REVIEW

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PHARMACOGENETIC MARKERS IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA THERAPY

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. Despite major advances in therapy, the treatment of ALL remains a significant challenge. Therapeutic protocols are based on the use of combinations of chemotherapeutic drugs. While such combinations increase treatment efficacy, they also complicate the assessment of toxicity. It should be noted that the variability in the occurrence of toxic responses to ALL therapy in children may be determined by the presence of gene variants that influence both the pharmacokinetics and pharmacodynamics of chemotherapeutic drugs. This review summarized and analyzed the most significant and well-studied pharmacogenetic markers to date associated with the toxicity and response to chemotherapeutic agents used in the treatment of pediatric ALL. In particular, pharmacogenetic markers for the following drugs were analyzed: anthracyclines (doxorubicin, daunorubicin), vincristine, glucocorticoids (prednisone, dexamethasone), L-asparaginase, methotrexate, alkylating agents (cyclophosphamide, ifosfamide), 6-mercaptopurine, cytarabine, and etoposide. At present, only a few genes, *TPMT* and *NUDT15*, have well-established clinical utility, whereas the clinical relevance of pharmacogenetic markers for other drugs used in pediatric ALL therapy remains under investigation. The review also highlights the main knowledge gaps in current research and outlines promising directions for future studies aimed at integrating pharmacogenetic testing into clinical practice for personalized treatment of ALL.

Keywords: acute lymphoblastic leukemia, pharmacogenetics, chemotherapy, toxicity, pediatric oncology.

Acute lymphoblastic leukemia (ALL) is a hematological malignancy characterized by the uncontrolled proliferation of abnormal, immature lymphoid cells, leading to the replacement of normal elements of the bone marrow and other lymphoid organs [1, 2]. Primarily, the pathological process is localized in the bone marrow, with subsequent dissemination to the spleen, lymph nodes, liver, and other organs and tissues. ALL is most commonly diagnosed in children, although the disease can

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also occur in adults. It is estimated that ALL accounts for 75—80% of all leukemia cases in children [3]. In 2021, 58,785 new cases of ALL were registered worldwide, with an incidence rate of 2.92 cases per 100,000 population [2]. The incidence and mortality rates of ALL are slightly higher among boys and vary considerably depending on the region [2, 3]. In Ukraine, according to the National Cancer Registry, 268 new cases were reported in 2021, with an incidence rate of 4.1 cases per 100,000 among the child population [4]. On average, experts report that approximately 280 cases of ALL are diagnosed annually in Ukraine among children aged 0—18 years [5].

It should be emphasized that, owing to decades of research and clinical trials, treatment strategies for ALL have been optimized, allowing for long-term relapse-free survival of patients. According to recent data from the Children's Oncology Group, the overall 10-year survival rate of pediatric patients with high-risk ALL is approximately 85% [6].

ALL therapy includes three main phases: induction, post-induction therapy (consolidation/intensification), and maintenance therapy [7]. The most common treatment regimens are based on the use of combinations of chemotherapeutic drugs, taking into account individual risk factors. The Figure presents a list of drugs used in the treatment of ALL in children, including those used in Ukraine [7]. It should be noted that this is an approximate list of the main drugs, which does not include supportive therapy agents or provide details of treatment blocks or regimens.

As previously noted, monotherapy is not performed at any stage of treatment, which, on the one hand, complicates the accurate assessment of the occurrence of toxic effects associated with a specific drug, and, on the other hand, toxicity of one component of the therapeutic regimen for ALL can reduce its overall efficacy or even force the discontinuation of the entire regimen [8, 9]. The selection or substitution of drugs in such cases often occurs through a trial-and-error approach.

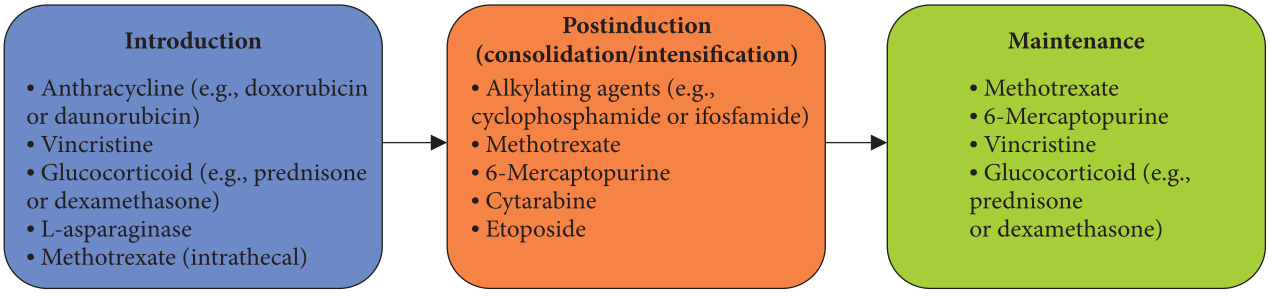
Variability in the occurrence of toxic responses to ALL therapy in children may be determined by the presence of gene variants that affect both the pharmacokinetics and pharmacodynamics of antileukemic drugs. Therefore, identification of pharmacogenetic markers of individual metabolism for each drug in the treatment regimen enables a personalized selection of the optimal therapy scheme for a child with ALL. Consequently, the search for pharmacogenetic predictors of toxic complications is of great relevance. This review aimed to summarize and analyze the most significant pharmacogenetic markers associated with the toxicity of drugs used in the chemotherapy of children with ALL.

Within the framework of this review, a systematic search and analysis of scientific sources were conducted to identify pharmacogenetic markers associated with both the toxicity and efficacy of the main chemotherapeutic agents used in the treatment of ALL in pediatric patients.

Anthracyclines (doxorubicin, daunorubicin)

Anthracyclines (doxorubicin, daunorubicin) are a group of cytotoxic antibiotics that induce DNA damage in leukemic cells and are widely used in the treatment of pediatric ALL. During therapy with doxorubicin and daunorubicin, the main adverse effects include cardiotoxicity and excessive myelosuppression.

Currently, the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) recommends genotyping pediatric ALL patients for the following gene variants: *RARG* rs2229774 and *UGT1A6* rs17863783



List of drugs used in the treatment of pediatric ALL

[10], which are considered to have the most consistent and convincing evidence of association with anthracycline-induced cardiotoxicity.

The role of other potentially significant pharmacogenetic markers is currently being investigated. In a retrospective multiethnic study involving 3,557 patients with ALL who received combination chemotherapy including anthracyclines, among 576 analyzed genetic variants, *UGT1A1* rs887829 and *PNPLA3* rs738409 were found to be associated with an increased risk of hepatotoxicity [11]. In the same study, the rs12283870 variant located between the *IGHMBP2* and *CPT1A* genes on chromosome 11 was associated with an increased risk of hyperbilirubinemia in ALL patients under 10 years of age.

A research group from Hungary analyzed 70 variants in 26 genes and found that variants in *CYP3A5*, *ABCC2*, *NQO1*, and *SLC22A6* may increase individual susceptibility of cardiotoxicity following anthracycline chemotherapy in pediatric ALL patients [12].

In the study by Krajinovic et al. [13], conducted on 251 pediatric ALL patients, an association analysis of 33 common variants in 12 genes revealed that *ABCC5* rs7627754 and *NOS3* rs1799983 variants may contribute to the risk stratification for anthracycline-induced cardiotoxicity.

Vincristine

Vincristine is a plant-derived alkaloid that inhibits microtubule formation, thereby blocking cell division in ALL. Among the most serious potential adverse effects of vincristine in pediatric oncology patients are neurotoxicity and excessive myelosuppression. Consequently, active searches are underway for biomarkers, including genetic ones that could predict the risk of such side effects.

A genome-wide association study of 1,100 children with ALL showed that the presence of *MCM3AP* rs1815857 is associated with a sixfold increase in the risk of vincristine-induced neuropathy [14]. Additionally, the rs924607 variant in the promoter region of *CEP72,* which encodes a centrosomal protein essential for microtubule formation and organization, has been shown to significantly increase the risk of vincristine-associated neurotoxicity in children with ALL in several independent studies [15—17].

It should be noted that vincristine, like most drugs, is a substrate for the P-glycoprotein transporter and undergoes metabolism by CYP3A4 and CYP3A5 isoforms, with CYP3A5 contributing to approximately 75% of the drug's intrinsic clearance [18]. Studies indicate that the presence of the functional *CYP3A5*3* (rs776746) variant, common among Europeans, increases the risk of vincristine neurotoxicity in pediatric ALL patients [19, 20]. The rs3740066 and rs12826 variants of the *ABCC2* gene, which encode the multidrug resistance-associated protein 2, are also associated with the development of vincristine neurotoxicity [21].

Glucocorticoids (prednisone, dexamethasone)

Glucocorticoids are immunomodulators with potent anti-inflammatory and lymphocytotoxic effects, which are widely used in ALL treatment protocols. Due to the biological activity of glucocorticoids, their administration to children with ALL may result in a wide spectrum of adverse effects. Moreover, some patients exhibit resistance to glucocorticoid therapy. It should be noted that there are relatively few studies investigating the genetic associations of glucocorticoid response in pediatric ALL patients.

Among potential biomarkers, the most relevant are the variants of the *NR3C1* gene, which encodes the glucocorticoid receptor. Certain variants of this gene may disrupt signaling pathways and lead to generalized resistance to glucocorticoid therapy, which, in turn, is associated with an increased risk of disease relapse and may negatively affect overall survival [22]. In a study involving 222 children with ALL, whose treatment protocols included glucocorticoids, patients with the GG genotype of *NR3C1* rs41423247 exhibited a poorer survival [23]. Another research group, in a retrospective study of 122 ALL patients, found that the *NR3C1* rs6198 variant was significantly associated with the insufficient reduction of blast cells by day 8 of the treatment, representing an unfavorable marker of therapy response [24]. According to the data published by El-Fayoumi et al. [25], ALL patients carrying the *NR3C1* rs56149945 variant had an increased predisposition to developing hyperglycemia during treatment.

Other biomarkers are also under active investigation. In a study by Anderer et al. [26], it was shown that in children with ALL, the presence of

a *GSTT1* gene deletion (null genotype) was associated with a significantly lower risk of poor response to prednisolone and disease relapse. In a genome-wide association study involving 2,535 pediatric patients with newly diagnosed ALL, two *ABCB1* gene variants, rs10264856 and rs4728709, were significantly associated with a higher dexamethasone clearance [27]. Karol et al. [28] reported that the rs10989692 variant near the glutamate receptor *GRIN3A* locus increased the risk of another important adverse effect, osteonecrosis, in pediatric patients.

L-asparaginase

L-asparaginase is an effective drug whose primary action is directed toward the selective elimination of leukemic blasts through the depletion of asparagine, an amino acid critically required for cell proliferation [29]. L-asparaginase currently represents a key component of ALL therapy. However, the use of L-asparaginase is associated with a high risk of serious adverse effects, including immunogenicity, hepatotoxicity, and pancreatotoxicity, which necessitates regular clinical and laboratory monitoring and often requires treatment discontinuation. This limits the optimal clinical use of the drug, and therefore, research is actively ongoing to identify genetic and molecular markers capable of predicting toxicity and development of the resistance to the drug.

The analysis of the current literature has shown that the variants of HLA system genes represent the most convincing marker of hypersensitivity to L-asparaginase. This was confirmed in multiple independent studies; however, the results vary depending on ethnic background [30—33]. For a cohort of pediatric patients of European descent (predominantly Franco-Canadian), the significant alleles associated with hypersensitivity were HLA-DRB1*07:01, DQA1*02:01, and DQB1*02:02 [30]. In Chinese pediatric patients, HLA-B*46:01 and DRB1*09:01 alleles were identified as key alleles [32].

Regarding the risk of adverse effects, numerous studies have identified the genetic associations with L-asparaginase toxicity in children with ALL. Specifically, recent research has shown that *GRIA1* rs4958351 is associated with the development of adverse effects, most commonly anaphylactic shock and pancreatitis; *ATF5* rs283526 with the risk of pancreatitis and impact on survival and *APOE* rs429358 with alterations in lipid profiles during therapy [34—36].

Methotrexate

Methotrexate is a synthetic folic acid antagonist that exhibits antitumor activity at high doses. It is widely used in the therapy of various forms of cancer, including pediatric ALL. The main adverse effects of methotrexate include hepatotoxicity, nephrotoxicity, neurotoxicity, and excessive myelosuppression, which can significantly limit the efficacy of therapy.

Numerous studies have demonstrated the role of the variants in genes encoding key components of the folate cycle, particularly *MTHFR* (rs1801131, rs1801133) and *SLC19A1* (rs1051266, rs1131596, rs2838958), in reducing methotrexate efficacy and contributing to the adverse effects such as mucositis, hepatotoxicity, and hematopoietic toxicity [37—46].

Other potential pharmacogenetic markers of methotrexate therapy are represented by the *ABCB1* gene variants. In the study by Guo et al. [47], patients with the TT genotype of *ABCB1* rs1045642 showed a higher incidence of adverse effects, including leukopenia, neutropenia, and oral mucositis, compared to patients carrying the CC genotype. Additionally, a meta-analysis encompassing 13 studies with 1,506 pediatric ALL patients demonstrated that *ABCB1* rs1045642 was significantly associated with methotrexate-induced hepatotoxicity [48].

Alkylating agents (cyclophosphamide, ifosfamide)

Alkylating agents disrupt DNA synthesis, leading to cell death; however, due to their nonspecific action on all rapidly proliferating cells, their use is associated with a wide spectrum of adverse effects.

It should be emphasized that, to date, there are no pharmacogenetic studies specifically in pediatric ALL populations; available data come only from related pediatric oncology groups. Analysis of these publications indicates that the greatest attention has been given to the genetic variants associated with variability in the detoxification enzyme activity. This is reasonable, as ifosfamide and cyclophosphamide are metabolized in the liver via cytochrome P450 enzymes. For instance, in the study by Mangó et al. [49],

CYP2B6 variants were shown to influence the risk of adverse effects during cyclophosphamide therapy in children with neuroblastoma. Another research group, led by ElShereef [50], found that *CYP3A5* variants (rs776746 and rs10264272) were significantly correlated with both efficacy and toxicity of cyclophosphamide in children with rhabdomyosarcoma. In children treated with ifosfamide for solid embryonal tumors, *CYP2C9* (rs1799853) and *CYP3A4* (rs2740574) variants were shown to affect drug pharmacokinetics, with the presence of *CYP3A4* rs2740574 being associated with an increased risk of a lack of the therapeutic response [51].

In addition, the detoxification pathway of these drugs involves their conjugation with glutathione, catalyzed by different glutathione S-transferase isoforms (GSTs). In a cohort of 76 children treated for various malignant diseases with ifosfamide, carriers of the *GSTP1* rs2495636 variant demonstrated an increased urinary excretion of the ifosfamide metabolites 2DCIF and 3DCIF and reduced creatinine clearance compared to homozygous wild-type carriers, suggesting a higher susceptibility to drug-induced toxicity [52].

6-Mercaptopurine

6-Mercaptopurine belongs to the class of purine antagonist drugs, exhibiting pronounced cytotoxic effects, including myelosuppression. Its use is associated with the risk of a wide spectrum of adverse effects.

Genotyping before 6-mercaptopurine therapy is currently the only pharmacogenetic test with well-established clinical significance for ALL. It is recommended by leading expert organizations, including the US Food and Drug Administration (FDA), the Clinical Pharmacogenetics Implementation Consortium (CPIC), and the Pharmacogenetics Working Group (DPWG), and is included in the corresponding clinical guidelines. Specifically, in ALL patients who are poor metabolizers (carrying two nonfunctional alleles) of the *NUDT15* and *TPMT* genes, the individualized dose adjustment of 6-mercaptopurine is recommended, often involving a significant reduction of the starting dose (e.g., from 10 mg/m²/day) to minimize the risk of severe toxic reactions [53].

It should be noted that there are population differences in the prevalence of variants leading to the poor metabolizer phenotype. For example, the nonfunctional allele *NUDT15*3* (rs116855232) is most frequent in Central/South and East Asian populations, with frequencies of 6.7% and 6.1%, respectively, whereas in Latin American and European populations, its prevalence is much lower — less than 1% [53].

Cytarabine

Cytarabine is an antimetabolite that inhibits DNA synthesis in ALL leukemic blasts, exerting cytotoxic effects. The most common adverse effects include excessive myelosuppression, gastrointestinal disturbances, and neurotoxicity (particularly at high doses).

The most promising and reproducible findings concern the variants in the *DCK* gene, which encodes deoxycytidine kinase, a key enzyme for cytarabine activation. In children with ALL, significant associations have been demonstrated between *DCK* variants and the risk of toxic complications: rs377182313 with an increased risk of mucositis and rs12648166 and rs4694362 with an increased risk of the hematologic toxicity [54, 55].

Some of these findings have been partially implemented in practice. For instance, *DCK* rs4694362, associated with the reduced intracellular cytarabine triphosphate levels, is included in the ACS10 research polygenic pharmacogenetic scale developed by Elsayed et al. [56]. This scale designed to predict cytarabine response in children with ALL is based on the identification of 10 variants in 9 genes, namely *DCK* (rs4643786), *CDA* (rs10916819), *CMPK1* (rs17103168, rs1044457), *NME4* (rs5841), *SLC29A1* (rs2396243), *RRM2* (rs1138729), *RRM1* (rs11030918), *CTPS1* (rs12067645), and *SLC28A3* (rs17343066). The ACS10 scale has not yet been implemented in standard clinical practice but is currently under evaluation in ongoing clinical research.

Etoposide

Etoposide is a topoisomerase II inhibitor that halts the division of leukemic cells in ALL, inducing apoptosis. Common adverse effects include excessive myelosuppression and gastrointestinal disturbances.

To date, only a few studies have investigated pharmacogenetic markers of etoposide use in

children with ALL, mostly focusing on their impact on drug exposure. In the study by Kishi et al. [57], the variants in *ABCB1*, *CYP3A5*, *GSTP1*, *UGT1A1*, and *VDR* were shown to differentially influence the etoposide clearance in pediatric ALL patients depending on the ethnic group. For example, on day 29 of therapy, the main predictors of drug clearance in Afro-American patients were *CYP3A5* rs776746 and *GSTP1* rs1695 variants. In Caucasian patients, only *ABCB1* variants (rs1045642 and rs2032582) were associated with etoposide clearance. Across all races, the *ABCB1* rs1045642 variant had a consistent effect on clearance, with higher clearance observed in patients with the CC genotype.

Thus, a number of pharmacogenetic markers have been identified that may influence the efficacy and toxicity of drugs used in pediatric ALL therapy. A summary of these data is presented in Table.

Discussion

Pharmacogenetics is a scientific discipline that studies how gene variants influence individual responses to drugs, particularly their efficacy and toxicity. It facilitates optimization of dosing and drug selection for individual patients and opens new opportunities for drug development. This approach is an essential strategy in personalized (precision) medicine, particularly in pediatric oncology, where it allows for dose optimization, reduction of adverse effects, and improved therapeutic outcomes. Therefore, performing such studies is highly relevant both for developing safer and more effective treatment protocols and implementing pharmacogenetic testing into clinical practice.

As indicated by the literature analysis, there are currently two main methodological approaches to pharmacogenetic research in children with ALL: candidate gene studies and whole-genome sequencing. It is important to note that, given the limited sample sizes and the specific nature of therapy in pediatric ALL patients, the most reproducible results have been obtained through the study of individual candidate genes associated with the action of specific drugs. A prime example of this is *NUDT15* and *TPMT* genotyping in ALL patients treated with 6-mercaptopurine. *NUDT15* and *TPMT* encode the enzymes nudix hydrolase 15 and thiopurine S-methyltransferase, which play a key role in 6-mercaptopurine metabolism. A reduced enzymatic activity due to genetic variants in these genes leads to the accumulation of the toxic 6-mercaptopurine metabolites, resulting in severe adverse effects. This is reflected in current clinical guidelines. Research on genetic variability in *NUDT15* and *TPMT* in ALL patients is ongoing.

It is noteworthy that significant gaps remain in the field. One key issue is the disparate extent of studies on different drugs. For example, the pharmacogenetics of methotrexate and 6-mercaptopurine in pediatric ALL is relatively well-studied, whereas data for etoposide and glucocorticoids are scarce, and no information is available for alkylating agents. There is also a lack of studies on different formulations of drugs, particularly various forms of L-asparaginase. Most pharmacogenetic studies have focused on patients receiving *E. coli*-derived L-asparaginase, highlighting the need to expand research to other formulations. Additionally, pharmacogenetic studies in pediatric ALL often focus on a single type of toxicity or endpoint, while other clinically relevant aspects remain unexamined. Given the uniqueness of the data, providing more comprehensive information on the impact of investigated gene variants on clinical and laboratory parameters is advisable.

Our review also highlighted another important aspect of pharmacogenetic research: the presence of ethnic and population differences in the distribution of genetic variants and, consequently, their impact on study outcomes. Therefore, results obtained in one population may not always be reproducible in another, especially if its genetic profile differs significantly from global data. This underscores the need for local studies and the creation of regional databases on pharmacogenetic research results and clinical recommendations.

Looking ahead, promising directions include expanding collaboration among research groups and clinical centers. This will allow for the formation of larger patient cohorts, increasing the statistical significance of research findings. Furthermore, multicenter studies will ensure representativeness of diverse ethnic and geographic groups, enabling assessment of variability in pharmacogenetic effects across populations.

It is also necessary to further expand the methodology for conducting pharmacogenetic studies in the context of risk of chemotherapy-induced

Pharmacogenetic markers for adverse effects of antileukemic drugs in children with ALL

Gene	Full name	Function / Role	Variant (rs)	Effect / Association	Reference
		Anthracyclines (doxorubicin, daunorubicin)			
RARG	Retinoic acid receptor gamma	Involved in the sodium-dependent transport and excretion of organic anions	rs2229774	↑ risk of cardiotoxicity	[10]
UGT1A6	UDP glucuronosyltransferase family 1 member A6	Catalyzes glucuronidation of drugs and xenobiotics	rs17863783	↑ risk of cardiotoxicity	[10]
UGT1A1	UDP glucuronosyltransferase family 1 member A1	Transforms small lipophilic molecules, such as drugs, into water-soluble, excretable metabolites	rs887829	↑ risk of hepatotoxicity	[11]
PNPLA3	Patatin-like domain 3, 1-acylglycerol-3-phosphate O-acyltransferase	Involved in lipid metabolism	rs738409	↑ risk of hepatotoxicity	[11]
IGHMBP2/CPT1A (intergenic variant)	—	—	rs12283870	↑ risk of hyperbilirubinemia	[11]
CYP3A5	Cytochrome P450 family 3 subfamily A member 5	Catalyzes many reactions involved in drug metabolism	rs4646450	↑ risk of cardiotoxicity	[12]
ABCC2	ATP binding cassette subfamily C member 2	Efflux transporter mediating drug excretion	rs3740066	↑ risk of cardiotoxicity	[12]
NQO1	NAD(P)H quinone dehydrogenase 1	Enzyme detoxifying quinones and protecting against oxidative stress	rs1043470	↑ risk of cardiotoxicity	[12]
SLC22A6	Solute carrier family 22 member 6	Involved in the sodium-dependent transport and excretion of organic anions	rs6591722	↑ risk of cardiotoxicity	[12]
ABCC5	ATP binding cassette subfamily C member 5	Efflux transporter for its substrate, cyclic nucleotides	rs7627754	↑ risk of cardiotoxicity	[13]
NOS3	Nitric oxide synthase 3	Produces nitric oxide, a biologic mediator in multiple processes	rs1799983	↑ risk of cardiotoxicity	[13]
		Vincristine			
MCM3AP	Minichromosome maintenance complex component 3 associated protein	Regulates DNA replication	rs1815857	↑risk of neuropathy	[14]
CEP72	Centrosomal protein 72	Involved in microtubule organization	rs924607	↑ risk of neurotoxicity	[15—17]
CYP3A5	Cytochrome P450 family 3 subfamily A member 5	Catalyzes many reactions involved in drug metabolism	rs776746	↑ risk of neurotoxicity	[19, 20]

ABCC2	ATP binding cassette subfamily C member 2	Efflux transporter for xenobiotic and endogenous compounds with broad substrate specificity	rs3740066, rs12826	↑ risk of neurotoxicity	[21]
		Glucocorticoids (prednisone, dexamethasone)			
NR3C1	Nuclear receptor subfamily 3 group C member 1	Mediates cellular response to glucocorticoids	rs41423247	↑ risk of relapse and fatal outcome	[23]
			rs6198	>1000 blasts/μL in peripheral blood on day 8 of treatment (poor response)	[24]
			rs56149945	↑ risk of hyperglycemia	[25]
GSTT1	Glutathione S-transferase theta 1	Catalyzes conjugation of reduced glutathione to various electrophilic compounds, facilitating detoxification	deletion (null genotype)	↓ risk of poor response and disease relapse	[26]
ABCB1	ATP binding cassette subfamily B member 1	Efflux transporter for xenobiotic compounds with broad substrate specificity	rs10264856	↑ dexamethasone clearance	[27]
near GRIN3A (intergenic variant)	—	—	rs10989692	↑ risk of osteonecrosis	[28]
		L-asparaginase			
HLA genes	Human leukocyte antigen complex	Involved in immune response; associated with hypersensitivity to certain drugs	different	↑ risk of hypersensitivity (anaphylaxis)	[30—33]
GRIA1	Glutamate ionotropic receptor AMPA type subunit 1	Mediates excitatory neurotransmission	rs4958351	↑ risk of adverse effects (anaphylaxis, pancreatitis)	[34]
ATF5	Activating transcription factor 5	Regulates transcription, stress response, and apoptosis; may affect chemotherapy sensitivity	rs283526	↑ risk of pancreatitis, and superior survival	[35]
APOE	Apolipoprotein E	Lipid transport protein influencing neurotoxicity and drug metabolism.	rs429358	changes in lipid profile during therapy	[36]
		Methotrexate			
MTHFR	Methylenetetrahydrofolate reductase	Involved in folate metabolism; affects methotrexate toxicity	rs1801131, rs1801133	↓ clearance, ↑ risk of toxicity (mucositis, hepatotoxicity, leukopenia, neutropenia)	[37—44]

End of Table

Gene	Full name	Function / Role	Variant (rs)	Effect / Association	Reference
SLC19A1	Solute carrier family 19 member 1	Folate transporter; mediating methotrexate uptake	rs1051266, rs1131596, rs2838958	↓ clearance, risk of toxicity (mucositis, hepatotoxicity)	[43—46]
ABCB1	ATP binding cassette subfamily B member 1	Efflux transporter for xenobiotic compounds with broad substrate specificity	rs1045642	risk of leukopenia, neutropenia, oral mucositis, and hepatotoxicity	[47, 48]
		Alkylating agents (cyclophosphamide, ifosfamide)			
CYP2B6	Cytochrome P450 family 2 subfamily B member 6	Catalyzes many reactions involved in drug metabolism	Functional variants → normal or rapid metabolizer	risk of hepatotoxicity and hematologic toxicity	[49]
CYP3A5	Cytochrome P450 family 3 subfamily A member 5	Catalyzes many reactions involved in drug metabolism	rs776746, rs10264272	Impact on cyclophosphamide efficacy and toxicity	[50]
CYP2C9	Cytochrome P450 family 2 subfamily C member 9	Catalyzes many reactions involved in drug metabolism	rs1799853	Impact on ifosfamide pharmacokinetics	[51]
CYP3A4	Cytochrome P450 family 3 subfamily A member 4	Catalyzes many reactions involved in drug metabolism	rs2740574	↑ risk of lack of therapeutic response	[51]
GSTP1	Glutathione S-transferase pi 1	Catalyzes detoxification of electrophilic compounds, including drug metabolites	rs2495636	↑ urinary excretion of ifosfamide metabolites (2DCIF, 3DCIF), ↓ creatinine clearance	[52]
		6-Mercaptopurine			
TPMT	Thiopurine S-methyltransferase	Metabolizes thiopurine drugs	Functional variants → poor metabolizer	↑ risk of leukopenia, neutropenia, and myelosuppression, requiring dose reduction	[53]
NUDT15	Nudix hydrolase 15	Catalyzes the hydrolysis of nucleoside diphosphates	Functional variants → poor metabolizer	↑ risk of leukopenia, neutropenia, and myelosuppression, requiring dose reduction	[53]
		Cytarabine			
DCK	Deoxycytidine kinase	Catalyzes phosphorylation of deoxyribonucleosides and nucleoside analogs	rs377182313	↑ risk of developing mucositis	[54]
			rs12648166	↑ risk of hematologic toxicity	[55]
			rs4694362	↑ risk of hematologic toxicity	[55]
		Etoposide			
ABCB1	ATP binding cassette subfamily B member 1	Efflux transporter for xenobiotic compounds with broad substrate specificity	rs1045642	↑ drug clearance in CC genotype carriers	[57]

toxicities by applying novel approaches, such as promoter methylation analysis, microRNA profiling, copy number variation analysis, and evaluation of mitochondrial DNA content and mutations. To date, only isolated studies have been conducted, but they show promising results. It has been demonstrated that promoter hypermethylation may have a more pronounced effect on gene function than genetic variants [58]. In a multi-omics analysis of 25 genes potentially associated with dexamethasone response, Shen et al. [59] concluded that dysregulation of these genes may occur due to the presence of copy number variations. In children with ALL, high expression levels of et-7c-5p, miR-106b-5p, miR-26a-5p, miR-155-5p, miR-191-5p, miR-30b-5p, and miR-31-5p were correlated with a favorable response to prednisone [60]. In an ex vivo study on primary samples from patients with acute myeloid leukemia, resistance to cytarabine was observed in patients with high mitochondrial DNA content [61].

Our review confirmed that the study of pharmacogenetic markers in the therapy of pediatric patients with ALL is highly relevant. Existing data indicate the proven benefit of integrating genetic markers into clinical protocols, which allows for improved treatment efficacy and reduced risk of toxic complications.

Conclusions

This review highlights the most well-known and significant genetic factors currently recognized to influence the efficacy and safety of chemotherapy in pediatric patients with ALL. While the number of genes with established clinical utility remains limited (e.g., *TPMT* and *NUDT15*), work is ongoing to assess the effectiveness of other pharmacogenetic markers. The review also identifies the main gaps in existing research and outlines promising directions for future investigations.

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ФАРМАКОГЕНЕТИЧНІ МАРКЕРИ ПРИ ТЕРАПІЇ ГОСТРОГО ЛІМФОБЛАСТНОГО ЛЕЙКОЗУ В ДІТЕЙ

Гострий лімфобластний лейкоз (ГЛЛ) є найпоширенішим злоякісним новоутворенням у дітей. Незважаючи на значний прогрес у терапії, лікування ГЛЛ залишається серйозним викликом. Терапевтичні протоколи базуються на використанні комбінацій хіміотерапевтичних препаратів. Хоча такі комбінації підвищують ефективність лікування, вони водночас ускладнюють оцінку токсичності. Варіабельність виникнення токсичних реакцій під час терапії ГЛЛ у дітей може бути зумовлена наявністю генетичних варіантів, які впливають як на фармакокінетику, так і на фармакодинаміку хіміотерапевтичних засобів. В огляді узагальнено та проаналізовано найзначущі й найкраще вивчені на сьогодні фармакогенетичні маркери, асоційовані з токсичністю та ефективністю хіміотерапевтичних препаратів, що застосовуються для лікування дитячого ГЛЛ. Розглянуто фармакогенетичні маркери для таких препаратів, як антрацикліни (доксорубіцин, даунорубіцин), вінкристин, кортикостероїди (преднізон, дексаметазон), L-аспарагіназа, метотрексат, алкілуючі агенти (циклофосфамід, іфосфамід), 6-меркаптопурин, цитарабін та етопозид. Наразі лише декілька генів — *TPMT* і *NUDT15* — мають добре підтверджене клінічне значення, тоді як клінічна релевантність фармакогенетичних маркерів для інших препаратів, що застосовуються в терапії дитячого ГЛЛ, залишається предметом подальших досліджень. В огляді також окреслено основні прогалини в сучасних знаннях і визначено перспективні напрями подальших досліджень, спрямованих на впровадження фармакогенетичного тестування в клінічну практику. Таким чином, введення фармакогенетичного тестування в протоколи педіатричної онкології є важливим кроком до персоналізованого лікування ГЛЛ.

Ключові слова: гострий лімфобластний лейкоз, фармакогенетика, хіміотерапія, токсичність, дитяча онкологія.