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GENE VARIANTS THAT MAY CAUSE ADVERSE DRUG REACTIONS IN NON-HODGKIN'S LYMPHOMA THERAPY: A GENOMIC AND BIOINFORMATICS APPROACH

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Abstract

Introduction. Chemotherapy remains a cornerstone treatment for most non-Hodgkin lymphoma (NHL) patients, yet it is frequently associated with significant adverse effects that compromise their quality of life. Emerging evidence highlights that genetic factors, particularly single nucleotide polymorphisms (SNPs), play a critical role in determining individual variability in treatment responses and susceptibility to drug-related complications. **Aim of this study:** to identify SNPs associated with chemotherapy-induced adverse events in NHL through advanced bioinformatics approaches, enabling personalized therapeutic strategies to mitigate risks. **Material abd Methods.** This study leveraged the PharmGKB database to identify SNPs associated with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. SNPs meeting inclusion criteria (Level of Evidence 1A-3, p<0.01) were prioritized for functional impact analysis using PolyPhen-2 scores. Data extraction and computational analysis utilized SNPnexus, HaploReg v4.2, Ensembl Genome Browser (GRCh37), and PharmGKB. The methodology employed a descriptive approach, relying exclusively on secondary data sources. **Results**. This study identified 11 SNPs that may be important for hematological toxicity, liver damage, and nausea risk. These genes are *SLC22A16*, *GSTP1*, *NAT2*, *ATM*, *ABCB1*, *CYP2B6*, *XRCC1*, *ERCC1*, *MUTYH PIK3R2*, and *PNPLA3*. In terms of priority and risk, the most significant variants were rs738409 (*PNPLA3*), rs12210538 (*SLC22A16*), rs2229109 (*ABCB1*), and rs56022120 (*PIK3R2*). The distribution of SNP alleles is more common in European populations than in Asians or Africans. **Conclusion**. For the first time, we found SNPs that indicate an increase in drug side effects. These SNPs rs738409, rs12210538, rs2229109 and rs56022120 increase the severity of NHL patients during chemotherapy. In order to ensure that these biomarkers can be used in clinical practice and to support the creation of precision medicine strategies, additional clinical validation is needed.

Key words: non-Hodgkin's lymphoma, adverse drug reactions, SNP, rs738409, rs12210538, rs2229109, rs56022120.

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ВАРИАНТЫ ГЕНОВ, КОТОРЫЕ МОГУТ БЫТЬ СВЯЗАНЫ С ПОБОЧНЫМИ РЕАКЦИЯМИ НА ЛЕКАРСТВЕННЫЕ ПРЕПАРАТЫ ПРИ ЛЕЧЕНИИ НЕХОДЖКИНСКОЙ ЛИМФОМЫ: ГЕНОМНЫЙ И БИОИНФОРМАТИЧЕСКИЙ ПОДХОД

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Аннотация

Введение. Химиотерапия остается краеугольным камнем лечения большинства пациентов с неходжкинской лимфомой (НХЛ), однако она часто связана со значительными побочными эффектами. Новые данные подчеркивают, что генетические факторы, в частности однонуклеотидные полиморфизмы (SNP), играют решающую роль в определении индивидуальных различий в ответах на лечение и восприимчивости к побочным эффектам. **Цель исследования –** выявление однонуклеотидных полиморфизмов, связанных с нежелательными реакциями на химиотерапию при лечении НХЛ, с использованием современных биоинформатических подходов, позволяющих разрабатывать персонализированные терапевтические стратегии для снижения риска осложнений. **Материал и методы.** В исследовании использовалась база данных PharmGKB для идентификации SNP, связанных с ритуксимабом, циклофосфамидом, доксорубицином, винкристином и преднизоном. SNP, соответствующие критериям включения (уровень доказательности 1A-3, p<0,01), были приоритетными для анализа функционального воздействия с помощью программы PolyPhen-2. Для получения и статистического анализа данных применялись SNPnexus, HaploReg v4.2, Ensembl Genome Browser (GRCh37) и PharmGKB. Методология исследования основывалась на описательном подходе, использовались исключительно вторичные источники данных. **Результаты.** Выявлено 11 SNP, которые могут ассоциироваться с гематологической токсичностью, повреждением печени и риском тошноты. К ним относятся гены: *SLC22A16, GSTP1, NAT2, ATM, ABCB1, CYP2B6, XRCC1, ERCC1, MUTYH, PIK3R2* и *PNPLA3*. С точки зрения риска возникновения побочных эффектов наиболее значимые варианты – rs738409 (*PNPLA3*), rs12210538 (*SLC22A16*), rs2229109 (*ABCB1*) и rs56022120 (*PIK3R2*). Аллели SNP более распространены в европейских популяциях по сравнению с азиатскими и африканскими. **Заключение.** Впервые мы обнаружили SNP, которые указывают на повышенный риск побочных эффектов лекарственной терапии. Эти SNP (rs738409, rs12210538, rs2229109 и rs56022120) усугубляют течение НХЛ во время химиотерапии. Для оценки возможности применения этих биомаркеров в клинической практике для опеределения персонализированной терапии необходима дополнительная клиническая валидация.

Ключевые слова: неходжкинская лимфома, побочные реакции на лекарственные препараты, однонуклеотидный полиморфизм, rs738409, rs12210538, rs2229109, rs56022120.

Introduction

There are numerous subtypes and varieties of non-Hodgkin lymphoma (NHL), which are cancers of the lymphoid cells. Each subtype and variety has its own unique set of biological, clinical, and histological features [1]. With an alarming rise in incidence rates over the past few decades, it has earned its place among the world's most common malignancies [2]. In the USA, for example, more than 80,350 new cases of NHL are thought to occur annually, making it one of the main reasons why people die from cancer [3]. NHL can present in various age groups, although it is more common in older adults [4]. Treatment of NHL typically involves a multimodal approach, including

chemotherapy, radiation therapy, and immunotherapy, each of which has varying degrees of effectiveness and side effect profiles [5]. Although progress has been made in the treatment of NHL, there are still significant challenges associated with resistance to therapy and the emergence of severe side effects, which require further research to understand the factors that influence individual response to treatment [6].

In recent years, studies on pharmacogenetics and pharmacogenomics have provided new insights into how genetic factors influence a patient's response to NHL therapy. Pharmacogenetics focuses on individual genetic variations that affect drug metabolism, while pharmacogenomics includes the study of the entire genome and how gene expression contributes to response to treatment [7]. Better personalized treatment methods can be achieved by gaining insight into these two areas; this will enable doctors to choose the most effective medications according to a patient's genetic profile, which in turn reduces the likelihood of adverse effects and increases the likelihood of a cure. Also, pharmacogenetic studies have demonstrated that different medications used to treat NHL have different effects and side effects depending on particular genetic variants. For instance, Conyers et al. (2018) discovered that patients receiving purine analog-based chemotherapy may have increased toxicity if they have variants in the *TPMT* gene. This provides evidence that tailoring dosages to individual patients' genotypes has the potential to enhance therapeutic efficacy while decreasing the likelihood of adverse effects [8].

A crucial aspect of this research is the identification of biomarkers that can be used to forecast how a certain therapy will be received, potentially changing the way we treat NHL. These biomarkers not only help in selecting the most effective drugs but also provide insight into disease prognosis and the possible development of resistance to treatment. In addition, pharmacogenetic research can help identify individuals at risk of severe side effects from the therapies used [9]. These side effects, such as myelosuppression, peripheral neuropathy, and immunological reactions, are often a barrier to continuing treatment and can significantly affect patients' quality of life [10]. With better knowledge of the genetic factors that affect drug tolerability, medical personnel can design safer and more effective treatment plans. This article aims to find the Single Nucleotide Polymorphism (SNP) which were associated with side effects in NHL drugs using bioinformatics-based methods.

Aim of this study: to identify SNPs associated with chemotherapy-induced adverse events in NHL through advanced bioinformatics approaches, enabling personalized therapeutic strategies to mitigate risks.

Material abd Methods

It is important to understand the structure of the human genome and understand the side effects of drugs by identifying genome variants. In this study, we integrated variants associated with drug side effects of NHL cancer using bioinformatics-based methods. This study was conducted using the PharmGKB (Pharmacogenomics Knowledge Base) (https://www.pharmgkb.org/) database with the keywords «Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone» accessed on November 03, 2024. This chemotherapy regimen is based on National Comprehensive Cancer Network (NCCN) (https://www.nccn.org/patientresources/patient-resources/guidelines-for-patients/non-hodgkin-lymphoma-resources) guidelines. SNPs were selected based on inclusion criteria, namely Level of Evidence (LOE) 1A-3 (Clinical Annotation), missense variant type, and had a p-value<0.01 as the limit of statistical significance based on genetic association tests listed in the database [5]. Priority analysis was performed using the PolyPhen-2 score (https://www.snp-nexus.org/v4/results/629178ab/) to determine the level of possible protein damage of each SNP. SNP data was extracted and analyzed using web-based software such as SNPnexus (https://www.snp-nexus.org/v4/), HaploReg v4.2 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php), Ensembl Genome Browser (https://grch37.ensembl.org/index.html) accessed on November 05, 2024. All analyses were carried out descriptively and based on secondary data.

Results

Genomic Variants Potentially Induce Side Effects of NHL Chemotherapeutic Drugs

Results from studies using the PharmGKB database showed that certain SNPs can raise the risk of adverse effects from the NHL drugs Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (R-CHOP). We identified genetic variant SNPs that have the potential to cause adverse drug events in NHL therapy using genomics and bioinformatics approaches. Table 1. Results from PharmGKB and HaploReg v4.2 present 11 significant SNPs associated with chemotherapy drug toxicity, involving genes such as *SLC22A16*, *GSTP1*, *NAT2*, *ATM*, *ABCB1*, *CYP2B6*, *XRCC1*, *ERCC1*, *MUTYH*, *PIK3R2*, and *PNPLA3*. These SNPs showed increased toxicity response based on significant values (p-value<0.01). These genetic variations were spread across different populations, such as European, East Asian, and multiethnic groups. We can learn a lot about how genetic diversity affects the likelihood of side effects from NHL chemotherapy meds from these findings. Although Rituximab was part of the R-CHOP regimen in this study, we did not obtain specific data on Rituximab-induced toxicity from the analyzed database. These limitations highlight the need for further research exploring genetic factors specifically associated with Rituximab-related side effects.

Priority analysis of genes causing adverse reactions to NHL

Gene prioritization analysis using the PolyPhen-2 database (accessed on 5/11/2024) with the aim of

Table 1/Таблица 1

PharmGKB, HaploReg v4.2, Ensembl results identified 11 significant SNPs associated with NHL chemotherapy drug toxicity

Результаты PharmGKB, HaploReg v4.2, Ensembl выявили 11 значимых однонуклеотидных полиморфизмов, связанных с токсичностью химиотерапевтических препаратов при НХЛ

No	Genes/ Гены	SNP	Nucleotide Change/ Изменение нуклеотидов	HGVS Notasi	Amino Acid Change (Protein)/ Изменение аминокислот (белок)	N	Population/ Популяция	Associated/ Toxicity/ Токсичность	p-value	PMID
1	*SLC22A16*	rs12210538	A>G	NC_000006.12:g.110438805A>G	p.Met375Thr	230	Multiple groups/ Несколько групп	Neutropenia/ Нейтропения	0.004	20179710
2	*GSTP1*	rs1695	A>G	NC_000011.10:g.67585218A>G	p.Ile105Val	102	East Asian/ Восточная Азия	Neutropenia/ Нейтропения	0.001	25008867
3	*NAT2*	rs1801280	T>C	NC_000008.11:g.18400344T>C	p.Ile114Thr	101	European/ Европа	Anemia/Анемия	0.001	24533712
4	*ATM*	rs1801516	G>A	NC_000011.10:g.108304735G>A	p.Asp1853Asn	320	NA/ Северная Америка	Nausea/Тошнота	0.005	29507678
5	*ABCB1*	rs2229109	C>T	NC_000007.14:g.87550493C>T	p.Ser400Asn	760	NA/ Северная Америка	Mucositis, neutropenia/ Мукозит, нейтропения	0.003	25637052
6	*CYP2B6*	rs2279343	A>G	NC_000019.10:g.41009358A>G	p.Lys262Arg	107	NA/ Северная Америка	Mucositis/ Мукозит	0.007	19005482
7	*XRCC1*	rs25487	T>C	NC_000019.10:g.43551574T>C	p.Gln399Arg	104	European/ Европа	Neutropenia, Nausea/ Нейтропения, тошнота	0.009	19786980
8	*ERCC1*	rs3212986	C>A	NC_000019.10:g.45409478C>A	p.Gln504Lys	321	European/ Европа	Neutropenia/ Нейтропения	0.006	29507678
9	*MUTYH*	rs3219484	C>T	NC_000001.11:g.45334484C>T	p.Val8Met	102	European/ Европа	Neutropenia/ Нейтропения	0.001	24533712
10	*PIK3R2*	rs56022120	C>T	NC_000019.10:g.18123979C>T	p.Thr196Met	3252	European/ Европа	Neutropenia/ Нейтропения	0.001	29593529
11	*PNPLA3*	rs738409	C>G	NC_000022.11:g.43928847C>G	p.Ile148Met	2283	Multiple groups/ Несколько групп	Hepatotoxicity/ Гепатотоксич-ность	0.001	24533712

Notes: HGVS – Human Genome Variation Society; N – sample size; all SNPs refer to missense variants affecting protein coding regions; amino acid changes are described using standard protein sequence numbering; created by the authors.

Примечания: HGVS – Human Genome Variation Society; N – размер выборки; все SNP относятся к миссенс-вариациям, влияющим на кодирующие области белков; изменения аминокислот описаны с использованием стандартной нумерации последовательностей белков; таблица составлена авторами.

prioritizing SNPs that have a higher potential risk of side effects of NHL drugs. The SNPs were categorized into three groups: benign, possibly damaging, and probably damaging based on PolyPhen-2 scores. If it is in the score between (0.00 to 0.15), it is benign, then if it is in the score (0.15 to 0.85), it is moderate (possibly damaging), but if it is in the score (0.85 to 1.0), it is very malignant (probably damaging) [11]. So that the gene variant is said to be increasingly malignant if the score is getting closer to one, from this, researchers exclude SNPs that have a potential risk of less than 0.15 (benign).

The results of the research from 11 SNPs analyzed with SNPNexus only got 4 variants of the highest data score. Priority analysis targeted the highest ratings of 0.944 and 0.912, two of the eight missense SNP variants rs738409 and rs12210538 being highly dangerous variants. Then, with scores of 0.755 (rs2229109) and 0.505 (rs56022120) are moderate variations, which can be dangerous. So that the 4 SNP data have great potential to cause side effects of NHL chemotherapy drugs. These variations have the potential to be used as biomarkers for the purpose of tracking therapies that may cause side effects of chemotherapy drugs used in NHL and for the purpose of predicting possible side effects [12].

Distribution of genetic variants causing adverse reactions

Table 3 and Figure 1 present the allele frequencies of gene variants associated with adverse drug reactions to NHL therapy across different global populations, including Africa, America, Asia, and Europe. These data were extracted from the 1000 Genomes Project using SNPnexus (https://snp-nexus.org/) and Ensembl Genome Browser (https://grch37.ensembl.org/).The purpose of this mapping is used to see the distribution of susceptibility to side effects of NHL drugs in various world populations. Allele frequencies are different in each population Allele frequencies for each SNP vary across African, American, European, and Southeast Asian populations, as presented in Table 3.

Discussion

SLC22A16

A number of small molecules are transported across the cell membrane by the *SLC22A16* gene, which is a member of the *SLC22* gene family [11]. *SLC22A16* in particular is known as an organic cation transporter. The protein encoded by this gene has an crucial role in the transportation of certain compounds into cells, such as Doxorubicin. Variants in the *SLC22A16* gene, which encodes the transporter for doxorubicin, can affect drug toxicity by altering the efficiency of doxorubicin uptake into cells. Loss-of-function variants decrease drug accumulation, reducing toxicity, but can also decrease therapeutic efficacy. On the flip side, doxorubicin accumulation is increased by gain-of-function variants or overexpression, which can lead to oxidative stress on the heart and hematological damage (such as neutropenia). Genetic polymorphisms such as rs12210538 have been linked to individual variation in sensitivity to doxorubicin side effects, making them relevant for pharmacogenomics-based personalized medicine [13].

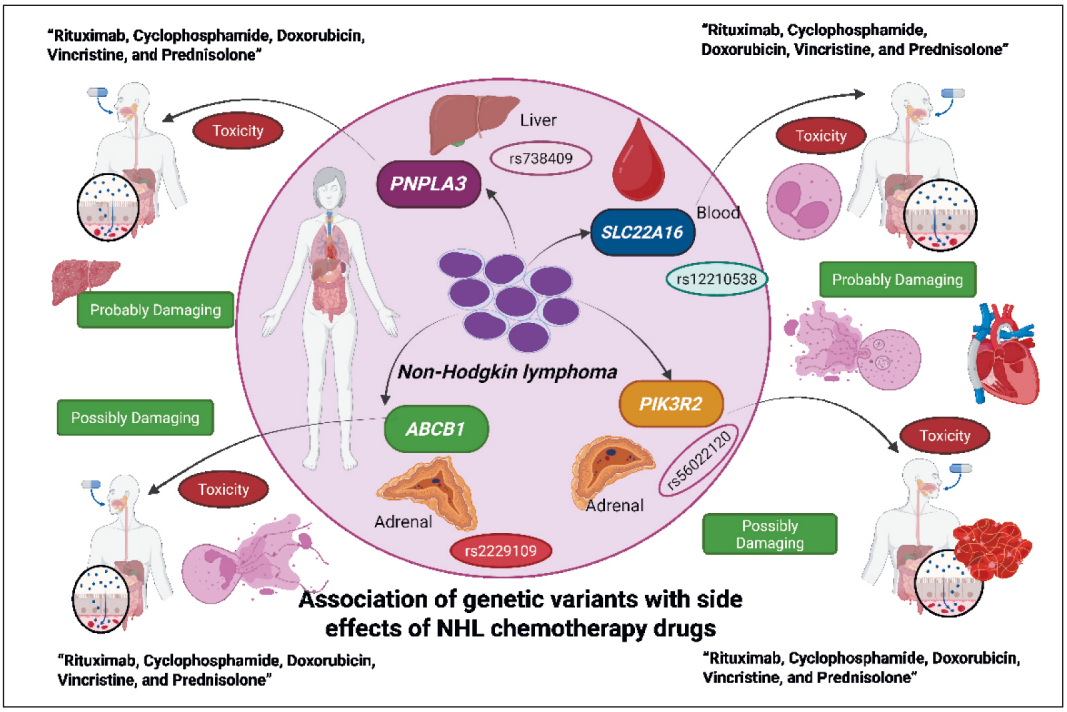

Fig. 1. Prioritized SNPs and their Associated Adverse Drug Effects in NHL Chemotherapy. Notes: created in BioRender by Muhammad Irham, L. (2025). https://BioRender.com/xik6jj9

Рис. 1. Приоритетные однонуклеотидные полиморфизмы и связанные с ними побочные эффекты химиотерапии при НХЛ. Примечание: рисунок выполнен в BioRender Мухаммадом Ирхамом, Л. (2025). https://BioRender.com/xik6jj9

Table 2/Таблица 2

Priority analysis of SNPs associated with adverse effects of NHL and their effect on protein levels

Приоритетный анализ однонуклеотидных полиморфизмов, связанных с неблагоприятными эффектами химиотерапии, и их влияние на уровень белка

No	SNP/ Однонуклеотидные полиморфизмы	Chromosome/ Хромосомы	Gene/ Гены	Score/ Счет	Prediction/ Прогноз	Consequence/ Последствия
1	rs738409	22	*PNPLA3*	0.944	Probably Damaging/ Вероятно повреждающий	Missense/ Миссенс-мутация
2	rs12210538	6	*SLC22A16*	0.912	Probably Damaging/ Вероятно повреждающий	Missense/ Миссенс-мутация
3	rs2229109	7	*ABCB1*	0.755	Possibly Damaging/ Вероятно повреждающий	Missense/ Миссенс-мутация
4	rs56022120	19	*PIK3R2*	0.505	Possibly Damaging/ Вероятно повреждающий	Missense/ Миссенс-мутация

Note: created by the authors.

Примечание: таблица составлена авторами.

Table 3/Таблица 3

Allele frequencies in various populations and their potential susceptibility to NHL adverse drug events

Частоты аллелей в различных популяциях и их потенциальная восприимчивость к побочным лекарственным эффектам при лечении НХЛ

No	Chr/ Хромосомы	Gene/ Гены	SNP/ Однонуклеотидные полиморфизмы	Allele/Аллели		Frequency/Частота				
				Ref	Alt	AFR	AMR	EAS	SAS	EUR
1	22	*PNPLA3*	rs738409	C	G	0.12	0.48	0.35	0.25	0.23
2	6	*SLC22A16*	rs12210538	A	G	0.01	0.15	0.00	0.09	0.24
3	7	*ABCB1*	rs2229109	C	T	0.00	0.02	0.00	0.01	0.03
4	19	*PIK3R2*	rs56022120	C	T	0.00	0.09	0.04	0.06	0.01

Notes: Chr – chromosome; Ref – reference; Alt – alternative; AFR – Africa; AMR – America; EAS – East Asian; SAS – South Asian; EUR – Europe; created bu the authors.

Примечания: Chr – хромосома; Ref – ссылка; Alt – альтернатива; AFR – Африка; AMR – Америка; EAS –Восточная Азия; SAS – Южная Азия; EUR– Европа; таблица составлена авторами.

A vulnerability to grade 3–4 Febrile Neutropenia (FN) was linked to the rs12210538 (A>G) polymorphism in the *SLC22A16* gene, according to an Iranian study. This study's findings highlight the critical need to assess genetic diversity as a potential contributor to cancer treatment-related side effects. Grade 3–4 FN was not significantly associated with *SLC22A16* polymorphisms in our study, however there was a trend in the data that pointed to the A allele of *SLC22A16* (rs12210538 A>G) as a potential risk factor. This is evident from the p-value=0.110 with OR=2.984 and CI=0.743–11.988, which indicates an increased risk although it has not reached the level of statistical significance. In contrast, the G allele of the same gene showed potential protection against the condition, with p=0.548, OR=0.78, and CI=0.35–1.72. These results suggest a pattern of differential effects of the two alleles in relation to susceptibility to FN, where the A allele tends to increase risk, while the G allele potentially provides a protective effect. The results are not yet statistically significant, but the patterns show that more samples and validation in more populations are needed to make these conclusions stronger [14].

Furthermore, these results emphasize the need to consider molecular factors, including genetic polymorphisms such as *SLC22A16*, when assessing cancer patients' likelihood of developing severe neutropenia, especially those in the high-risk category. The identification of such genetic biomarkers will support precision medicine approaches, where patient treatment and monitoring can be personalized based on individual genetic profiles. By understanding these genetic variations, it is hoped that clinicians will be able to identify patients who are more susceptible to toxic side effects such as grade 3–4 neutropenia and optimize prevention strategies and management of cancer therapy to improve patient clinical outcomes [14].

GSTP1

Being the most abundant GST expressed in adult lungs, glutathione S-transferase P1 (*GSTP1*) is an isoenzyme within the glutathione-S transferase (GST) enzyme system. There is a robust correlation between *GSTP1* and cellular oxidative stress regulation, cell death suppression, and cytotoxic metabolism enhancement, according to recent studies [15]. Cyclophosphamide and other chemotherapy medications are detoxified in large

part by the glutathione S-transferase P1 enzyme, which is encoded by the *GSTP1* gene [16]. Metabolic activation of the prodrug cyclophosphamide yields a cytotoxic molecule and other hazardous byproducts, including acrolein, which can cause harm to normal cells. The enzyme *GSTP1* helps reduce toxicity by binding these toxic metabolites using glutathione molecules so that the metabolites are more easily excreted [17].

Polymorphisms in the *GSTP1* gene, particularly the A>G nucleotide substitution (rs1695), may affect the enzymatic activity of *GSTP1*. This substitution can reduce the enzyme's detoxification capacity, resulting in the accumulation of toxic metabolites from chemotherapy agents. Such impaired metabolism is associated with an increased risk of treatment-related adverse effects, including neutropenia and gastrointestinal toxicity, in patients undergoing cyclophosphamide-based therapy [18]. A study involving 102 Japanese female patients receiving cyclophosphamide and epirubicin chemotherapy found a significant association between the A>G variant and the incidence of FN, with a p-value of 0.001. These findings indicate that the A>G polymorphism in *GSTP1* may serve as a useful pharmacogenetic biomarker for cancer patients to use in predicting the efficacy and safety of their treatments, opening the door to a more tailored method of cancer care [19].

NAT2

A number of xenobiotic chemicals contain aromatic and heterocyclic amines, which are processed in phase II of the metabolic pathway by the enzyme N-acetyltransferase 2 (*NAT2*). The main function of the *NAT2* gene is to regulate the metabolism of various drugs, including cyclophosphamide, a chemotherapeutic agent often used in cancer treatment. Polymorphisms in the *NAT2* gene cause variations in the activity of the enzyme in converting drugs in the body, which impacts the effectiveness of treatment as well as the risk of toxicity. This variation in activity divides *NAT2* phenotypes into three main categories, namely fast acetylators, intermediate acetylators, and slow acetylators. Individuals with the slow acetylator phenotype have a slower metabolism, so drugs such as cyclophosphamide tend to stay longer in the body in their active form. This increases the risk of side effects and toxicity, including significant anemia in patients undergoing chemotherapy [20].

This study demonstrated a significant association between the T>C nucleotide substitution in the *NAT2* gene (rs1801280) and an increased risk of anemia in individuals receiving cyclophosphamide-based chemotherapy. This single nucleotide polymorphism is believed to alter the enzymatic activity of *NAT2*, disrupting drug metabolism and causing accumulation of cyclophosphamide in the body. As a result, increased drug levels can cause hematological toxicity, especially anemia, due to damage to red blood cells. Statistical analysis showed a strong correlation, with an OR of 5.65, 95 % CI of 2.23–14.33, and p-value of 0.0002. This variant T>C causes metabolic changes that cause cyclophosphamide to build up in the body. This leads to anemia and damage to red blood cells [21].

These findings highlight the importance of nucleotide substitutions for the *NAT2* polymorphism prior to initiation of cyclophosphamide therapy to predict the risk of hematologic toxicity, including anemia. Clinicians can adapt medicine doses or pick alternative therapeutic procedures to lessen the likelihood of side effects by understanding the patient's acetylation phenotype. This method is consistent with precision medicine's tenets, which, according to each patient's unique genetic makeup, seek to optimise therapy efficacy while minimising toxicity. Furthermore, this study also emphasizes the need for additional research with larger and more diverse populations to validate these results, as well as to comprehend the deeper molecular mechanisms linking *NAT2* polymorphisms to the incidence of anemia in patients undergoing chemotherapy.

ATM

The *ATM* (Ataxia Telangiectasia Mutated) gene is a gene that encodes an important protein kinase that functions in DNA repair, cell cycle regulation, and response to genetic damage. Variants in this gene can lead to impaired DNA repair function, thereby increasing susceptibility to chemotherapy-induced genetic stress. In the context of chemotherapy-induced nausea toxicity, polymorphisms in the *ATM* gene (rs1801516), have been linked to a higher risk of nausea in patients undergoing chemotherapy. Studies show that patients with the rare A allele of this polymorphism have up to twice the risk of experiencing nausea compared to non-carriers. In fact rare homozygotes for this variation can really more than nine times increase the likelihood of experiencing severe nausea [22].

Research by K. Tecza et al. [18] examined how specific genetic variations influence the risk of nausea in chemotherapy patients. One key finding was the significant association between the G>A nucleotide substitution in the *ATM* gene (rs1801516) and the occurrence of early acute nausea in breast cancer patients. Individuals carrying the A allele showed a markedly increased risk of severe nausea during the early phase of treatment, with an OR of 9.31 (95 % CI: 1.94–45.25; p=0.005). When this genetic factor was combined with younger age (≤39 years), the cumulative risk increased substantially, reaching an OR of 23.5 (95 % CI: 1.85–299.04; p=0.014). These findings underscore the importance of integrating genetic and clinical factors in predicting chemotherapy-induced nausea, highlighting the potential utility of the G>A variant in ATM as a biomarker for treatment risk assessment [18].

ABCB1

The efflux transporters for the medication R-CHOP, which is used to treat NHL, are encoded by the ATP-binding cassette subfamily B member 1 (*ABCB1*) and *ABCC1* genes. It has long been recognised

that *ABCB1* acts as a transporter for hydrophobic medicines, including anthracyclines, etoposide, and vinca alkaloids, which are commonly administered during NHL treatment. Multiple treatment-related side effects were associated with the rs2229109 *ABCB1* gene variant in this investigation. Serious side effects, including FN (P=0.039) and vomiting (P=0.043), were associated with rs2229109 in the R-ACVBP treatment group. On the other hand, according to Jordheim et al. (2015), the same polymorphism was linked to diarrhoea (p=0.041), vomiting (p=0.031), and mucositis (p=0.004) in the R-CHOP group. Studies conducted by Amin (2013) and S. Yao et al. (2014) demonstrated that certain SNP in this gene were not always associated with serious haematologic or gastrointestinal side effects in breast cancer patients using doxorubicin and cyclophosphamide. But this study found a substantial connection for SNP rs2229109. The rs2229109 polymorphism is a non-synonymous polymorphism, so it is likely to produce a variety of proteins with different activities, which may affect the toxicity response to therapy [23].

According to one Iranian study, having the genetic variant (rs10276036 C>T) in *ABCB1* makes one more likely to experience grade 3–4 FN. There was no statistically significant correlation between the *ABCB1* gene variant and grade 3–4 FN, according to the analysis. Having said that, there was a trend towards an increased risk of grade 3–4 FN associated with the C allele of the *ABCB1* polymorphism (rs10276036 C>T) (p=0.315, OR=1.50, 95 % CI=0.67–3.31). In contrast, the T allele of the same polymorphism appeared to have a protective effect against this condition (p=0.13, OR=0.51, 95 % CI=0.21–1.22). This finding indicates a potential contribution of certain alleles of the *ABCB1* gene in influencing the body's response to chemotherapy, although not strong enough to reach statistical significance. Further evaluation of the molecular role of this gene may provide additional insights into managing the risk of toxicity in cancer patients [14].

CYP2B6

CYP2B6 is a gene that encodes an enzyme in the cytochrome P450 family, which plays an significant role in drug metabolism, including chemotherapy. Genetic polymorphisms in *CYP2B6* can affect the body's ability to metabolize these drugs, which in turn can affect side effects such as nausea that often occur in patients undergoing cancer therapy. Variants such as rs2279343 are known to affect enzymatic activity and influence the risk of chemotherapy-induced toxicities. Research suggests that individuals with certain variants of *CYP2B6* may be more susceptible to gastrointestinal toxicity, including nausea, during cancer therapy. When managing nucleotide substitutions-based treatments to lessen adverse effects such as nausea, it is vital to take this pharmacogenomic feature into account since the distribution of this polymorphism differs between populations [24, 25].

The *A>G* nucleotide substitution in the *CYP2B6* gene (rs2279343) has been significantly associated with the risk of oral mucositis in patients undergoing HLA-identical hematopoietic stem cell transplantation and receiving cyclophosphamide-based conditioning. According to data from PharmGKB, the presence of the G allele was linked to a higher risk of mucositis, while the A allele appeared to have a protective effect. Statistical analysis showed a p-value of 0.007 and OR of 3.03 (95 % CI: 1.37–6.73), suggesting that this variant may serve as a predictive marker for mucositis-related toxicity in patients receiving cyclophosphamide therapy [26].

XRCC1

One gene involved in the excision base repair (BER) pathway is *XRCC1*, which stands for X-ray repair cross-complementing 1. This gene helps restore the integrity of DNA damaged by external factors such as radiation or chemical compounds. The *XRCC1* protein acts as an adaptor that recruits important enzymes to repair oxidized or alkylated DNA bases, making it a key element in maintaining genome stability. Polymorphisms in the *XRCC1* gene, particularly the rs25487 variant, have been associated with variations in response to chemotherapy, including toxic side effects such as nausea and severe neutropenia. The DNA repair pathway involving *XRCC1* plays a critical role in repairing damage induced by chemotherapeutic agents such as cyclophosphamide, doxorubicin, fluorouracil, and cisplatin. In a cohort study involving 322 breast cancer patients receiving cyclophosphamide, doxorubicin, and fluorouracil (FAC) chemotherapy, the T>C nucleotide substitution in the *XRCC1* gene (rs25487) was significantly associated with an increased risk of nausea. Statistical analysis showed a strong correlation, with a p-value of 0.032, OR of 3.13, and 95 %, CI of 1.1–8.94, suggesting that this variant may influence gastrointestinal side effects during chemotherapy [21]. In a separate study of 104 ovarian cancer patients treated with cisplatin and cyclophosphamide, the same T>C variant was associated with a higher risk of severe neutropenia. The analysis yielded a p-value of 0.009, OR of 3.02, and CI of 1.33–6.88, indicating that this polymorphism contributes to hematological toxicity across different therapies and patient populations. These findings suggest that the SNP rs25487 in *XRCC1* plays an important role as a predictive biomarker in NHL chemotherapy toxicity [27].

ERCC1

This nucleotide excision repair (NER) pathway is involved in DNA repair, and one gene that contributes to this process is *ERCC1*. In order to fix DNA damage caused by genotoxic agents, such as ultraviolet radiation and toxic chemicals used in chemotherapy, the *ERCC1* protein collaborates with other proteins like XPF. To avoid cancer-causing variant buildup, this DNA repair mechanism is crucial. Cancer treatments such as cisplatin-cyclophosphamide can

have different effects in different people depending on *ERCC1* polymorphisms, such as the one in the rs3212986 variant. Tumour response to chemotherapy and normal tissue toxicity can be influenced by these genetic differences, which may impact DNA repair efficiency [28].

The C>A nucleotide substitution in the *ERCC1* gene (rs3212986) has been reported to have a significant association with the risk of neutropenia in breast cancer patients undergoing chemotherapy with the FAC regimen (fluorouracil, doxorubicin, and cyclophosphamide). In a cohort study involving 321 female patients, the presence of the A allele was associated with an increased risk of severe neutropenia, while the C allele appeared to confer a protective effect. The analysis yielded a statistically significant result with a p-value of 0.006, OR of 5.45, and a 95 % CI of 1.62–18.29, indicating a strong association between the C>A polymorphism and hematological toxicity during treatment. These results suggest that SNP rs3212986 may be a candidate genetic biomarker in predicting the risk of hematological toxicity in cancer patients receiving chemotherapy [18].

MUTYH

The *MUTYH* gene (MutY homolog) is a gene involved in DNA repair, specifically in the oxidative base repair process. It encodes a glycosylase enzyme that repairs base pairing errors that occur due to oxidative damage, such as the variant of guanine to 8-oxoguanine. The main role of the *MUTYH* gene is to maintain genome stability by preventing the accumulation of variants that can lead to disease, including cancer. DNA damage is the main mechanism used by chemotherapy drugs to kill cancer cells. Cancer patients may have impaired DNA repair capabilities due to polymorphisms or variants in the *MUTYH* gene. Haematologic toxicity, mucositis, and other DNA damage-related organ damage may become more likely as a result of this [29].

Several studies suggest that variants or genetic variants in *MUTYH* may contribute to the toxicity of chemotherapy drugs, especially if the drugs produce significant oxidative stress or DNA damage, such as cyclophosphamide or other alkylating agents. Patients with *MUTYH* variants is potentially more susceptible to the adverse consequences of chemotherapy due to the lack of ability to repair DNA damage induced by such therapy. The results demonstrated that the C>T nucleotide substitution in the MUTYH gene (rs3219484) was significantly associated with the incidence of severe neutropenia in patients undergoing chemotherapy. This variant was linked to an increased risk of grade 3–4 neutropenia, with a highly significant p-value of 0.001, OR of 0.01, and a 95 % CI of 0.00–0.22. The presence of the C allele appeared to increase susceptibility to hematological toxicity, whereas the T allele was associated with a reduced risk. These findings strengthen the potential of the rs3219484 SNP as a predictive genetic biomarker in the management of chemotherapy-induced neutropenic toxicity [21].

PIK3R2

Part of the PI3K-AKT-mTOR signalling cascade, the *PIK3R2* gene encodes the phosphoinositide-3 -kinase (PI3K) regulatory subunit p85β. Growth, survival, and metabolism are just a few of the critical cellular processes regulated by this system. Variants or overexpression of *PIK3R2* can accelerate cancer cell development and contribute to chemotherapy resistance in several malignancies, including leukaemia and lymphoma, which activate this pathway. One of the most important targets in cancer treatment, especially for leukaemia, is the PI3K-AKT-mTOR signalling pathway. Inhibitors targeting this pathway have demonstrated promise in enhancing treatment outcomes and overcoming chemotherapy resistance. Although direct research into the specific association of *PIK3R2* with chemotherapy side effects is limited, alterations to this pathway could potentially affect drug toxicity, including cyclophosphamide-based chemotherapy and other treatments that affect hematology [30].

Multiple studies have reported a significant association between the C>T nucleotide substitution in the *PIK3R2* gene (rs56022120) and the incidence of chemotherapy-induced neutropenia in women with breast cancer. In patients treated with a combination of cyclophosphamide, epirubicin, and fluorouracil, this variant was identified as a key risk factor. A genome-wide association study (GWAS) involving 3,252 patients (1,617 cases and 1,635 controls) demonstrated that the presence of the T allele was strongly associated with an increased risk of grade 3–4 neutropenia. Statistical analysis revealed a highly significant p-value of 2.29×10^{-6} and an OR of 3.12, indicating a strong correlation between the C>T polymorphism in PIK3R2 and susceptibility to hematological toxicity during chemotherapy. This connection is also influenced by the mTOR, PI3K, and P53 pathways, which are implicated in regulating the response to chemotherapy treatments. Thus, these SNPs have great potential to aid in understanding variations in individual responses to chemotherapy treatment and open up the possibility of developing more appropriate therapeutic strategies in the future [31].

PNPLA3

It is essential for the regulation of hepatic lipid metabolism that the *PNPLA3* gene, also known as adiponutrin, be present. It is highly linked to cirrhosis, NAFLD (non-alcoholic fatty liver disease), and an increased risk of hepatocellular carcinoma. This association is mainly associated with the rs738409 variant, which involves the substitution of isoleucine for methionine at position 148. This polymorphism may reduce the ability to metabolize lipids and increase fat accumulation in the liver, leading to susceptibility to oxidative stress. In the context of chemotherapy with drugs such as vincristine, doxorubicin, prednisone, and cyclophosphamide, *PNPLA3* has been associated with hepatotoxicity. The rs738409 variant may worsen liver damage caused by

the side effects of these drugs, especially in patients with a genetic susceptibility to fat accumulation in the liver. Doxorubicin and cyclophosphamide create stress and inflammation in the liver, and this effect is made worse by the presence of the *PNPLA3* (rs738409) genetic variation. Systemic toxicity and chemotherapeutic medication efficacy may also be affected by metabolic impairment caused by this variation [32].

Vincristine, daunorubicin, prednisone, cyclophosphamide, and asparaginase were among the chemotherapy drugs examined in a study involving patients with acute lymphoblastic leukemia (ALL). The analysis revealed that the C>G nucleotide substitution in the *PNPLA3* gene (rs738409) was significantly associated with a higher risk of severe hepatotoxicity (grade 3–4), with an OR of 2.69 (95 % CI: 1.09–6.64; p=0.029). Additionally, this variant showed a near-significant association with moderate to severe hepatotoxicity (grade 2–4), with an OR of 2.06 (95 % CI: 0.99–4.29; p=0.051), indicating its potential role in contributing to liver damage. Another study conducted in a cohort of 2,283 pediatric patients with precursor cell lymphoblastic leukemia treated with multi-agent chemotherapy regimens including cyclophosphamide, cytarabine, daunorubicin, doxorubicin, mercaptopurine, methotrexate, pegaspargase, thioguanine, and vincristine also found a significant association between the presence of the G allele and elevated liver enzyme levels. This association yielded an OR of 1.26 (95 % CI: 1.12–1.41; p=0.0001), further supporting the role of the C>G variant in *PNPLA3* as a key contributor to chemotherapy-induced hepatic toxicity [33].

Prioritization Analysis of Genes that Induce Side Effects of NHL Drugs

Patients receiving R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy are at a higher risk of liver toxicity if they have the rs738409 variant in the *PNPLA3* gene. This variant causes substitution of the amino acid isoleucine to methionine, which significantly impairs the function of *PNPLA3* in lipid metabolism in the liver. As a result, fat accumulation in the liver (hepatic steatosis) occurs, which makes hepatocytes more susceptible to damage from oxidative stress induced by hepatotoxic drugs such as doxorubicin [34]. Also, because the active medication concentration is already high in the body, the hepatic metabolic dysfunction brought on by this variant can make systemic toxicity much worse. The R-CHOP treatment includes the drugs doxorubicin and cyclophosphamide, both of which are known to induce liver cell membrane damage by producing reactive oxygen species (ROS) and liver injury by interfering with enzyme metabolic pathways in the liver. The presence of the rs738409 variant increases susceptibility to these toxicity effects, so patients with this variant require closer monitoring of liver function, such as routine measurement of ALT and AST enzymes during therapy. Personalised medicine makes use of the rs738409 variant as a biomarker to determine which patients are most likely to experience liver toxicity. This information can then be used to modify treatment plans, such as reducing the dosage of drugs that are known to be harmful to the liver or switching to safer alternatives. Thus, the identification of the rs738409 variant in the *PNPLA3* gene may contribute significantly to the safer and more effective management of cancer therapy [35].

In patients undergoing R-CHOP chemotherapy, the rs12210538 variant in the *SLC22A16* gene is linked to an elevated risk of neutropenia and cardiotoxicity [36]. The doxorubicin transporter protein is encoded by the *SLC22A16* gene; the rs12210538 variant, which is deemed «Probably Damaging,» changes the protein's function. Based on data from various genetic sources, this variant changes the amino acid methionine (Met) to Threonine (Thr) at position 375 in the OCT6 (Organic Cation Transporter 6) protein encoded by *SLC22A16*.This variant may increase the accumulation of doxorubicin in hematopoietic cells, thereby exacerbating the effects of bone marrow suppression leading to a decrease in neutrophil count. This increases the patient's susceptibility to serious infections during therapy. Additionally, this variant could heighten the danger of cardiotoxicity, as doxorubicin produces ROS that harm the heart. This is particularly true if the drug accumulates more in cardiac tissue than usual as a result of transporter malfunction. As a result, patients with this variant are more prone to cardiomyopathy or congestive heart failure, which are serious complications of doxorubicin therapy. Clinically, the presence of the rs12210538 variant in *SLC22A16* can be used as a genetic biomarker to predict toxicity, allowing clinicians to adopt mitigating measures, such as doxorubicin dose adjustment, use of cardioprotective agents such as dexrazoxane, or drug replacement with less toxic agents [12]. Furthermore, patients carrying this variant must undergo stringent monitoring of their haematologic and cardiac functions, which includes the preventative administration of granulocyte colony-stimulating factor (G-CSF) and examinations of heart function, such as echocardiography. The discovery of the rs12210538 variant has major implications for the development of personalised medicine with the goal of making cancer treatments safer and more effective.

Neutropenia toxicity in patients receiving R-CHOP treatment is significantly associated with the rs2229109 variant in the *ABCB1* gene. One transporter protein that helps cells remove medicines, including doxorubicin and other chemotherapeutic treatments, is encoded by the *ABCB1* gene [37]. Position 400 of the P-glycoprotein protein has the amino acid Serine (Ser) substituted for Asparagine (Asn) due to the rs2229109 variant. The rs2229109 variant, which is a missense variation in amino acids and has a “Possibly Damaging” rating, has the potential to decrease the transporter’s effectiveness and increase the buildup of doxorubicin in bone marrow haematopoietic cells. It is possible

that neutrophil precursors will be more severely damaged by the elevated doxorubicin concentration in haematopoietic cells, leading to severe neutropenia. Chemotherapy often causes neutropenia, a condition that puts patients at increased risk for dangerous infections. Due to less effective drug metabolism, people with the rs2229109 variant may be at a higher risk of experiencing bone marrow suppression caused by doxorubicin. In clinical practice, this variant can be utilised as a biomarker to forecast the likelihood of neutropenia in R-CHOP patients, enabling doctors to take precautions like giving G-CSF to patients before they get the treatment or adjusting the dosage of doxorubicin. If you want to catch neutropenia early, it's best to have your blood count checked more frequently. Therefore, the discovery of the rs2229109 variant in the *ABCB1* gene is significant for the control of neutropenia toxicity and lends credence to the idea that personalised medicine can enhance cancer treatment safety [38].

Individuals receiving R-CHOP chemotherapy may be at increased risk for neutropenia toxicity if they carry the rs56022120 variant in the *PIK3R2* gene. Haematopoietic cells and all other cells rely on specific signalling pathways for their survival, differentiation, and proliferation; one such pathway is encoded by the *PIK3R2* gene [39]. The rs56022120 variant, which is classified as Possibly Damaging and causes an amino acid change (missense), may disrupt the normal function of PI3K in supporting hematopoiesis. The p85-β protein, which is a regulatory subunit of phosphoinositide 3-kinase (PI3K), undergoes an amino acid change due to the rs56022120 variant in the *PIK3R2* gene. Specifically, this variant changes the amino acid Threonine (Thr) to methionine (Met) at position 196 in the protein. This disruption may lead to a decreased ability of hematopoietic precursor cells to develop into neutrophils, especially when affected by the toxicity of drugs such as doxorubicin in the R-CHOP protocol. Doxorubicin, which is one of the main components of R-CHOP, is known for its properties to cause oxidative stress and DNA damage in hematopoietic cells. The presence of the rs56022120 variant in *PIK3R2* may exacerbate these effects by weakening signaling mechanisms that protect cells from apoptosis, thereby increasing the risk of severe neutropenia [36]. Prophylactic administration of G-CSF and more stringent haematologic monitoring during treatment may be necessary for patients with this variant to reduce the likelihood of neutropenia. As a result, the discovery of the *PIK3R2* gene variant rs56022120 could pave the way for safer and more effective personalised therapy by serving as a biomarker for the prediction and management of neutropenia toxicity.

Distribution of Genetic Variants of induce advers drug reaction

NHL treatment-related adverse effects may be influenced by the distribution patterns of allele frequencies of SNP differences between groups, as shown in Table 3 and Figure 2. SNP rs738409 in the *PNPLA3* gene has an alternative allele G with

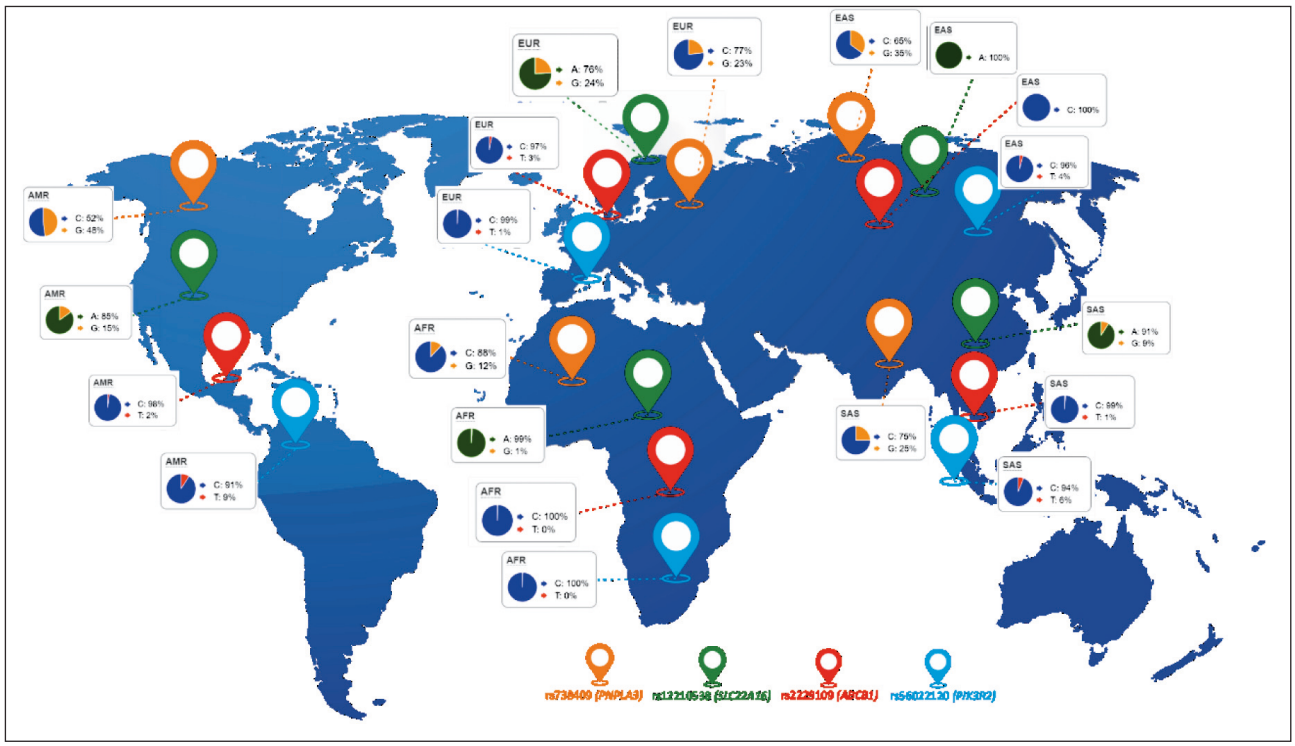

Fig. 2. An overview of allele frequency analysis for gene expression across different continents of the world. Notes: AFR – Africa; AMR – America; SAS – South Asia; EAS – East Asia Summit; EUR – Europe; created by the authors

Рис. 2. Частота аллелей экспрессии генов на разных континентах. Примечания: AFR – Африка; AMR – Америка; SAS – Южная Азия; EAS – Восточная Азия; EUR – Европа; рисунок выполнен авторами

the highest frequency in American (AMR) (0.48) and East Asian (EAS) (0.35) populations, followed by South Asian (SAS) (0.25) and European (EUR) (0.23) populations, while African (AFR) has the lowest frequency (0.12). This distribution indicates potential differences in drug response or risk of side effects between populations based on these genetic alleles. According to earlier research, the *PNPLA3* G alternative allele is linked to poor liver metabolism, which may exacerbate side effects of drugs, especially those metabolized in the liver.

Other SNPs, such as rs12210538 in the *SLC22A16* gene, showed the highest alternative G allele frequency in the EUR population (0.24) and the AMR population (0.15), while EAS had no frequency (0.00), and lower values were found in SAS (0.09) and AFR (0.01). This variation is relevant as *SLC22A16* is an organic transporter that plays a role in drug pharmacokinetics. Related studies have shown that variations in this gene may affect sensitivity to chemotherapeutic agents, such as anthracyclines, which are often used in NHL therapy. The different frequencies of these SNPs emphasize the importance of a precision medicine approach in NHL treatment, taking into account population genetic variation to optimize efficacy and minimize the risk of side effects.

Other than rs738409 and rs12210538, all of the SNPs in the table display distinct distribution patterns that should be taken into account when dealing with NHL treatment. The EUR population has the highest frequency of the alternative T allele for SNP rs2229109 in the *ABCB1* gene (0.03), while other populations, like those in AFR and EAS, have extremely low frequencies or none at all (AFR: 0.00, EAS: 0.00). The ABCB1 gene encodes P-glycoprotein, an important protein in the mechanism of drug removal from cells. Previous research has demonstrated that medication resistance can be influenced by changes in this gene, particularly in relation to specific chemotherapeutic drugs utilised to treat NHL. The low frequency in non-European people could mean that drug resistance is less likely, but it could also mean that drug toxicity from over-accumulation is more likely.

When looking at the *PIK3R2* gene SNP rs56022120, the T alternative allele was most common in the AMR population (0.09), followed by EAS (0.04), SAS (0.06), and EUR (0.01), but was completely absent in AFR (0.00). All cells, including lymphoma cells, rely on the *PI3K-Akt* signalling pathway, of which *PIK3R2* is an integral component. There has been a rise in the use of *PI3K* inhibitor-based treatments for NHL, and genetic studies on this pathway have connected certain SNP polymorphisms with varying responses to these treatments. Understanding the efficacy of targeted treatments in specific ethnic groups and the likelihood of adverse effects like metabolic dysfunction may be possible by comparing the prevalence of these alleles in various populations. Previous studies have also demonstrated that variation in the prevalence of polygenic diseases can often be explained by differences in allele frequencies across populations. For example, research on liver cancer incidence has shown that populations with higher frequencies of risk alleles tend to have a greater disease burden [40]. This supports the hypothesis that genetic variation, especially in minor alleles, contributes to the interethnic variability in drug-induced toxicity [37]. These findings highlight the relevance of considering population-specific allele distributions when developing pharmacogenomic approaches to minimize adverse drug reactions.

Thus, the variation in SNP frequencies across these populations suggests the importance of considering genetic data in the design and delivery of individualized therapies. In order to foster the creation of treatments based on precision medicine, additional research is required to validate the link between these SNPs and drug toxicity and clinical response in particular subjects. Since these genetic variants were derived from studies that utilised genomic and bioinformatics databases, it is essential to keep in mind that they have limitations. New variant annotations have been added to the PharmGKB database, which necessitates further examination. To validate the outcomes of this investigation, more testing utilising experimental and clinical trials is necessary.

Conclusion

Using a bioinformatics method, this study was able to identify SNP that may cause chemotherapy-related side effects in patients with NHL. Of the 192 SNPs that met the inclusion criteria, 11 validated SNPs showed relevance to drug toxicity, including *SLC22A16*, *GSTP1*, *NAT2*, *ATM*, *ABCB1*, *CYP2B6*, *XRCC1*, *ERCC1*, *MUTYH*, *PNPLA3*, and *PIK3R2* genes. These genetic variations affect drug metabolism and toxicity responses, such as neutropenia, hepatotoxicity, nausea, and other organ damage. Allele distribution across populations showed differences in susceptibility to drug side effects, emphasizing the importance of precision medicine approaches in NHL therapy. SNPs such as rs738409 (*PNPLA3*) and rs12210538 (*SLC22A16*) have different frequencies among populations, providing insights for personalization of therapy based on patients' genetic profiles. Prioritization analysis showed SNPs most at risk for adverse events, such as rs738409, rs12210538, rs2229109 and rs56022120. This study demonstrates the great potential of using genomic data to develop predictive biomarkers in managing adverse events of NHL therapy. However, further experimental and clinical studies are needed to validate these findings and support their clinical applicability.

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Conflict of interests

The authors declare that they have no conflict of interest.

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