RESEARCH ARTICLE

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Association of B-Lineage Lymphoblastic Leukaemia Gene Polymorphisms with Poor Prognostic Features

Aigul Bazarbayeva[1]*, Lyazat Manzhuova[2], Gulnara Svyatova[3], Galina Berezina[4], Farida Sarsekbayeva[5], Diana Kamalova[1]

Abstract

Objective: Of this study was to analyse the correlation of gene polymorphisms with clinical and laboratory data of paediatric patients with B-lineage acute lymphoblastic leukaemia with prognostically unfavourable features. **Methods:** A study of 200 children with B-lineage acute lymphoblastic leukaemia (B-ALL) treated with polychemotherapy programmes was conducted. Analysis by sex revealed a statistically insignificant predominance of the group of boys over girls (54%). The mean age of the subjects was 9.3±0.2 years. Genotyping of polymorphic loci was performed using TaqMan method of single site-specific amplification and genotyping. The data of patients with initial prognostically unfavourable clinical and laboratory data in the form of initial leukocytosis from 50 to 99 thousand – 10 (5%), over 100 thousand – 16 (8%), initial CNS lesion in the form of neuroleukaemia – 5 (2.5%), initial splenomegaly more than 6 cm – 12 (6%); patients with poor response to therapy, having absolute number of blast cells in peripheral blood over 1,000 on day 8 of treatment according to the protocol (response to prednisolone prophase) – 13 (7%), with unsatisfactory response to treatment on Day 15 – 40 patients (20%) and on Day 33 – 4 children (2%); also patients who developed relapse of the disease – 17 (9%). **Results:** According to the findings, of all 24 gene variants, 13 variants (54%), namely, *HLA* – rs6457327, *TNF* – rs1800630 and rs2229094, *GATA3* – rs3824662, *TP53* – rs1042522, *CASP9* – rs4661636, *CASP8* – rs10505477, *CEBPE* – rs2239633; *PIP4K2A* – rs7088318, *CASC8* – rs10505477, *IRF4* – rs87207, *CYP1A1* – rs4646903 and rs7089424 of *ARID5B* gene were found to be associated with B-ALL and unfavourable prognostic features. **Conclusions:** The findings of this study revealed significant associations of polymorphic genetic variants, which may serve as a basis for the development of effective methods for predicting the risk of relapse development and the timeliness of intensification of B-ALL treatment. Prompt genetic counselling of children with identified unfavourable genotypes of the investigated gene polymorphisms will make it possible to predict the development of relapse, resistance and/or poor response to B-ALL treatment, and to propose an individual strategy for monitoring children's health in the short and long term.

Keywords: Genetic predisposition- genomic mutations- leukaemia- gene polymorphisms- biomarkers- disease prediction

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Introduction

The current view of the problem of B-lineage acute lymphoblastic leukaemia (B-ALL) reflects the rapid development of science in molecular genetics, pharmacogenomics, pharmacogenetics, and related fields during the last decade [1-3]. Due to the full-genomic methods of research, the heterogeneity of B-ALL at the molecular level has been proved, which indicates the diversity of pathogenetic mechanisms of the tumour process and determines the specific features of the clinical course of the disease, differences in sensitivity or resistance to the applied therapy, and opens opportunities for targeting [3-5].

The detection of molecular genetic abnormalities in patients is crucial for the diagnosis, classification and prognosis of the disease course, as this pathology is markedly diverse [5]. Furthermore, by determining lineage identity, blast cell maturity stage, accurate diagnosis of leukaemia variant and stratification of risk groups, these studies may be useful for theorising the patterns of leukaemogenesis to improve the outcome of concrete pathology therapy [6, 7]. Advances in the treatment of acute leukaemia like modern protocol polychemotherapy,

*[1]Department of Science and Postgraduate Education, Scientific Center of Pediatrics and Pediatric Surgery, Almaty, Republic of Kazakhstan. [2]Scientific Center of Pediatrics and Pediatric Surgery, Almaty, Republic of Kazakhstan. [3]Republican Medical and Genetic Counselling Centre, Scientific Center for Obstetrics, Gynecology and Perinatology, Almaty, Republic of Kazakhstan. [4]Department of Strategic Development and Science, Scientific Center for Obstetrics, Gynecology and Perinatology, Almaty, Republic of Kazakhstan. [5]Department of Biostatistics, Scientific Center of Pediatrics and Pediatric Surgery, Almaty, Republic of Kazakhstan. *For Correspondence: bazarbay.aigul@gmail.com*

radiation therapy, immunotherapy, and haematopoietic stem cell transplantation have brought improved survival in children. However, despite tremendous progress, leukaemia stays a disease in which some patients have an unsatisfactory response to therapy, some relapses, and disease progression [8-10]. Thus, the issue of further investigation of biological characteristics of leukaemic cells and tumour substrate markers is still relevant. The aetiology of the disease in children is complex and genetic predisposition is considered an essential factor in the development of leukaemia.

Studies on the frequency of unfavourable alleles and genotypes of genome-wide association studies (GWAS) of associated polymorphisms are being actively conducted in different countries, which will allow predicting susceptibility to disease, identifying the biological bases of disease susceptibility for the development of new therapeutic strategies and probabilistic outcomes of diseases [11-13]. GWAS are based on genome-wide genotyping to identify polymorphisms [14]. GWAS have advanced the understanding of susceptibility to B-cell precursor acute lymphoblastic leukaemia. However, according to the literature, much of the inherited risk is still unidentified, especially in the Central Asian region [15, 16]. B-ALL-associated genetic polymorphisms are a critical issue. Recently, much evidence has been gathered that genetic polymorphisms underlie individualised medication sensitivity. The identification of associations of polymorphic alleles of genes with a particular disease and its response to therapy helps not only to identify disease mechanisms and investigate its nature, but also to develop therapies that accommodate the biochemical features of each patient.

Based on the analysis of polymorphic allele frequencies, more accurate information about the molecular genetic nature of the disease can be obtained, which may allow for the prevention of these diseases, and in case of disease – individualised selection of therapy. The leading strategy for identifying single nucleotide polymorphisms (SNPs) associated with B-lineage ALL is GWAS, the principles of which have been described in various publications. The first GWAS was to determine susceptibility to all identified risk genes *ARID5B*, *IKZF1*, and *CEBPE* in children of European descent [9-11]. Subsequent GWAS with larger sample sizes and ethnic diversity identified additional significant SNPs in *PIP4K2A*, *GATA3, ARID5B, IKZF1* [17-19], and showed a high genetic contribution to B-cell ALL regardless of the ethnic origin of the patients, the SNPs *CEBPE* and *CDKN2A* were significant mainly in European patients with ALL.

Researchers performing GWAS have advanced the understanding of susceptibility to B-cell precursor acute lymphoblastic leukaemia [20, 21]. It has long been assumed that candidate gene polymorphisms make a genetic contribution to the development of all haematological malignancies, but evidence for significant risk alleles of individual nosologies has only recently emerged. As with many multifactorial diseases, positive associations have been reported for various polymorphisms, which were replicated in subsequent studies [22-24]. Data from the scientific literature suggest the need to analyse the frequencies of unfavourable alleles and genotypes of GWAS associated polymorphisms in each individual ethnic population, which will allow predicting the population frequency, effectiveness of therapy and probabilistic outcomes of B-ALL.

Materials and Methods

The study was approved by the local ethical commission of Asfendiyarov Kazakh National Medical University (Almaty, Republic of Kazakhstan), application No. 1189 dated 28 September 2021. At the initial stage of the study, inclusion and exclusion criteria were developed and validated to select individuals with the nosologies under study.

Inclusion criteria

- ethnicity – Kazakhs for at least three generations;
- age – children from 0 to 18 years old;
- active disease or a history of B-lineage acute lymphoblastic leukaemia, with confirmation of the disease in medical records;
- signed voluntary informed consent of the legal representative to take part in the project.

Questionnaire forms were developed and validated for the study. Blood sampling was performed in 200 children with B-lineage acute lymphoblastic leukaemia. Written informed consent was obtained from the parents or legal representatives of all children included in this study. Verification of the patients' diagnosis was based on immunophenotypic and morphological examination of blast cells in peripheral blood and bone marrow samples according to the FAB classification criteria. Cytogenetic study of bone marrow cells by direct karyotyping and FISH methods was also performed.

Venous blood was collected under sterile conditions into K2EDTA containers. DNA was extracted from whole blood samples by the saline method using proteinase K and DNA-Sorb-B kit (AmpliSens). DNA concentration was measured on a Nano Drop Lite Spectrophotometer (USA) with DNA purity rate ≥1.6. Molecular genetic studies were performed by real-time polymerase chain reaction on a Step One Plus device (Applied Biosystems, USA). Genotyping of polymorphic loci was performed using TaqMan method of single site-specific amplification and genotyping.

The results of DNA genotyping of children's blood samples were provided by the Republican Medical Genetic Consultation at the Scientific Centre for Obstetrics, Gynaecology, and Perinatology. Statistical tests of significance and χ^2 analysis were performed using PLINK software [25]. Differences in the specific weight of alleles and genotypes were assessed using the χ^2 criterion with odds ratio (OR, 95% CI). The results of the analysis in all cases are considered statistically significant at the level $p<0.05$.

Results

In the distribution of 200 patients with B-lineage leukaemia by age: children aged 1-5 years made up 24.5%

(49 children), 6-10 years – 41% (82 children), the age group over 11 years old consisted of 69 children – 34.5%. Analysis by sex revealed a statistically insignificant predominance of the group of boys over girls (54%). The mean age of the sample at the time of oncology diagnosis was 9.3±0.2 years. Only two children had low birth weight (1.8 kg and 2.2 kg) – 1%, over 4 kg – 6% (12); the remaining 93% had normal birth weight. The patients were distributed by blood type as follows: 0 (I) – 26%, A (II) – 37%, B (III) – 26%, AB (IV) – 11%. In the study group by cytomorphological form according to FAB classification, children with L2 (59.9%) and L1 (37.1%) variants prevailed, L3 type was only 3%. According to the results of cytogenetic study of bone marrow blast cells, chromosomal abnormalities were detected in 37.4% of patients. It is a well-known fact that one of the important factors in improving the effectiveness of treatment in ALL has been the determination of the risks of treatment failure and relapse, and the division of all patients with ALL into groups with prognostic risk factors depending on the initial characteristics of the tumour and the patients' response to the treatment [26, 27].

To divide into risk groups, initial biological "risk criteria" characterising the patient are used, such as age, "tumour mass" indices – the initial number of leukocytes in peripheral blood; the level of enlargement of the liver, spleen, lymph nodes, the presence of extramedullary lesions such as central nervous system (CNS), testicles; according to them the prognosis and treatment options are determined. In addition, poor prognostic signs are as follows: ≥1,000 blasts/μL of blood after 1 week of treatment; 5% or more blasts in bone marrow on Day 15 of treatment, absence of complete remission on Day 33 of therapy – over 5% blasts in the punctate, provided there is sufficient bone marrow cell count and regeneration of myelopoiesis, 5 nucleus-containing cells/μL in the liquor and presence of blast cells on cytospin, presence of leukaemic infiltrates, absence of mediastinal tumour reduction ≥30% of the initial size [28, 29]. For instance, one of the following criteria is sufficient to assign a patient to the high-risk group (HRG): >1,000/μL blast count on Day 8 after one week of prednisolone therapy or no remission on Day 33 of treatment.

At initial admission, patients were distributed according to the initial leukocyte level as one of the prognostic features: leukopenia up to 4×10^9/l was present in 27% (54) of children, leukocytosis from 20 to 50 thousand – 19% (38), hyperleukocytosis from 50 to 100 thousand – 5% of children (10), and over 100 thousand – 8% (16). Thus, leucocytosis over 20 thousand was found in 32% of patients. Analyses were also performed on the initial clinical findings detected at the initial diagnosis of the disease. Thus, fever was noted in 63.7% of patients, skin haemorrhages were detected in 45% of children, haemorrhages on mucous membranes – in 20%, hyperplastic syndrome in the form of gingivitis – 2.8%, lymphoadenopathy – 45.9%, hepatomegaly over 6 cm – 65%, splenomegaly over 6 cm – 46.4%, leukaemia – 1%. Septic foci on primary hospitalisation were 3.4%, of which pneumonia, otitis media, angina, and enteropathy were the main ones.

To search for associations of carrying significant polymorphisms of genes associated with the risk of B-ALL in children of Kazakh population, genetic characteristics of SNP polymorphisms of genes were selected according to GWAS analyses; therefore, when carrying out statistical processing on the name of genes and alleles, genetic characteristics of polymorphisms of genes were used, presented by geneticists of the Scientific Centre of Obstetrics, Gynaecology and Perinatology, which are presented in Table 1.

Earlier in this study, we identified significant associations with the risk of childhood B-ALL development, and showed that carriage of minor allele A of the protective rs1801157 polymorphism of the CXCL12 gene reduces the risk of B-ALL development in the Kazakh population by 40% (OR=2.32, 95% CI: 1.555-3.466), which was confirmed by the analysis of all existing genetic models – allelic, trend, genotypic, dominant, and recessive ($p<0.05$). The findings of this study revealed significant associations of polymorphic genetic variants, which may underlie the development of effective methods for predicting the risk of development, early diagnosis, and prompt treatment of B-ALL. Genetic variations in genes for molecules that are important for the immune response associated with disease progression may prove to be essential factors in amplifying intrinsic biological differences, thereby influencing clinically different outcomes. In this regard, the study considered the data of patients with initial prognostically unfavourable clinical and laboratory data in the form of initial leukocytosis from 50 to 99 thousand – 10 (5%), over 100 thousand – 16 (8%), initial CNS lesion in the form of neuroleukaemia – 5 (2.5%), initial splenomegaly over 6 cm – 12 (6%); patients with poor response to therapy, having absolute number of blasts in blood over 1,000 on Day 8 of treatment according to the protocol (response to prednisolone prophase) – 13 (7%), with unsatisfactory response to treatment on Day 15 – 40 patients (20%) and Day 33 – 4 children (2%); also patients who developed relapse of the disease – 17 (9%). The total number of such patients turned out to be 87. Thus, patients with prognostically unfavourable clinical and laboratory data were selected from 200 children of the main group treated under polychemotherapy programmes for B-lineage leukaemia.

The prevalence of alleles and genotypes of various genes associated with initially unfavourable clinical findings, relapse development and poor response to therapy were then analysed. GWAS associated genes in children with B-ALL were categorised according to their functional characteristics into 6 groups: HLA and immune response systems, B-cell transcription and differentiation genes, haematopoietic cell differentiation genes, apoptosis genes, oncogenes, oncosuppressors, and genes of phase I of the xenobiotic detoxification system. A comparative analysis of allele and genotype frequencies of 24 polymorphic variants of 19 genes in 200 children with B-ALL was performed. No statistically significant results were obtained for patients with marked hepatomegaly, splenomegaly. In the group with hyperleukocytosis over $50*10^9$/l, the number of patients turned out to be 26 (13%), of which 62% (16 children) had hyperleukocytosis over

Table 1. Genetic Characteristics of SNP Polymorphisms of Genes, GWAS associated with B-ALL

No.	Gene name	Chr	rs	A1	A2	Position
	HLA system and immune response genes					
1	*HLA* (Human Leukocyte Antigens (class II))	6	rs2647012	G	A	32696681
2	*HLA* (Human Leukocyte Antigens (class I))	6	rs6457327	C	A	31106253
3	*IL10* (Interleukin 10)	1	rs1800896	G	A	206773552
4	*IL1RN* (Interleukin 1 Receptor Antagonist)	2	rs4251961	T	C	113116890
5	*TNF* (Tumour Necrosis Factor)	6	rs1800630	C	A	31574699
6	*TNF* (Tumour Necrosis Factor)	6	rs2229094	T	C	31572779
7	*CXCL12* (C-X-C Motif Chemokine Ligand 12)	10	rs1801157	G	A	44372809
8	*GATA3* (GATA Binding Protein 3)	10	rs3824662	A	C	8062245
9	*TLR1* (Toll Like Receptor 1)	4	rs4833103	A	C	38813881
	B-cell transcription and differentiation genes					
10	*IRF4* (Interferon Regulatory Factor 4)	6	rs872071	A	G	411064
11	*ARID5B* (AT-Rich Interaction Domain 5B)	10	rs7089424	T	G	61992400
12	*ARID5B* (AT-Rich Interaction Domain 5B)	10	rs10740055	C	A	61958720
13	*IKZF1* (IKAROS Family Zinc Finger 1)	7	rs4132601	T	G	50402906
	Genes of haematopoietic cell differentiation					
14	*PIP4K2A* (Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Alpha	10	rs7088318	A	C	22564019
	Apoptosis genes					
15	*CEBPE* (CCAAT Enhancer Binding Protein Epsilon)	14	rs2239633	G	A	23119848
16	*CASP8* (Caspase 8)	2	rs6736233	C	G	201254251
17	*CASP9 (*Caspase 9)	1	rs4661636	C	T	15496566
18	*CASP9* (Caspase 9)	1	rs1052576	A	G	15506048
	Oncogenes					
19	*CASC8* (Cancer Susceptibility 8)	8	rs10505477	A	G	127395198
Oncosuppressors						
20	*CDKN2A* (Cyclin Dependent Kinase Inhibitor 2A)	9	rs3731249	C	T	21970917
21	*TR53* (Tumour Protein p53)	17	rs1042522	C	G	7676154
	Phase I genes of the xenobiotic detoxification system					
22	*CBR3* (Carbonyl Reductase 3)	21	rs1056892	G	A	36146408
23	*CYP1A1* (Cytochrome P450 Family 1 Subfamily A Member 1)	15	rs1048943	T	C	74720644
24	*CYP1A1* (Cytochrome P450 Family 1 Subfamily A Member 1)	15	rs4646903	A	G	74719300

Note: *, were not included in the IlluminaOmni 2.5-8 Chip SNP polymorphisms panel; Chr, chromosome number; rs, polymorphism identifier (SNP Identifier); A1, wild-type allele (normal), and A2, minor (unfavourable) allele. Source: compiled by the authors of this study.

$100*10^9$/l. When comparing the group of patients with hyperleukocytosis over $50*10^9$/l and normal leukocytes, statistically significant data on the gene – HLA – rs6457327, ($p<0.05$) were revealed (Table 2). This table also includes data for patients with initial neuroleukaemia.

Analysis of replicative genotyping polymorphism results revealed a significantly higher proportion of gene polymorphism rs6457327 *HLA*, rs2229094 *TNF*, rs3824662 *GATA3*, rs872071 *IRF4*, rs7089424 *ARID5B*, rs2239633 *CEBPE*, rs4661636 *CASP9*, rs1042522 *TR53*, rs10505477 *CASC8* in the group of patients with neuroleukaemia at initial diagnosis of underlying disease compared with patients without initial neuroleukaemia ($p <0.05$). Therewith, the rs6457327 polymorphism of the *HLA* gene of the HLA system and immune response was detected significantly often in both patients with hyperleukocytosis and patients with initial neuroleukaemia. Comparative analysis of gene polymorphisms in groups of patients with adverse clinical and laboratory data by Plinc programme revealed highly significant differences in higher carriage of minor unfavourable alleles in the group with hyperleukocytosis for rs1800630 polymorphism in *TNF* gene ($p<0.0001$; OR1=3.943) (Table 3). The rs4661636 and rs1052576 polymorphisms of the *CASP9* gene were also identified as important and possible markers of hyperleukocytosis and accordingly unfavourable prognostic sign.

In many randomised clinical trials, early response to therapy is considered one of the key prognostic factors. The quality of the early response is assessed by bone marrow and peripheral blood picture at strictly time points. “Early responders” – patients with tumours that are highly sensitised to treatment can subsequently receive less intensive therapy without the risk of reducing their survival. Therefore, considering that assessment of response to ongoing treatment on specific days of the

Table 2. Gene Polymorphisms of Patients with B-ALL associated with Hyperleukocytosis over 50*10^9/l and Neuroleukaemia

No.	Gene name		Rs	Group with hyperleukocytosis and with normal white blood cells	Group with and without neuroleukaemia	P	
						With hyperleukocytosis	With neuroleukaemia
1	*HLA*	Human Leukocyte Antigens	rs2647012	13,2,1/11,13,2	43,25,8/1,4,0	0.24282775	0.069721
2	*HLA***		rs6457327	4,5,7/6,11,9	18,25,33/0,2,3	0.031707*	0.010473*
3	*IL10*	Interleukin 10	rs1800896	8,2,6/12,1,13	41,4,31/3,0,2	0.144665	0.072723
4	*IL1RN*	Interleukin 1 Receptor Antagonist	rs4251961	2,3,11/3,13,10	7,24,45/1,2,2	0.214169	0.0789
5	*TNF*	Tumour Necrosis Factor	rs1800630	6,7,3/16,8,2	34,21,21/4,1,0	0.214169	0.008789
6	*TNF**		rs2229094	1,10,5/1,13,12	10,31,35/0,3,2	0.120951	0.038572*
7	*CXCL12*	C-X-C Motif Chemokine Ligand 12	rs1801157	9,7,0/16,8,2	44,28,4/4,1,0	0.107163	0.076751
8	*GATA3**	GATA Binding Protein 3	rs3824662	13,1,2/7,15,4	28,40,8/2,3,0	0.312088	0.053697*
9	*TLR1*	Toll Like Receptor 1	rs4833103	14,2,0/16,6,4	54,17,5/4,0,1	0.068875	0.113009
10	*IRF4*	Interferon Regulatory Factor 4	rs872071	3,7,6/5,15,6	10,42,24/0,3,2	0.14993	0.053274*
11	*ARID5B**	AT-Rich Interaction Domain 5B	rs7089424	2,8,6/4,14,8	15,41,20/0,3,2	0.064806	0.040893*
12	*ARID5B*		rs10740055	3,9,4/5,12.9	14,46,16/0,2,3	0.181211643	0.072723
13	*IKZF1*	IKAROS Family Zinc Finger 1	rs4132601	7,9,0/15,7,4	40,35,1/3,1,1	0.18503	0.092116
14	*PIP4K2A*	Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Alpha	rs7088318	3,9,4/11,13,2	25,42,9/2,2,1	0.18503	0.062328
15	*CEBPE**	CCAAT Enhancer Binding Protein Epsilon	rs2239633	8,7,1/14,11,1	32,37,7/1,3,1	0.09968	0.058281*
16	*CASP8*	Caspase 8	rs6736233	16,0,0/14,1,1	76,0,0/4,1,0	0.5	0.215362
17	*CASP9**	Caspase 9	rs4661636	9,5,2/8,6,12	29,26,21/1,1,3	0.214169025	0.004871*
18	*CASP9*	Caspase 9	rs1052576	0,12,4/20,6,0	0,76,0/0,5,0	0.364219	0.211325
19	*CASC8**	Cancer Susceptibility 8	rs10505477	5,5,6/5,14,7	10,40,26/0,2,3	0.181211643	0.049839*
20	*CDKN2A*	Cyclin Dependent Kinase Inhibitor 2A	rs3731249	14,2,0/25,1,0	70,6,0/5,0,0	0.238646	0.186013
21	*TP53**	Tumour Protein p53	rs1042522	1,12,3/3,12,11	10,36,30/0,4,1	0.14993	0.037633*
22	*CBR3*	Carbonyl Reductase 3	rs1056892	7,9,0/8,14,4	34,41,1/0,5,0	0.064565	0.086173
23	*CYP1A1*	Cytochrome P450 Family 1 Subfamily A Member 1	rs1048943	3,3,10/5,3,18	8,19,49/0,0,5	0.14993	0.078187
24	*CYP1A1*		rs4646903	13,2,1/11,13,2	43,25,8/1,4,0	0.242828	0.069721

Source: compiled by the authors of this study.

protocol is a vital prognostic factor and, in some cases, requires stratification and intensification of therapy, genotype frequencies were analysed in children with B-ALL who responded and did not respond on Days 8, 15, and 33 of the protocol therapy (Table 4).

A poor prognostic sign is the detection of over 1,000 blasts/μL on Day 8 of prednisolone treatment, i.e., having an absolute blast count >1,000 in peripheral blood on Day 8 of glucocorticosteroid treatment and in whom the absolute blast cell count in peripheral blood was <1,000. A good response on Days 15 and 33 of therapy is considered to be less than 5% blast cells in the bone marrow. A poor or slow response is the presence of blast cells greater than 5%. rs3824662 of *GATA3*, rs4661636 of *CASP9* gene, and rs1042522 of *TR53* gene were found to be statistically significant genes of poor response to therapy on Days 8, 15, and 33 of treatment ($p<0.05$). The data in Table 4 show that for patients who did not respond to treatment at cytoreductive prophase (Day 8) and Day 33 of therapy, rs6457327 of *HLA*, rs1800630 of *TNF* gene, rs872071 of *IRF4*, rs7089424 of ARID5B gene, rs2239633 of *CEBPE*, and rs10505477 of *CASC8* gene were statistically

Table 3. Comparative Analysis of Gene Polymorphisms in Groups of Patients with Unfavourable Clinical and Laboratory Data according to the Plinc Programme

Gene	CHR	SNP	A1	A2	Group	MAF	χ^2	P	OR
CASP8	2	rs6736233	C	G	Relapses	0.1667	11.62	0.0006518	5.646
					No relapses	0.03421			
CASP9	1	rs4661636	T	C	Hyperleukocytosis	0.5769	9.485	0.002072	2.48
					No hyperleukocytosis	0.3547			
		rs1052576	G	A	Hyperleukocytosis	0.5962	6.363	0.01166	2.119
					No hyperleukocytosis	0.4106			
TNF	6	rs1800630	A	C	Hyperleukocytosis	0.7692	17.58	2.752e-005	3.943
					No hyperleukocytosis	0.4581			

Note: CHR, chromosome; A1, common allele; A2, minor allele; MAF, minor allele frequency; χ^2, Pearson's correlation coefficient; OR, odds ratio; p, observed significant difference, ($p<0.05$); Source: compiled by the authors of this study.

Table 4. Gene Polymorphisms of Patients with PrognosticallyUnfavourable Data. Correlation with response to treatment on Days 8, 15, and 33 of therapy

No.	Gene name		Rs	Group – responders and non-responders			P		
				Day 8	Day 15	Day 33	Day 8	Day 15	Day 33
1	*HLA*	Human Leukocyte Antigens	rs2647012	42,21,7/4,9,0	43,25,8/16,22,2	43,25,8/2,2,0	0.093313	0.126456	0.06414
2	*HLA***		rs6457327	18,22,30/4,4,5	18,25,33/12,16,12	18,25,33/0,1,3	0.013726*	0.060059	0.010102*
3	*IL10*	Interleukin 10	rs1800896	39,4,27/5,1,7	41,4,31/17,3,20	41,4,31/2,0,2	0.084063	0.106645	0.073778
4	*IL1RN**	Interleukin 1 Receptor Antagonist	rs4251961	7,22,41/1,2,10	7,24,45/7,15,18	7,24,45/1,0,3	0.059764*	0.134852	0.073599
5	*TNF***	Tumour Necrosis Factor	rs1800630	34,21,15/3,7,3	34,21,21/12,19,9	34,21,21/1,2,1	0.04381*	0.086616	0.016768*
6	*TNF**		rs2229094	10,30,30/1,3,9	10,31,35/1,21,18	10,31,35/0,3,1	0.034783*	0.020639	0.039821
7	*CXCL12*	C-X-C Motif Chemokine Ligand 12	rs1801157	40,26,4/9,3,1	44,28,4/27,11,2	44,28,4/2,2,0	0.075005	0.069225	0.080601
8	*GATA3****	GATA Binding Protein 3	rs3824662	27,35,8/2,11,0	28,40,8/13,23,4	28,40,8/0,4,0	0.037364*	0.048587*	0.051121*
9	*TLR1*	Toll Like Receptor 1	rs4833103	52,16,2/7,4,2	54,17,5/20,7,13	54,17,5/4,0,0	0.146691	0.213961	0.108186
10	*IRF4***	Interferon Regulatory Factor 4	rs872071	9,38,23/1,8,4	10,42,24/5,21,14	10,42,24/1,2,1	0.047961*	0.063179	0.057874*
11	*ARID5B***	AT-Rich Interaction Domain 5B	rs7089424	14,37,19/1,4,8	15,41,20/9,15,16	14,37,20/0,3,1	0.0569*	0.114836	0.038689*
12	*ARID5B*		rs10740055	13,43,14/1,6,6	14,46,16/8,18,14	14,46,16/1,2,1	0.085649	0.137967	0.06941
13	*IKZF1*	IKAROS Family Zinc Finger 1	rs4132601	38,32,0/8,4,1	40,35,1/23,13,4	40,35,1/3,0,1	0.099148	0.128372	0.091909
14	*PIP4K2A**	Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Alpha	rs7088318	25,37,8/7,6,0	25,42,9/20,15,5	25,42,9/2,1,1	0.052	0.125487	0.06414
15	*CEBPE***	CCAAT Enhancer Binding Protein Epsilon	rs2239633	29,34,7/5,8,0	32,37,7/15,18,7	35,37,7/1,2,1	0.04381*	0.09238	0.05907*
16	*CASP8*	Caspase 8	rs6736233	71,5,0/12,1,0	76,0,0/37,2,1	76,0,0/3,1,0	0.19246	0.233968	0.215306
17	*CASP9****	Caspase 9	rs4661636	26,23,21/6,3,4	29,26,21/16,10,14	29,26,21/2,0,2	0.001379*	0.022666*	0.005409*
18	*CASP9*	Caspase 9	rs1052576	0,70,0/2,10,1	0,76,0/3,33,4	0,76,0/0,2,2	0.225949	0.259936	0.219229
19	*CASC8**	Cancer Susceptibility 8	rs10505477	11,35,24/3,9,1	10,40,26/6,17,17	10,40,26/0,1,3	0.038094*	0.08464	0.051748*
20	*CDKN2A*	Cyclin Dependent Kinase Inhibitor 2A	rs3731249	65,5,0/12,1,0	70,6,0/38,2,0	70,6,0/4,0,0	0.190418	0.177748	0.186375
21	*TP53****	Tumour Protein p53	rs1042522	7,35,28/1,6,6	10,36,30/4,16,20	10,36,30/0,2,2	0.053979*	0.051121*	0.039821*
22	*CBR3*	Carbonyl Reductase 3	rs1056892	34,36,0/3,7,3	34,41,1/15,19,6	34,41,1/1,3,0	0.113344	0.147668	0.087106
23	*CYP1A1*	Cytochrome P450 Family 1	rs1048943	10,10,50/2,2,9	8,19,49/3,10,27	8,19,49/0,2,2	0.11313	0.072156	0.089368
24	*CYP1A1*	Subfamily A Member 1	rs4646903	40,23,7/4,9,0	43,25,8/16,22,2	28,40,8/2,2,0	0.080837	0.126456	0.06414

Source: compiled by the authors of this study.

significant gene polymorphisms. It is known that despite the success of first-line therapy, relapses are difficult to treat [30]. The prognosis of recurrence is crucial because the development of relapse reflects ineffective treatment and is often fatal. In this study to date, of the 200 patients with B-ALL examined, 17 (9%) developed a relapse. Gene polymorphisms were compared between patients who developed relapse and patients who were alive at the time of the study and in remission. We have identified gene polymorphisms associated with an increased risk of relapses in B-lineage ALL and, consequently, poor survival, suggesting the need for treatment intensification (Table 5).

Thus, the studied genotypes: from HLA system and immune response genes – rs1800630 and rs2229094 of *TNF* gene, rs6457327 *HLA*, from oncosuppressors – rs1042522 *TP53*, rs4646903 *CYP1A1*, from apoptosis genes – rs2239633 *CEBPE*, rs6736233 *CASP8*, from oncogenes – rs10505477 *CASC8*, form haematopoietic cell differentiation genes – rs7088318 *PIP4K2A* may be markers of B-ALL relapse in children. Thus, genotypes correlating with prognostically unfavourable clinical data – hyperleukocytosis, neuroleukaemia, high risk group for relapses and poor response to treatment – have been identified. Thus, 13 variants of gene polymorphisms are HLA system and immune response genes: *HLA* – rs6457327, *TNF* – rs1800630 and rs2229094, *GATA3* – rs3824662; oncosuppressor *TR53* – rs1042522, rs4646903 *CYP1A*, apoptosis genes: *CASP9* – rs4661636, *CASP8* – rs10505477, *CEBPE* – rs2239633; haematopoietic cell differentiation gene – *PIP4K2A* – rs7088318, B-cell transcription and differentiation gene rs872071 – *IRF4*, rs7089424 of *ARID5B* gene and oncogene *CASC8* – rs10505477 were identified as the most significant and correlated with prognostically unfavourable factors of patients with B-lineage leukaemia (Table 6).

Four polymorphisms of genes – rs6457327 – *HLA*, *TR53*, rs2229094 – *TNF*, rs4661636 – *CASP9*– were identified as the most important in terms of significance, which were found in patients with five unfavourable prognostic factors such as neuroleukaemia, hyperleukocytosis, relapse, and poor response to therapy in

Table 5. Gene Polymorphisms of B-ALL Patients associated with Relapse Development

No.	Gene name		Chromosome	Rs	Position	Group – relapses, no relapse	P
		HLA system and immune response genes					
1	*HLA*	Human Leukocyte Antigens	6	rs2647012	32696681	43,25,8/6,7,4	0.088007
2	*HLA**		6	rs6457327	31106253	18,23,32/4,9,4	0.028595*
3	*IL10*	Interleukin 10	1	rs1800896	206773552	41,3,29/4,4,9	0.115753
4	*IL1RN*	Interleukin 1 Receptor Antagonist	2	rs4251961	113116890	7,23,43/3,7,7	0.091752
5	*TNF**	Tumour Necrosis Factor	6	rs1800630	31574699	33,20,20/7,5,5	0.018243*
6	*TNF**		6	rs2229094	31572779	10,29,34/1,8,8	0.032944*
7	*CXCL12*	C-X-C Motif Chemokine Ligand 12	10	rs1801157	44372809	41,28,4/6,10,1	0.090444
8	*GATA3*	GATA Binding Protein 3	10	rs3824662	8062245	27,38,8/5,9,3	0.060022
9	*TLR1*	Toll Like Receptor 1	4	rs4833103	38813881	51,17,5/14,1,2	0.100082
		B-cell transcription and differentiation genes					
10	*IRF4*	Interferon Regulatory Factor 4	6	rs872071	411064	9,40,24/5,10,2	0.067951
11	*ARID5B*	AT-Rich Interaction Domain 5B	10	rs7089424	61992400	14,39,20/4,6,7	0.06132
12	*ARID5B*		10	rs10740055	61958720	12,45,16/2,6,5	0.085011
13	*IKZF1*	IKAROS Family Zinc Finger 1	7	rs4132601	50402906	38,34,1/12,5,0	0.085083
		Genes of haematopoietic cell differentiation					
14	*PIP4K2A**	Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Alpha	10	rs7088318	22564019	26,38,9/5,12,0	0.032944*
		Apoptosis genes					
15	*CEBPE**	CCAAT Enhancer Binding Protein Epsilon	14	rs2239633	23119848	31,36,6/6,10,1	0.056059*
16	*CASP8*	Caspase 8	2	rs6736233	201254251	69,4,0/9,7,1	0.230943
17	*CASP9*	Caspase 9	1	rs4661636	15496566	27,25,21/7,3,7	0.00809
18	*CASP9*	Caspase 9	1	rs1052576	15506048	0,76,0/0,16,1	0.216176
		Oncogenes					
19	*CASC8**	Cancer Susceptibility 8	8	rs10505477	127395198	11,37,25/1,10,6	0.031377*
		Oncosuppressors					
20	*CDKN2A*	Cyclin Dependent Kinase Inhibitor 2A	9	rs3731249	21970917	67,6,0/16,1,0	0.184536
21	*TP53**	Tumour Protein p53	17	rs1042522	7676154	9,35,29/1,7,9	0.042396*
22	*CBR3*	Carbonyl Reductase 3	21	rs1056892	36146408	33,39,1/8,8,1	0.094075
23	*CYP1A1*	Cytochrome P450 Family 1	15	rs1048943	74720644	8,18,47/4,1,12	0.086713
24	*CYP1A1**	Subfamily A Member 1	15	rs4646903	74719300	41,24,8/10,7,0	0.054036*

Source: compiled by the authors of this study

the decreased time frame. Next, the GATA-binding protein 3 (*GATA3*) gene rs3824662, the apoptosis gene *CEBPE* – rs2239633, and the oncogene CASC8 were isolated. The B-cell transcription and differentiation gene rs872071 *IRF4*, rs7089424 of *ARID5B* gene, and rs1800630 of *TNF* gene were next in significance. Recent studies also support the association of several polymorphisms of the genes described above with acute B-lymphocyte leukaemia. Moreover, the expression of other genes is associated with single nucleotide substitutions, which in the long term can also be used as prognostic markers of ALL.

Discussion

The results of this study highlight the significant impact of genetic polymorphisms on the clinical outcomes of paediatric patients with B-lineage acute lymphoblastic leukaemia (B-ALL). Our analysis identified 13 gene variants associated with unfavourable prognostic features, indicating the potential for these polymorphisms to serve as markers for predicting disease progression, treatment response, and the risk of relapse.

I. Demianenko and A. Bakhmach [31] focused on the level of lipoprotein lipase (*LPL*) gene expression depending on the nature of mutations in the TP53 sequence. The product of LPL is an enzyme synthesised in muscle and adipose tissue that hydrolyses fats and is responsible for the uptake of lipoproteins by cells. Substitution at G at the rs1042522 and rs1642785 *TP53* loci correlated with low LPL expression levels. Considering that such SNPs in *TP53* are markers of relapses, unfavourable ALL course and poor response to therapy, it is likely that low lipoprotein lipase levels could be a prognostic negative indicator.

One of the unfavourable effects of tumour necrosis factor-alpha is to encourage the development of lymphomas through the activation of biochemical cascades that promote anti-apoptotic and pro-inflammatory

Table 6. Significant Gene Polymorphisms of B-ALL Patients with Prognostically Unfavourable Data

	Criterion	P	Gene name	Chr	rs	A1	A2	Position
1	Response on Day 8	0.013726	*HLA* (Human Leukocyte Antigens (class I))	6	rs6457327	C	A	31106253
	Response on Day 33	0.010102						
	relapse	0.028595						
	hyperleukocytosis	0.031707						
	neuroleukaemia	0.010473						
2	Response on Day 8	0.053979	*TR53* (Tumour Protein p53)	17	rs1042522	C	G	7676154
	Response on Day 15	0.051121						
	Response on Day 33	0.039821						
	relapse	0.042396						
	neuroleukaemia	0.037633						
3	Response on Day 8	0.020639	*TNF* (Tumour Necrosis Factor)	6	rs2229094	T	C	31572779
	Response on Day 15	0.020639						
	Response on Day 33	0.039821						
	relapse	0.032944						
	neuroleukaemia	0.038572						
4	Response on Day 8	0.001379	*CASP9* (Caspase 9)	1	rs4661636	C	T	15496566
	Response on Day 15	0.022666						
	Response on Day 33	0.005409						
	neuroleukaemia	0.004871						
	hyperleukocytosis	0.002072						
5	Response on Day 8	0.04381	*CEBPE* (CCAAT Enhancer Binding Protein Epsilon)	14	rs2239633	G	A	23119848
	Response on Day 33	0.051121						
	relapse	0.051121						
	neuroleukaemia	0.058281						
6	Response on Day 8	0.037364	*GATA3* (GATA Binding Protein 3)	10	rs3824662	A	C	8062245
	Response on Day 15	0.048587						
	Response on Day 33	0.051121						
	neuroleukaemia	0.053697						
7	Response on Day 8	0.038094	*CASC8* (Cancer Susceptibility 8)	8	rs10505477	A	G	127395198
	Response on Day 33	0.051748						
	relapse	0.031377						
	neuroleukaemia	0.049839						
8	Response on Day 8	0.047961	*IRF4* (Interferon Regulatory Factor 4)	6	rs872071	A	G	411064
	Response on Day 33	0.057874						
	neuroleukaemia	0.053274						
9	Response on Day 8	0.0569	*ARID5B* (AT-Rich Interaction Domain 5B)	10	rs7089424	T	G	61992400
	Response on Day 33	0.038689						
	neuroleukaemia	0.040893						
10	Response on Day 8	0.04381	*TNF* (Tumour Necrosis Factor)	6	rs1800630	C	A	31574699
	relapse	0.018243						
	hyperleukocytosis	2.752e-005						
11	Response on Day 8	0.052	*PIP4K2A* (Phosphatidylinositol-5-Phosphate 4-Kinase Type 2 Alpha	10	rs7088318	A	C	22564019
	relapse	0.032944						
12	relapse	0.0006518	*CASP8* (Caspase 8)		rs6736233	A	G	201254251
13	relapse	0.054036	*CYP1A1** (Cytochrome P450)	15	rs4646903	A	G	74719300

Note: Chr, chromosome; A1, common allele; A2, minor allele; p, observed significance of differences; only significant differences ($p<0.05$) were selected.

processes. The ClinVar database indicates that the C to A substitution at the rs1800630 locus is a protective factor in the development of Alzheimer's disease. However, as demonstrated in this paper, rs1800630 is a marker of hyperleukocytosis, relapse, and treatment unresponsiveness in ALL. In particular, Abdalhabib et al. [32] examined a mutation of the TNF promoter region rs1800629, where A is replaced by G at position (-308). The study revealed a statistically significant higher frequency of the GA genotype in 71% of patients compared to healthy individuals. This finding indicates a potential correlation between the rs1800629 mutation and an increased risk of developing the B-lineage form of ALL, while no such association was observed in T-lineage leukaemia.

B.W. MacNabb and J. Kline [33] also highlighted those mutations in other TNF gene loci are associated with acute lymphoblastic leukaemia (ALL), reinforcing the significance of genetic variations in this context. Furthermore, W. Boukouaci [34] has identified the rs1800630 locus as a key marker for assessing hyperleukocytosis and treatment resistance in ALL patients.

Furthermore, the literature indicates that one of the polymorphisms of genes associated with B-ALL is rs4661636 in the Caspase 9 gene. Previous studies by W.J. Liu [35] have demonstrated a correlation between this gene and other forms of cancer, including oesophageal adenocarcinoma and non-Hodgkin's lymphoma. These findings highlight the critical prognostic markers of B-ALL related to mutations in various loci of histocompatibility complex 2, Caspase 9, tumour necrosis factor, and p53 protective protein genes [36].

The study has several limitations. The sample size is adequate for preliminary findings, but a larger cohort would enhance the robustness of the conclusions. The research's focus on a single ethnic group, Kazakh children, may limit its applicability to broader populations. Future research should include diverse ethnic groups to better understand the genetic landscape of B-ALL. The retrospective design may introduce biases in data collection and analysis. The study primarily examines polymorphisms at a genetic level, without delving deeply into the functional mechanisms influencing disease progression and treatment outcomes.

The study highlights the importance of genetic screening in pediatric B-lineage acute lymphoblastic leukemia (B-ALL) patients, highlighting the need for routine genotyping for specific gene polymorphisms. Genetic counseling should be provided to families, especially those with unfavorable genotypes, to discuss potential implications for treatment strategies and prognosis. The study emphasizes the need for stratifying patients based on their genetic profiles alongside traditional clinical indicators, developing risk-adapted treatment protocols, and considering more aggressive treatment strategies for high-risk patients. Multicenter studies with larger sample sizes are essential for validation, and future research should investigate the functional impacts of identified polymorphisms on gene expression and disease progression. Collaborative research across different ethnic populations will enhance the understanding of genetic predispositions to B-ALL and facilitate the development of more effective targeted therapies. Healthcare providers should be educated on the implications of genetic findings in B-ALL to integrate this knowledge into clinical decision-making.

In conclusion, the principal goal of modern acute leukaemia therapy is to achieve a higher survival rate and considerably prolong remission. In the context of this issue, it is of paramount importance to determine the prognosis of the course of the disease at the time of diagnosis, since rational treatment at the early stages of leukaemia can considerably increase survival and improve the quality of life of patients. In this regard, it is most relevant to investigate and identify prognostic factors.

The findings show that of all 24 gene variants, 13 variants (54%) were identified as the most unfavourable: *HLA* – rs6457327, *TNF* – rs1800630 and rs2229094, *GATA3* – rs3824662, *TP53* – rs1042522, *CASP9* – rs4661636, *CASP8* – rs10505477, *CEBPE* – rs2239633; PIP4K2A – rs7088318, *CASC8* – rs10505477, *IRF4* – rs87207, rs4646903 – *CYP1A1*, and rs7089424 of ARID5B gene. Today, it is more justified to stratify patients into risk groups and apply a risk-adapted approach with more intensive therapy regimens in case of high probability of relapse/refractory disease course and the key indicators of risk stratification are tumour extent and response to induction therapy. *GATA3* rs3824662, *CASP9* rs4661636, and *TR53* rs1042522 genes were detected in all patients who did not respond to treatment on Days 8, 15, and 33 of therapy and are associated with poor prognosis.

Alleles and genotypes of genes associated with relapse development were identified with high probability. The findings of this study revealed significant associations of polymorphic genetic variants, which may serve as a basis for the development of effective methods for predicting the risk of relapse development and the timeliness of intensification of B-ALL treatment. Prompt genetic counselling of children with identified unfavourable genotypes of the investigated gene polymorphisms will make it possible to predict the development of relapse, resistance and/or poor response to B-ALL treatment, and to propose an individual strategy for monitoring children's health in the short and long term.

Author Contribution Statement

All authors contributed equally in this study.

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