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CXCL12 and *TP53* genetic polymorphisms as markers of susceptibility in a Brazilian children population with acute lymphoblastic leukemia (ALL)

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Abstract Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Genetic polymorphisms in the 3′UTR region of the *CXCL12* (rs1801157) and *TP53* codon 72 (rs1042522) genes may contribute to susceptibility to childhood ALL because they affect some important processes, such as metastasis regulation and tumor suppression. Thus the objective of the present study was to detect the frequency of two genetic polymorphisms in ALL patients and controls and to add information their impact on genetic susceptibility and prognosis. The *CXCL12* and *TP53* polymorphisms were tested in 54 ALL child patients and in 58 controls by restriction fragment length polymerase chain reaction and allelic specific chain reaction techniques, respectively. The frequencies of both allelic variants were higher in ALL patients than in the controls and indicated a positive association: OR = 2.44; 95 % CI 1.05–5.64 for *CXCL12* and OR = 2.20; 95 % CI 1.03–4.70 for *TP53*. Furthermore, when the two genetic variants were analyzed together, they increased significantly more than fivefold the risk of this neoplasia development (OR = 5.24; 95 % CI 1.39–19.75), indicating their potential as susceptibility markers for ALL disease and the relevance of the allelic variant combination to increased risk of developing malignant tumors. Future studies may indicate a larger panel of genes involved in susceptibility of childhood ALL and other hematological neoplasias.

Keywords ALL · *CXCL12* · *TP53* · Polymorphisms · Genetic susceptibility

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Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disorder that originates from one single hematopoietic precursor committed to the B- or the T cell lineage. Acquisition by the precursor of a series of genetic abnormalities disturbs its normal maturation process, leading to differentiation arrest and proliferation of the transformed cell. As a consequence, an immature B- or T cell clone accumulates in the bone marrow resulting in the suppression of normal hematopoiesis and in various extramedullary sites [1].

Although overall incidence is rare, leukemia is the most common type of childhood cancer. It accounts for 30 % of all cancers diagnosed in children under 15. Within this population, ALL occurs approximately five times more frequently than acute myelogenous leukemia and accounts for ~78 % of all childhood leukemia diagnoses [2]. In Brazil, for the year 2012, INCA (National Cancer Institute) estimated ~8.510 new cases of leukemias. Among children and adolescents it is the most common type of cancer, accounting for 29 % of all malignant tumors diagnosed and the highest incidence is in the range of 1–4 years of age [3].

Epidemiologic studies of acute leukemias have examined possible risk factors, including genetic, infectious, and environmental, in an attempt to determine etiology but only one environmental risk factor (ionizing radiation) has been significantly linked to ALL [2]. Recent genetic association studies on cancer risk, including those for ALL, have focused on the effects of single nucleotide polymorphisms in some genes that regulate important processes, such as inflammation and tumor suppression.

In contrast to the immune/inflammatory setting in which chemokines act primarily as chemoattractants of leukocytes, in cancer, they also induce the motility of endothelial cells and tumor cells [4]. CXCL12, a chemokine expressed in various tumors, binds to chemokine receptor 4 (CXCR4) and is considered to play an important role in tumor growth and invasion [5]. Many authors have investigated the rs1801157 polymorphism of this gene in disease pathogenesis [6–9] but its value as a susceptibility marker is not well determined.

Mutations in the *TP53* gene are considered to represent the most common genetic alterations in human cancers [10]. It is known that *TP53* effectively acts like tumor suppressor, controlling damaged cell proliferation and thus protecting against malignancy. Thus, several studies have focused on *TP53* polymorphisms as risk factors for malignant disease. A polymorphic site (rs1042522) at codon 72 in exon 4 encodes either an arginine amino acid (Arg) or a proline (Pro) residue [11]. Several studies have reported epidemiological differences in the prevalence or prognostic significance of p53 mutants with Arg or Pro in certain cancer types, but the biological significance of this genetic variant also remains unclear [12].

Additionally, a study in cultured fibroblasts from Moskovits et al. [13] sought to further elucidate the molecular mechanisms whereby *TP53* in stromal cells exerts its tumor suppressor activity over cancer cells. They report that, within both human and mouse fibroblasts, p53 protein can suppress the production of *CXCL12* and, abrogation of *TP53* expression in fibroblasts promotes *CXCL12* secretion, increasing the migration and invasiveness of tumor cells. The suppression of *CXCL12* production by *TP53* may attenuate tumor development and metastasis.

Our research group has been studying polymorphisms related to the immune system and tumor development in different cancer types. Nevertheless, there are no data relating polymorphisms in *CXCL12* and *TP53* genes simultaneously and their possible association with ALL in Brazilian population. Within this context, in the present report, we attempt to investigate associations between genetic polymorphisms in the *CXCL12* and *TP53* genes and the risk of ALL in Brazilian child patients from the Southern region, Paraná. We also related our molecular data with ALL progression and prognosis through the correlation with the high or low risk clinical parameter.

Materials and methods

Studied population for ethics

Following approval from the Human Ethics Committee of the State University of Londrina [No. 214/09-CAAE (Presentation of Certificate of Appreciation for ethics) No. 0164.0.268.000-09] 10 mL of peripheral blood was collected from ALL patients and controls. A Term of Free Informed Consent was signed by all sample donors.

The case group consisted of 54 patients (29 males and 25 females) (mean age 7.31 range ± 5.28 years) with confirmed diagnoses of ALL in childhood (those with ALL diagnosed after 21 years old were excluded) that were recruited from two institutions of Londrina, Parana, Brazil: Cancer Hospital of Londrina and University Hospital of Londrina. A total of 58 (30 males and 28 females) samples from individuals were collected in the same region of patients (Londrina, Parana, Brazil), with similar median age to case group (mean age 10.35 range ± 5.81 years) and were used as control group. The control group consisted of healthy individuals, mostly free of neoplasia and not hospitalized. Most of our sample, both patients and controls, were predominantly Caucasian, a prevalent population in southern Brazil due to European colonization.

DNA extraction

Genomic DNA was isolated from 200 μL peripheral blood cells using the Biopur Kit (Biometrix Diagnostica) according to the manufacturer's instructions. After precipitation with ethanol, the pellet was resuspended in 50 μL of Biopur Kit specific buffer and quantified by spectrophotometry for later use in genotyping analyses.

Genetic polymorphisms

Polymerase chain reaction (PCR): CXCL12 gene

DNA (100 ng) was analyzed using PCR with specific primers for *CXCL12* 3′UTR-F1 (forward 5′-CAGTCAACCTGG GCAAAGCC-3′) and *CXCL12* 3′UTR-R2 (reverse 5′-CCT GAGAGTCCTTTTGCGGG-3′) (GenBank accession number L36033). Samples were amplified using the buffer kit plus 1.25 U of *Taq* polymerase (Invitrogen™, Carlsbad, CA, USA). PCR conditions were: 5 min denaturation at 94 °C, 35 cycles of 1 min at 94 °C, 1 min at 60 °C and 1 min at 72 °C, and 10 min elongation at 72 °C in a thermocycler (PCR-Sprint Hybaid—Guelph, ON, Canada). The PCR products

were analyzed by electrophoresis on 10 % acrylamide gel and detected by a nonradioisotopic technique using a commercially available silver staining method.

PCR products were subjected to restriction digestion by incubating with *Msp*I (Promega, Madison, WI, USA) for 3 h at 37 °C. The restriction digestion products were analyzed by electrophoresis as described above. The *CXCL12* GG genotype yielded 100 and 193 base pair products, while the AA genotype yielded a 293 base pair product.

PCR: TP53 gene

DNA (100 ng) was analyzed using PCR with specific primers for *TP53*-F1 (forward 5′-GCCAGAGGCTGCTCC CCC-3′) and R1 (reverse 5′-CGTGCAAGTCACAGACTT-3′) for Pro allele and F2 (forward 5′-TCCCCCTTGCCGT CCCAA-3′) and R2 (reverse 5′-CTGGTGCAGGGGCCA CGC-3′) for Arg allele, (GenBank accession number U94788). Samples were amplified using the buffer kit plus 1.25 U *Taq* polymerase (Invitrogen™, Carlsbad, CA, USA). PCR conditions were: 3 min denaturation at 94 °C, 35 cycles of 30 s at 94 °C, 30 s at 57 °C for Pro allele and 60 °C for Arg allele and 30 s at 72 °C with a 10 min for final elongation at 72 °C in a thermocycler (PCR-Sprint Hybaid—Guelph, ON, Canada). The PCR products were analyzed by electrophoresis as described above for the *CXCL12* gene. The *TP53* Pro allele yielded 178 base pair products, while the Arg allele yielded a 136 base pair product.

Statistical analysis

A *T* test was used to compare the median ages between patients and controls.

For the genotypic frequencies analysis, the *CXCL12*-3′A as well as *TP53*-Pro were grouped for the presence of at least one variant allele versus double wild-type genotypes, considering a small number of homozygous individuals for both allelic variants in the population and their considered dominant effect.

The gene frequencies observed in patients and controls were compared using contingency tables to calculate the odds ratios (OR) with a confidence interval (CI) of 95 %, in an association study. For these genes in which the three genotypes were identified, a 3 × 2 contingency table was constructed, with the considered wild type genotype as reference (OR = 1.0), to determine the OR value for heterozygotes and rare genotypes, using the DPP Braile Biomedical program (http://www.braile.com.br).

The different genotypes of *CXCL12* and *TP53* were compared with the high or low risk clinical parameter. Statistically significant relationships between this parameter and genotypes were also determined using the DPP Braile Biomedical program (http://www.braile.com.br) for OR and 95 % CI calculations.

Results

The mean ages of cases and controls were: mean age 7.31 range ± 5.28 years and mean age 10.35 range ± 5.81 years, respectively. There was no statistically significant difference between the ages of the cases and controls ($P > 0.05$).

Association between polymorphisms and ALL neoplasia

CXCL12 (rs1801157) and *TP53* (rs1042522) polymorphisms were genotyped in 54 patients with ALL and the 58 control individuals. For the *CXCL12* gene, we found a frequency of 61.11 % (33/54) and 79.32 % (46/58) of homozygous prevalent, 33.34 % (18/54) and 18.96 % (11/58) of heterozygotes and 5.55 % (3/54) and 1.72 % (1/58) of rare homozygous among patients and controls, respectively. For *TP53* gene, we observed a frequency of 44.44 % (24/54) and 63.80 % (37/58) of homozygous prevalent, 42.60 % (23/54) and 32.75 % (19/58) of heterozygotes and 12.96 % (7/54) and 3.45 % (2/58) of rare homozygous among patients and controls, respectively. Statistical analyses showed a positive association for both genetic variants analyzed individually in relation to ALL susceptibility: *CXCL12* (OR = 2.44; 95 % CI 1.05–5.64) and *TP53* (OR = 2.20; 95 % CI 1.03–4.70). In this analysis we consider only the presence of the genetic variant, at least in heterozygous. Homozygotes for both mutations were also more frequent in patients than in controls, but the results were not statistically significant (data not shown).

In addition, the relationship was analyzed between ALL risk and the combination of the simultaneous presence of two polymorphisms, at least in heterozygous. In this case, a relevant statistical significance was also observed for ALL development (OR = 5.24; 95 % CI 1.39–19.75). Finally, we analyzed the simultaneous presence of one of the allelic variants occurring at least in heterozygous in combination with the presence of a homozygous mutation in the other gene, that is, carrier three considered risk alleles, and also found a strong tendency for ALL development, but not significant (OR = 5.90; 95 % CI 0.67–52.19).

Association between polymorphisms and low or high risk ALL

The ALL patients were diagnosed and then classified into high recurrence risk and low recurrence risk groups. Among the 54 patients with ALL, 17 were considered of low risk and 37 of high risk, according to the clinical and laboratorial findings at diagnosis, as defined by the Brazilian Group for Childhood Leukemia Treatment in the GBTLI LLA-99 which is based on the Cancer Therapy Evaluation Program, proposed by the National Cancer Institute (INCA, 2012). The diagnosis includes age, leukocyte count, immunophenotyping, involvement of tissues other than bone marrow and responsiveness to the treatment.

When the genotype data were analyzed for ALL to be low risk or high risk, the results indicated that the presence of mutations did not influence this clinical parameter either in isolation, or when the risk genotypes were analyzed simultaneously, as follows: *CXCL12* (OR = 0.61; 95 % CI 0.19–1.96), *TP53* (OR = 0.58; 95 % CI 0.18–1.88) dual genotype (OR = 0.56; 95 % CI 0.15–2.11). Although the results were not significant, the genetic variants tended to be more present in the low risk patients.

Of the 54 patients, 11 died and only 2 of these patients were considered low risk. Of the 11 patients who died, eight patients had at least one risk allelic variant and three of them had inherited mutations in both the genes studied, two of which were those originally considered low risk. However, the sample for the parameter death ($n = 11$) precluded a better analysis in relation to genotypic data.

Discussion

ALL is the most common malignancy affecting children and in recent years we have witnessed tremendous advances in the success of treatment of childhood ALL, with over than 80 % patients cured. However, much remains to be done to improve treatment outcome in this neoplasia [14, 15].

One of the current lines of research that seeks markers that may aid in the diagnosis, prognosis and therapy in different cancers includes the study of polymorphic allelic variants. According to Fletcher and Houlston [16] a substantial proportion of human cancers arise in carriers of large numbers of low penetrance susceptibility alleles and thus, much of the inherited cancer risk still remains to be discovered that highlights the need for ongoing efforts. Within this context, in this study we investigated two genetic variants in *CXCL12* and *TP53* genes in patients and controls in a search for markers that may identify individuals more susceptible to the development of ALL, as well as a better genetic characterization related to clinical outcome. As previously mentioned in the methodology, both sample groups were composed predominantly of Caucasian individuals from Southern Brazil. However, due to the high degree of miscegenation of the Brazilian population and the need to use genetic markers to the correct ethnic characterization of individuals in our country, these data have not been explored in relation to the variants analyzed. As mentioned, the individuals in the case group and control group were collected in the same region (Londrina, Parana, Brazil).

According to Ayala et al. [17], the importance of tumor microenvironment for cancer progression has been widely recognized in recent years. Interaction of cancer cells with their immediate stromal microenvironment overcoming the physiological barrier function of stromal cells synergizes growth, angiogenesis and initiation of an invasive and metastatic phenotype of the cancer cell. Also according to these authors high expression of CXC chemokine ligand 4 (CXCR4) by leukemic blasts and activation of the CXCR4–CXCL12 axis is involved in leukemia progression and disruption of normal hematopoiesis. Thus leukemia associated bone microenvironment markers could be used as prognostic or predictive indicators of disease progression and/or treatment outcome. In the present study we investigated a genetic variant in the *CXCL12* gene (rs1801157) and found a positive association with ALL development (OR = 2.44; 95 % CI 1.05–5.64), which may be indicative of the role of this gene as a marker for susceptibility to the development of ALL.

The tumor suppressor gene *TP53* is an essential player in maintaining genome integrity and has a well-established role in protecting against cancer development [18]. The polymorphism on 72 codon (Arg72Pro) (rs1042522) of this gene is an important and the most studied SNP that may be associated with cancer risk [19–21]. Two studies that analyzed *TP53* codon 72 in a Brazilian population found similar frequencies for this genetic variant: 41–50 % for Arg/Arg, 35.4–42.6 % Arg/Pro and 14.6–16.4 % Pro/Pro [22, 23]. Thurow [24] also analyzed the genotype distribution in a Brazilian population and showed a predominance of the Arg amino acid with a frequency of 46.9 % Arg/Arg, 42.2 % Arg/Pro and 10.9 % Pro/Pro. According to these authors, the individuals without family history of cancer were associated with Arg amino acid, so the Pro allele may be more frequent in cancer patients. In the present study we investigated the genetic variant on 72 codon in the *TP53* gene and found a positive association with ALL development (OR = 2.20; 95 % CI 1.03–4.70). Nevertheless, this gene may be another potential marker for susceptibility to ALL development. According to Liu [25], in a meta-analysis which included 1,964 colorectal cancer cases and 2,943 controls, the combined results showed that

there was no significant difference in genotype distribution [Arg/Arg (OR = 0.86, 95 % CI 0.68–1.08); Pro/Pro (OR = 1.27, 95 % CI 0.96–1.68); Pro/Arg (OR = 1.04, 95 % CI 0.92–1.17)] between cancer and non-cancer individuals. Also, no statistical association was found between this genotype and stage, histological differentiation and lymph node metastasis. To investigate the relevance of this same allelic variant in ALL susceptibility, Do [26], genotyped 114 cases and 414 newborn controls from Wales (UK) and found a risk association with gene dosage effect ($P = 0.002$) resulting in a strong association of homozygous genotype (OR = 2.9, 95 % CI 1.5–5.6) and no sex effect. The authors have therefore identified *TP53* codon 72 as a possible risk modifier for childhood ALL. Thus, the genetic variant analyzed in the *TP53* gene may be involved in ALL development, but not in other cancer types.

Although the associations found in this study for *CXCL12* (rs1801157) and *TP53* (rs1042522) genes were not very strong, they indicated a more than two-fold risk for ALL development in both independent analyses and these genes should be considered in Meta-analyzes as potential susceptibility markers.

A positive association was also found when the two considered risk genotypes for *CXCL12* and *TP53* genes were inherited together (OR = 5.24; 95 % CI 1.39–19.75). This is the most important factor of our findings, since inherited allelic variants alone usually contribute little to the risk of developing malignant tumors, but the combination of genotypes at risk may have a more effective contribution. According to Fletcher and Houlston [16], much of the inherited susceptibility to cancer is likely to result from a polygenic model in which there is co-inheritance of genetic variants, each of which has a modest individual effect and can cause a wide range of risks in the population.

Although the LLA should always be considered a serious disease, it is important to identify prognostic factors to stratify patients into risk groups, which allows a specific therapeutic approach. High-risk patients are treated with more effective therapy, while low-risk patients have better survival and may be spared the deleterious effects of aggressive treatments [27–29]. Among the 54 patients with ALL in this sample, 17 were considered low risk and 37 high risk and when the genotype data were analyzed in relation to this, the results indicated that the presence of allelic variants did not influence this clinical parameter, either in isolation or when both polymorphisms were inherited simultaneously, as follows: *CXCL12* (OR = 0.61; 95 % CI 0.19–1.96), *TP53* (OR = 0.58; 95 % CI 0.18–1.88) and dual genotype (OR = 0.56; 95 % CI 0.15–2.11). Also, despite the low number of subjects ($n = 11$) who died in our sample some interesting trends were observed. Although most patients who died were considered high risk ($n = 9$), two patients who died were initially considered low risk, but had inherited the double risk genotype. Thus, it is noteworthy that, in the future, the classification of ALL as high or low risk may include data on the genetic profile of the patients, including the genes we studied in addition to others pre-established for a better characterization of these subgroups.

In conclusion, our results indicated that *CXCL12* and *TP53* genes could be potential markers for susceptibility in ALL, either independently but especially when both risk genotypes are inherited simultaneously. Although we observed no association with high and low risk for ALL development, in the future this data could be promising. Therefore, the study of other allelic variants in genes involved in important biological processes may lead to the establishment of a panel of molecular markers to detect individuals prone to the development of ALL, as well as patients with a poor outcome prognosis.

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Conflict of interest The authors report no declarations of interest.

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