility.

The *XRCC1* protein is one of the most important proteins for base excision repair (BER) [26–28]. This pathway is also important to repair DNA damages caused by oxidation and alkylation [28]. Polymorphic alterations in this gene have been associated with ALL risk in infants [48–50].

We seek to interpret the observed allelic differences for these three INDEL polymorphisms based on their frequencies in parental populations and on the ethnic contribution of the group of patients and control. Whereas the ethnic contribution of Amerindian in the group of patients higher than in the group of controls, such alleles could be differentially represented both in Amerindian ancestral group as in the group of patients in the admixed population, independent of the allele effect on the development of B-cell ALL. Data of the analyses of ancestral populations (European, African and Amerindian) presented in Table 5do not favor this interpretation. On the contrary, they indicate that the observed differences between cases and controls, regarding polymorphisms in *CASP8* (rs3834129), *CYP19A1* (rs11575899) and *XRCC1* (rs3213239) genes, cannot be explained based on differences in contribution between the two ethnic groups.

For the polymorphism in *CASP8* (rs3834129) gene, Ins/Ins genotype is underrepresented among the patients in comparison to the controls and it was associated as a protection factor for B-cell ALL. In the investigated sample of Amerindian individuals, the frequency of Ins allele (0.77) was higher than in European (0.53) and African (0.50) individuals.

For the polymorphism in *CYP19A1* (rs11575899) gene, Del allele was underrepresented in the sample of patients in comparison to the controls and it was associated as a protection factor for B-cell ALL. In the investigated sample of Amerindian individuals, the frequency of this allele (0.36) is intermediate to European (0.42) and African (0.32) individuals.

For the polymorphism in *XRCC1* (rs3213239) gene, Del/Del genotype is overrepresented in the group of patients. However, the frequency of Del allele is greatly reduced among Amerindian (0.02) in comparison to African (0.37) and European (0.33).

## 5. Conclusions

In conclusion, these data demonstrate that the investigated INDEL polymorphisms in the CASP8 (rs3834129), *CYP19A1* (rs11575899), and *XRCC1* (rs3213239) genes, as well as Amerindian genetic ancestry, are significantly important for B-cell ALL susceptibility in Brazilian Amazon children. To the best of our knowledge, this is the first study to describe the influence of these INDEL polymorphisms to B-cell ALL development and to associate Amerindian genetic ancestry with the development childhood B-cell ALL in an admixed Brazilian population.

## Conflict of interest

The authors have no competing financial interests to declare.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2015.08.008.

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