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INFLUENCE OF *IKZF1* GENETIC VARIANTS ON THE SUSCEPTIBILITY AND PROGNOSIS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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SUMMARY

Introduction: Acute lymphoblastic leukemia accounts for about 75% of childhood cancers. The development of the disease results from interactions between genetic and environmental factors; however, susceptibility in children and adolescents is still not fully understood. The transcription factor IKAROS, encoded by the IKZF1 gene, regulates lymphocyte development, and its genetic variants are common in ALL and associated with higher relapse risk. **Objective:** To evaluate the genetic polymorphisms rs4132601 and rs10272724 of the IKZF1 gene and their relationship with susceptibility and prognosis in children with ALL. **Materials and Methods:** DNA samples from 59 patients diagnosed with ALL at the Londrina Cancer Hospital were analyzed. Variants were assessed after DNA amplification by polymerase chain reaction and genotyping by restriction fragment length polymorphism. Prognostic parameters were evaluated, and case-control association tests were performed. **Results:** No variant showed an association with susceptibility to ALL ($p>0.05$). However, the rs10272724 variant correlated with a poorer treatment response ($\rho=0.288$; $p=0.047$) and a higher risk of death ($\rho=0.301$; $p=0.024$), regardless of ALL subtype or relapse. The rs4132601 variant showed a moderate correlation with an increased risk of relapse ($\rho=0.520$; $p=0.001$), but not with disease classification, treatment response, or mortality. **Conclusion:** Although any variants were not associated with susceptibility to ALL, the polymorphisms analyzed showed an association with relevant prognostic parameter, such as treatment response, relapse, and chance of death. The findings support the hypothesis that IKZF1 gene variants may have prognostic value in childhood acute lymphoblastic leukemia, contributing to more individualized treatments and advances in oncohematology.

KEYWORDS: Acute lymphoblastic leukemia; IKAROS transcription factor; Gene variants; Disease susceptibility; Cancer prognosis.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a hematopoietic neoplasm that affects the precursor cells of B and T lymphocytes, characterized by chromosomal and genetic alterations that significantly interfere with the cell cycle. Furthermore, ALL is the most common leukemia in childhood, accounting for approximately 30% of all childhood cancers and 80% of leukemias.[1] Although the etiology of ALL is not fully understood, it is believed that environmental and genetic factors are involved in its development.[2]

Even with advances in chemotherapy, which raise the survival rate to 90%[3], genetic predisposition in ALL remains a crucial factor. Research indicates that alterations in regulatory genes, such as the *IKZF1* gene that encodes the IKAROS protein, a transcription factor essential for the regulation of lymphopoiesis, have been

associated with poor prognosis in ALL, treatment resistance, and a higher relapse rate.[4,5] In particular, specific genetic variants, such as the polymorphisms rs4132601 (T>G) and rs10272724 (T>C), have been identified as influencing the risk of developing the disease and the therapeutic response in dominant inheritance models.[6,7] Therefore, it is essential to evaluate these variants in children with ALL, since early diagnosis and a better genetic understanding can improve treatment and reduce cancer recurrence rates.

Given the high prevalence of ALL in children, the clinical relevance of *IKZF1* and its specific genetic polymorphisms, this work is justified by the need to better understand the influence of these genetic variants on the development and progression of ALL. Identifying molecular markers associated with prognosis can provide valuable support for early diagnosis and personalized treatment, with the potential to reduce recurrence rates and improve patient clinical outcomes. Furthermore, this study contributes to the advancement of scientific knowledge about the genetic basis of ALL, aligning with the growing demand for more precise and individualized therapeutic approaches.

Therefore, this study aimed to investigate the allelic and genotypic frequencies of the rs4132601 and rs10272724 variants of the *IKZF1* gene in individuals with ALL, as well as to analyze the possible implications of the polymorphic variants on the susceptibility and prognosis of these patients.

MATERIALS AND METHODS

This project was approved by the Human Research Ethics Committee (opinion no. 5987599; CAAE no. 59515722.7.0000.5231). The study proposal was presented to the program participants, who signed an informed consent form or assent form, independently and with full understanding, confirming their participation.

The project was a retrospective, experimental, quantitative study. The study population consisted of patients diagnosed with ALL from the Londrina Cancer Hospital (HCL), of both sexes, aged between three months and 19 years at the time of sample collection. Samples were collected from 92 patients. DNA extraction was performed using the Salting Out method, as described by Miller et al., 1997. Finally, the samples were quantified by spectrophotometry using a NanoDrop Lite 2c (ThermoFisher) instrument.

Study Population

The experimental group included patients diagnosed with ALL from the HCL, of both sexes, aged between three months and 19 years at the time of collection. Ninety-two peripheral blood samples were collected in tubes containing anticoagulant (ethylenediaminetetraacetic acid, EDTA). The tubes were centrifuged and the leukocyte pellet was used for DNA extraction. Patients who were seriously ill, unconscious, and/or febrile at the time of sample collection were excluded from the group.

The parameters of the Brazilian Group for the Treatment of Childhood Leukemias (GBTLI) were considered for the classification of disease risk, namely, white blood cell count at diagnosis, presence of blasts at diagnosis, age at diagnosis, and ALL subtype (including ALL-B and ALL-T). In addition, parameters of sex, risk of relapse, relapse, and treatment phase at the time of sample collection were analyzed.

Variant Analysis

An in silico analysis of the *IKZF1* gene was performed using the NCBI dbSNP tool, and primer design was carried out using the online Primer Blast software. (https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE_TYPE=BlastSearch and https://www.ncbi.nlm.nih.gov/tools/primer-blast/).

The rs10272724 variant is located downstream of the last exon of *IKZF1*, approximately 300 nucleotides away, at position 50409515, where a thymine is replaced by a cytosine (T>C). Next, a region of approximately 400 base pairs flanking the rs10272724 variant region was selected.

The rs4132601 variant is located downstream of exon 8, in the 3' untranslated region (UTR) of the gene, at nucleotide 50402906 of the NC_000007.14 reference sequence, involving a thymine to guanine substitution (T>G). Next, a 301-base region was selected for the possible identification of primers to flank the variant region.

Primer Design

Variant rs10272724

The primer pair that amplifies a 349 base pair product was chosen, consisting of the forward primer: AGGGTAGGGGATGGTTCTGG, and the reverse primer: CAAAGCATCGGCCTCCATGA. Primer-Blast was used for primer design. Furthermore, the fragment generated by computational amplification was analyzed using the NEB Enzyme Restriction Finder program to identify an enzyme that could cut the fragment, both in the presence and absence of the rs10272724 variant. The *Hinf* I enzyme was able to recognize the variant region, cleaving the T allele into two fragments, one of 201 and another of 148 base pairs, while it did not recognize the C allele site, maintaining the 349 base pair fragments after the enzymatic digestion reaction.

Variant rs4132601

A sense primer sequence was selected by PickPrimer analysis, selecting a 301-base pair region. A reverse primer was designed for each allele of the rs4132601 variant (allele-specific PCR, AS-PCR). The final sequences were as follows: Sense primer: TCATGGATTTCTCTGCTCAC; Antisense primer for the T allele: ATGCAATCACAGAGAAAGAT; and

Antisense primer for the G allele: ATGCAATCACAGAGAAAGAC.

PCR For Variant Analysis

With the synthesized primers, dilution and concentration quantification were performed, followed by the polymerase chain reaction (PCR). Approximately 100 ng of DNA were amplified in the reaction, using about 1.25 mM of dNTPs, 2.5 µM of each primer, 50 mM of $MgCl_2$, 10% Buffer, and 1.25 U of Taq polymerase. All PCR reactions were carried out in a 2720 thermal cycler (ThermoFisher Scientific™, USA), using a negative control and a positive control to detect potential contaminants and to confirm the success of the reactions, respectively. Additional amplification rounds were performed on 20% of randomly selected samples to assess the reproducibility of the results.

Genotyping

For variant rs10272724, the PCR products were subjected to enzymatic digestion (RFLP) with the *Hinf* I enzyme and incubated at 37 °C for two hours. For variant rs4132601, two tubes were prepared for each sample: one containing the Sense and Antisense T primer mix, and the other containing the Sense and Antisense G primer mix. In both cases, the generated fragments were analyzed by 10% polyacrylamide gel electrophoresis for 1 hour and 30 minutes at 110 Volts, followed by silver nitrate ($AgNO_3$) staining. Genotype identification was performed by comparison with a 100 base pair (bp) molecular weight marker.

Statistical Analysis

Descriptive statistical analysis was performed using data collected from the medical records of patients with ALL. Means, standard deviations, medians, interquartile ranges, and the standard error of the mean were assessed. In addition, the distribution of variables was evaluated to determine the suitability of parametric or non-parametric analyses.

It was possible to amplify and genotype only 59 samples from patients with ALL. The low DNA concentration, along with the absence of material for amplification due to its use in other projects, is believed to be the cause of this loss of samples for genetic analysis.

The wild-type homozygous (TT), heterozygous (TG), and variant homozygous (GG) genotypes accounted for 62.71%, 32.20%, and 5.08% of cases, respectively. Control population genotypes were obtained from the NCBI genetic database through the Alpha Project.[8] For variant rs4132601, genotypes were calculated for 7,228 individuals from the Latin American 2 population, using allele frequencies of 0.7486 and 0.2514 for alleles T and G, respectively.

The frequencies of the heterozygous (TC) and variant homozygous (CC) genotypes were 25.42% and 5.08%, respectively, in the case group, and 36.04% and 5.68% in the control group. Genetic data from a disease-free control population were also obtained from the NCBI genetic database through the Alpha Project. For rs10272724, genotypes were calculated from a sample of 1,232 individuals from the Latin American 2 population, using allele frequencies of 0.7638 and 0.2362 for alleles T and C, respectively.

For continuous variables, mean comparison tests (Student's t-test) or median comparison tests (Mann–Whitney U) were performed, along with correlation analyses (Spearman). For nominal and categorical variables, Fisher's exact test were used to assess potential associations with clinical data. The case–control association study was estimated using the odds ratio (OR) with a 95% confidence interval. Statistical analyses were conducted using SPSS® software, version 22.0 (SPSS® Inc.; Illinois, USA), with two-tailed tests and a 5% significance level.

Associations between genetic data were tested considering genotypic models (heterozygotes or variant homozygotes vs. wild-type homozygotes), dominant models (heterozygotes and variant homozygotes vs. wild-type homozygotes), and recessive models (variant homozygotes vs. wild-type homozygotes and heterozygotes).

RESULTS

Clinical data was obtained from the patients included in the study. The clinical characteristics of patients with ALL are presented in **Table 1**.

Table 1: Clinical and demographic characteristics of patients with ALL.

		n	%
Gender	Female	43	46.7
	Male	49	53.3
Classification	B- ALL	53	57.6
	T- ALL	11	11.9
	NA	28	30.4
Risk of relapse	Low	32	34.8
	High	60	65.2
Death	No	70	76.0
	Yes	22	24.0
Leukocyte count	<50.000	54	76.0
	50.000-100.000	11	15.5

	>100.000	6	8.4
Treatment phase	Untreated	12	18.2
	Under treatment	29	43.9
	Off treatment	25	37.8
Age at diagnosis	<1 year	7	7.6
	1 a 10 years	46	50.0
	>10 years	39	42.4

Table 2: Allelic and genotypic frequencies and case-control association study between IKZF1 variants rs4132601 and rs10272724 and the risk of ALL.

		Case		Control				
		n	**%**	**n**	**%**	**p**	**OR**	**CI 95%**
Allelic Frequency rs4132601	**T**	93	78.8	10281	71.1	0.248	0.76	0.488 – 1.170
	G	25	21.2	3635	25.1			
Allelic Frequency rs10272724	**T**	97	82.2	1882	76.4	0.18	0.7	0.424 – 1.122
	C	21	17.8	582	23.6			
Genotypic Frequency rs4132601	**TT**	37	62.71	4050	56.03	ref	ref	ref
	TG	19	32.20	2721	37.65	0.41	0.76	0.446 – 1.342
	GG	3	5.08	457	6.32	0.79	0.72	0.231 – 2.21
Genotypic Frequency rs10272724	**TT**	41	69.49	718	58.28	ref	ref	ref
	TC	15	25.42	444	36.04	0.09	0.59	0.32 – 1.07
	CC	3	5.08	70	5.68	>0.99	0.75	0.238 – 2.243
Genetic Model								
	Dominant							
	TG+GG vs TT	22 vs 37		3178 vs 4050		0.36	0.76	0.45 - 1.28
	TC+CC vs TT	18 vs 41		514 vs 718		0.1	0.61	0.347 – 1.089
	Recessive							
	GG vs TG+TT	3 vs 56		457 vs 6771		> 0.99	0.79	0.258 – 2.322
	CC vs TC+CT	3 vs 56		70 vs 1162		> 0.99	0.89	0.285 – 2.77

n=number; p= Fisher's exact test; OR= odds ratio; IC= confidence interval

Table 3: Correlation between carriers of the variant allele (G) of rs4132601 and the variant allele (C) of rs10272724 in IKZF1 and the prognostic parameters of patients with ALL.

		Type of ALL	Risck	Responder	Death	Relapse
rs4132601	Corr.Coef. (ρ)	0.213	-0.052	0.074	-0.083	0.520
	p	0.125	0.701	0.612	0.541	**0.001***
rs10272724	Corr.Coef. (ρ)	0.169	-0.028	0.288	0.301	0.199
	p	0.232	0.836	**0.047***	**0.024***	0.134

For variant rs4132601, the wild-type homozygous (TT), heterozygous (TG), and variant homozygous (GG) genotypes accounted for 62.71%, 32.20%, and 5.08%, respectively. Genotypes from controles were obtained from 7,228 individuals from the Latin American 2 population, using allele frequencies of 0.7486 and 0.2514 for alleles T and G, respectively. The genotype distributions were in Hardy–Weinberg equilibrium in the case group ($\chi^2 = 0.08$; $p = 0.784$) and in the control group ($\chi^2 = 9.08$; $p = 0.99$). The case-control association study is presented in Table 2.

It can be observed that there was no association between the alleles or genotypes of the *IKZF1* rs4132601 variant and the risk of developing ALL ($p > 0.05$). Likewise, no susceptibility associations were found for the dominant and recessive genetic models ($p > 0.05$). The influence of the rs4132601 variant was also evaluated alongside clinical disease parameters through correlation analysis. No significant correlations were found between carriers of the variant allele of rs4132601 and the type of ALL, treatment response type, or death (Table 3).

Otherwise, a moderate positive correlation was observed between the presence of the rs4132601 variant allele and disease relapse (Spearman correlation coefficient $\rho = 0.520$; $p = 0.001$). Therefore, it can be inferred that patients carrying the variant allele, with TG or GG genotypes, exhibited more disease relapse compared to patients with the TT genotype.

No association was observed for alleles or genotypes of the *IKZF1* rs10272724 variant with susceptibility to ALL ($p > 0.05$). Likewise, no association was found for disease risk in the recessive and dominant genetic models ($p > 0.05$). Correlation testing was used to

evaluate the influence of the rs10272724 variant on clinical disease parameters. Results showed no significant correlation between carriers of the TC or CC genotypes of rs10272724 and the type of ALL, risk, or presence of relapse.

Interestingly, a significant correlation was found between carriers of the C allele and treatment response profile (Spearman correlation coefficient $\rho = 0.288$; $p = 0.047$) and death ($\rho = 0.301$; $p = 0.024$). Thus, patients with TC or CC genotypes exhibited slower treatment response and a higher death rate compared to patients with the TT genotype.

DISCUSSION

The analysis revealed that the rs4132601 variant of the IKZF1 gene showed no association with susceptibility to ALL or with most clinical parameters. However, carriers of the variant allele demonstrated a higher likelihood of disease relapse compared to individuals with the wild-type genotype. In contrast, the rs10272724 variant was not linked to overall disease risk or relapse, but patients carrying the C allele were more frequently associated with a slower treatment response and worse clinical outcomes, including increased mortality.

ALL is a malignant hematological neoplasm characterized by uncontrolled proliferation of lymphoblasts, resulting from genetic mutations that block cellular differentiation and promote clonal expansion.[9] The expansion of knowledge about the genetic profile of ALL, as highlighted by Chang et al.[10], has contributed to improved prognosis and therapeutic personalization, making the investigation of variants such as those in the IKZF1 gene highly relevant.

The *IKZF1* gene encodes the IKAROS protein, a transcription factor essential for the differentiation and function of hematopoietic cells. IKAROS belongs to a family of related proteins that regulate the development and function of lymphocytes, especially B cells.[11] Accordingly, Vairy et al.[12] demonstrate that alterations in the *IKZF1* gene can result in unfavorable clinical outcomes in ALL due to the impairment of this protein's regulatory function.

In this study, two genetic variants of the *IKZF1* gene were evaluated: rs4132601 and rs10272724. The first, involving a thymine-to-guanine substitution, was associated with an increased risk of recurrence. However, no significant association was observed with the initial risk of the disease, ALL subtype, treatment response, or direct mortality. Relapse, nonetheless, is strongly linked to poorer outcomes, as demonstrated by Souza and Oliveira[13] who reported an 81% mortality rate among relapsed patients.

The literature points to contrasting results regarding rs4132601. In a study of Tunisian children, Mahjoub et al.[14] observed that the G allele was associated with an increased risk of developing ALL. A possible explanation would be the ethnic-geographic difference, since this study involved only patients from North Africa, while the present study was restricted to Brazilian children. This bias was also highlighted by Dai et al.[15], who, in a meta-analysis of 33 studies, found an association of the variant with ALL only in individuals of European ethnicity, warning about the scarcity of data in other populations.

In addition, Wu, Liu, and Wang[7], analyzing 2,281 children with ALL and 2,923 controls, reinforced the association between rs4132601 and ALL in Caucasian and Asian populations. In their analysis, the T allele was linked to a reduced risk of ALL, with TT, TT+TG, and TG genotypes considered protective. However, only one Brazilian study was included in that meta-analysis, which did not identify this association, indicating the need for further national investigations to better understand the variant in the local population.

Recent studies reinforce the clinical relevance of *IKZF1* alterations in both susceptibility and prognosis of pediatric ALL. A meta-analysis conducted by Srinivasan et al.[16], involving 32 studies, demonstrated that gene deletion is associated with poorer clinical outcomes, including lower overall survival and higher risk of recurrence. In this context, Lin et al.[17] analyzed pediatric patients with B-cell precursor ALL in southern China and observed that those with *IKZF1* deletion had a lower initial response, as well as significantly lower rates of disease-free survival and overall survival compared to the wild-type *IKZF1* group.

Consistent with this, Bahari et al.[18], in a study of an Iranian population, that was done on 110 children diagnosed with ALL and 120 healthy children, reported that the rs4132601 (T>G) and rs10272724 (T>C) polymorphisms were significantly associated with increased risk of developing ALL in children. These findings underscore the potential of *IKZF1* as a genetic marker of both risk and prognosis and highlight the importance of ethnically diverse genetic studies.

The second variant investigated, rs10272724, involves the substitution of thymine for cytosine and was associated with increased mortality and slower therapeutic response. Mullighan et al.[19], in a study with 479 children, identified the presence of this variant as a factor related to lower survival and worse response to treatment. Similar data were found by Pastorczak et al.[20], who analysed 398 ALL cases and 731 controls from Poland; and Li et al.[21] in a meta-analysis with 8333 cases and 36036 controls. These studies demonstrated the association between polymorphisms of the *IKZF1* gene and increased risk of ALL, reinforcing the role of these mutations in a worse evolution of the disease.

Moreover, reviews published elsewhere discuss the clinical impact of the rs10272724 variant on treatment response. Studies, such as that of Mullighan et al.[19], indicate that the identification of this variant can guide more targeted or combined therapeutic strategies, with the aim of improving the clinical response and prognosis of affected patients.

Despite the relevant findings, the present study faced methodological limitations. The analysis was carried out with only 59 samples, all from a single geographic region. This restriction compromises the representativeness of the data and the generalization of the results, in addition to possible technical limitations, such as low DNA concentration and absence of reagents, which made amplification difficult in some samples.

In view of this, in future studies it is valid to expand the number of samples and include individuals from different Brazilian regions, enabling a more comprehensive and representative analysis of national genetic diversity. In addition, functional investigations of rs4132601 and rs10272724 *IKZF1* variants can contribute to the understanding of the molecular mechanisms of ALL and support the development of more effective and personalized therapies for affected patients.

CONCLUSION

This study identified relevant associations between genetic variants and the prognosis of acute lymphoblastic leukemia. The presence of the C allele of the rs10272724 variant was significantly associated with a slower response to treatment and a higher probability of death, while the rs4132601 variant of the *IKZF1* gene showed an important relationship with a higher risk of recurrence. On the other hand, neither variants showed an association with susceptibility to the development of ALL or its subtypes. In addition, no correlation was observed between response to treatment in the case of rs4132601, nor between recurrence and rs10272724.

The findings of this study reinforce the promising role of these genetic variants of the *IKZF1* gene as potential prognostic biomarkers in pediatric ALL within the context of onco-hematology. Early identification of these polymorphisms can contribute to the individualization of treatment, enabling targeted interventions in patients at higher risk of complications or recurrence. In addition, this study expands the knowledge about the genetic factors involved in the clinical evolution of ALL and offers new perspectives for medicine related to hematological neoplasms.

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