Gustinanda et al. Scr Med. 2026 Jan-Feb;57(1):49-57. DOI:10.5937/scriptamed57-58439

ORIGINAL ARTICLE

Gene Variants That May Enhance the Effectiveness of Non-Hodgkin Lymphoma Therapy: Genomic and Bioinformatics Approaches

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Abstract

Background/Aim: Non-Hodgkin lymphoma (NHL) is a cancer of the lymphatic system with a high incidence rate globally. Patient responses to therapies such as chemotherapy and immunotherapy often vary, which is thought to be related to individual genetic differences. The development of genomic and bioinformatic technologies allows the identification of gene variants that play a role in the effectiveness of therapy, thus opening up opportunities for personalised treatment of NHL. This study aimed to identify genetic variants that have the potential to improve the effectiveness of therapy in NHL patients.

Methods: This study used a bioinformatics approach to analyse genetic and clinical data available in several database sources, including *PharmGKB, HaploReg v4.2, GTEx Portal* and *Ensembl*.

Results: This study identified two significant genetic variants, rs396991 in the *FCGR3A* gene and rs3957357 in the *GSTA1* gene, that play a role in improving the effectiveness of NHL therapy. The rs396991 variant showed increased affinity for IgG1 and effectiveness of antibody-dependent cellular cytotoxicity (ADCC) mechanism in rituximab therapy. Meanwhile, the rs3957357 variant in *GSTA1* was associated with better event-free survival in patients receiving R-CHOP chemotherapy. High expression of *FCGR3A* gene in immune tissues and *GSTA1* gene in liver also supports their biological roles in therapy response.

Conclusions: Genetic variations in *FCGR3A* (rs396991) and *GSTA1* (rs3957357) have potential as predictive biomarkers of R-CHOP therapy effectiveness in NHL patients. These findings support the application of genetic analysis as a basis for more personalised and effective therapeutic strategies in the treatment of NHL.

Key words: Lymphoma, non-Hodgkin; Genes; *FCGR3A*; *GSTA1*; Polymorphism, single nucleotide; rs396991; rs3957357.

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Citation:
Gustinanda R, Irham LM, Supadmi W, Amukti DP, Adikusuma W, Chong R, et al. Gene variants that may enhance the effectiveness of non-Hodgkin lymphoma therapy: genomic and bioinformatics approachess. Scr Med. 2026 Jan-Feb;57(1):49-57.

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Received: 24 April 2025
Revision received: 31 May2025
Accepted: 31 May 2025

Introduction

Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of lymphatic system cancers, with great variation in clinical presentation, disease course and response to therapy.[1, 2] Although immunochemotherapy regimens such as rituximab, cyclophosphamide, doxorubicin,

vincristine and prednisolone (R-CHOP) have become the standard of care and provide favourable outcomes in some patients, many experience therapeutic failure or significant toxicity.[3] Clinical factors such as the International Prognostic Index (IPI) have been used to predict therapeutic outcomes, but have not been able to fully explain the differences in response between individuals.[4]

Recent years have seen a rise in the focus on host genetic variables as potential causal factors. The efficacy and toxicity of R-CHOP regimens may be influenced by single nucleotide polymorphisms (SNPs) in genes involved in drug metabolism, detoxification, transport and immune response, according to pharmacogenetic research.[5] For NHL, the gold standard therapy is R-CHOP.[6] Enzymes belonging to the cytochrome P450 family that catalyse the conversion of cyclophosphamide to its active form as well as the metabolism of vincristine and prednisone; isoforms of glutathione S-transferase that aid in the detoxification of doxorubicin and vincristine as well as the scavenging of oxygen radicals from doxorubicin; ATP-binding cassette transporters that expedite the removal of doxorubicin, vincristine and prednisone from cells; subunits of NAD(P)H oxidase that contribute to the formation of oxygen radicals; glucocorticoid receptors; and Fcγ receptors that are involved in the cellular cytotoxicity mechanism caused. Understanding the role of SNPs in these genes provides a strong basis for the development of more personalised therapies.[7-11]

This article aimed to identify the role of gene variants in improving the effectiveness of NHL therapy through genomic and bioinformatic approaches.

Methods

This study used a bioinformatics approach to analyse genetic and clinical data available in several database sources, including *PharmGKB, HaploReg v4.2*, *GTEx Portal* and *Ensembl*.[12, 13] The research steps included:

Identification of gene variants that increase the effectiveness of NHL therapy

Data from *PharmGKB* were used to identify associations between polymorphisms and therapeutic efficacy. SNPs were filtered from the *PharmGKB* database based on Level of Evidence (LOE) ranging from 3 to 1A, which represents moderate to strong pharmacogenomic associations. To ensure statistical and clinical relevance, only variants supported by cohort studies involving more than 100 individuals and showing a p-value < 0.01 were included in the analysis. Functional validation was conducted using *HaploReg* v4.2 to identify whether the SNPs were located in coding regions, affected transcription factor binding

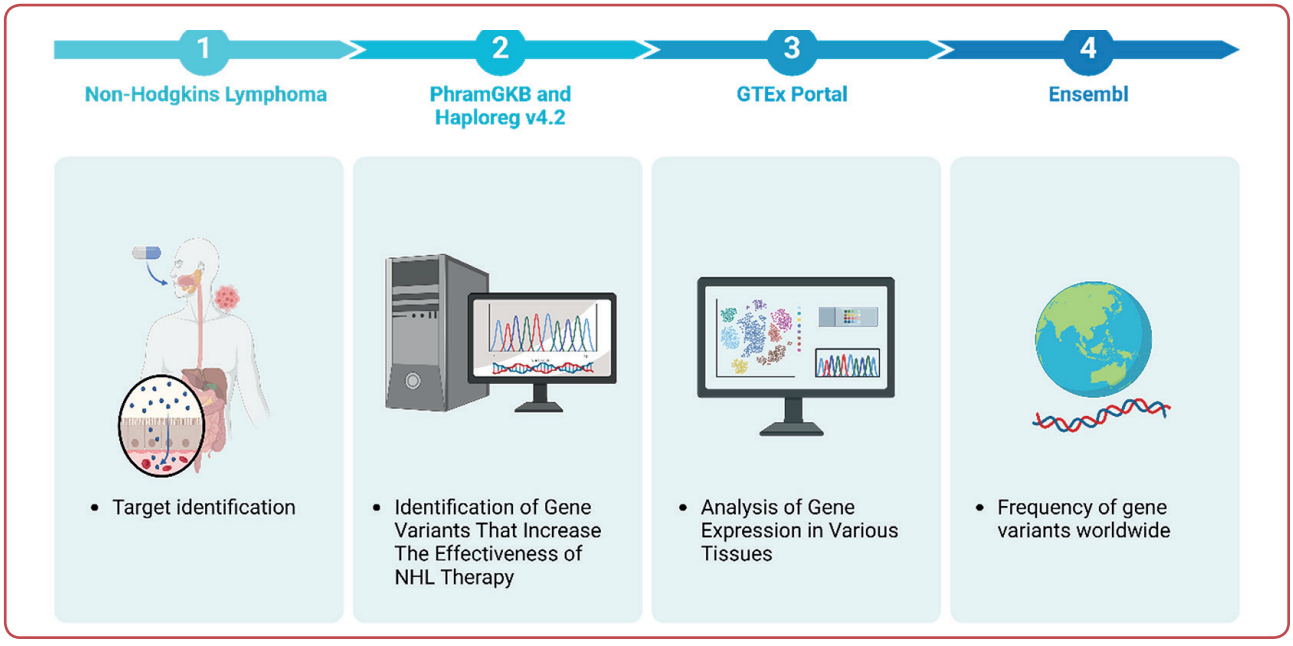


Figure 1: The bioinformatics process used to discover gene variants that increase the effectiveness of non-Hodgkin lymphoma drugs

sites, or were linked with regulatory motifs. This analysis was performed by comparing therapeutic outcomes (therapeutic response) between individuals with genotypes to NHL treatment.

Gene expression analysis in various tissues

Data from the *GTEx Portal* were used to explore gene expression in various body tissues, especially spleen and blood vessels, which play an important role in NHL cancer pathogenesis. Comparison of gene expression between individuals with different genotypes was performed to see differences in expression patterns that may affect response to therapy.[12, 14]

Frequency of gene variants worldwide

Using the *Ensembl* database to search gene sequences and look for polymorphisms associated with efficacy.[15] These polymorphisms were then linked to the affinity between the receptor and the drug in a population with NHL (Figure 1).

Results

Based on research that has been conducted, it was found that SNP can affect the effectiveness of NHL treatment (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone), which was identified through the *PharmGKB* database. A total of 90 SNPs of effectiveness accessed on 11 February 2025 associated with therapeutic effectiveness met the inclusion criteria and showed significance based on LOE 1A-3. This LOE was determined based on the number of studies supporting an association between genetic variation and drug response, with support from cohort studies involving more than 100 samples and showing SNP significance ($p < 0.01$).[16]

SNPs obtained from *PharmGKB* were further validated for gene coding and missense expression using *HaploReg v4.2*, resulting in 2 validated SNPs associated with therapeutic efficacy (Table 1). This validation is important to ensure that the identified SNPs have a significant clinical impact in determining patient response to LNH chemotherapy therapy.

The results of *FCGR3A* gene expression analysis showed that this gene is highly expressed in immune system tissues, particularly lymph, lymphocytes and immune-related organs such as tonsils and spleen (Figure 2). Violin plot images

Table 1: Genetic variants and their relationship with drug efficacy in non-Hodgkin lymphomas

Variant	Genes	Sig	N	Phenotype categories	Drugs	Association
rs396991	*FCGR3A*	Yes	113	Efficacy	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP therapy)	Allele C is associated with increased complete response rate when treated with rituximab in people with lymphoma, large B-Cell, diffuse as compared to allele A
rs3957357	*GSTA1*	Yes	106	Efficacy	Cyclophosphamide, doxorubicin, prednisone, rituximab, vincristine	AA + AG Patients with the AA + AG genotype and diffuse large B-cell lymphoma may have a longer event-free survival time when treated with the R-CHOP chemotherapy regimen as compared to patients with the GG genotype. Other genetic and clinical factors may also influence event-free survival time

Sig: significance; N: number of cases;

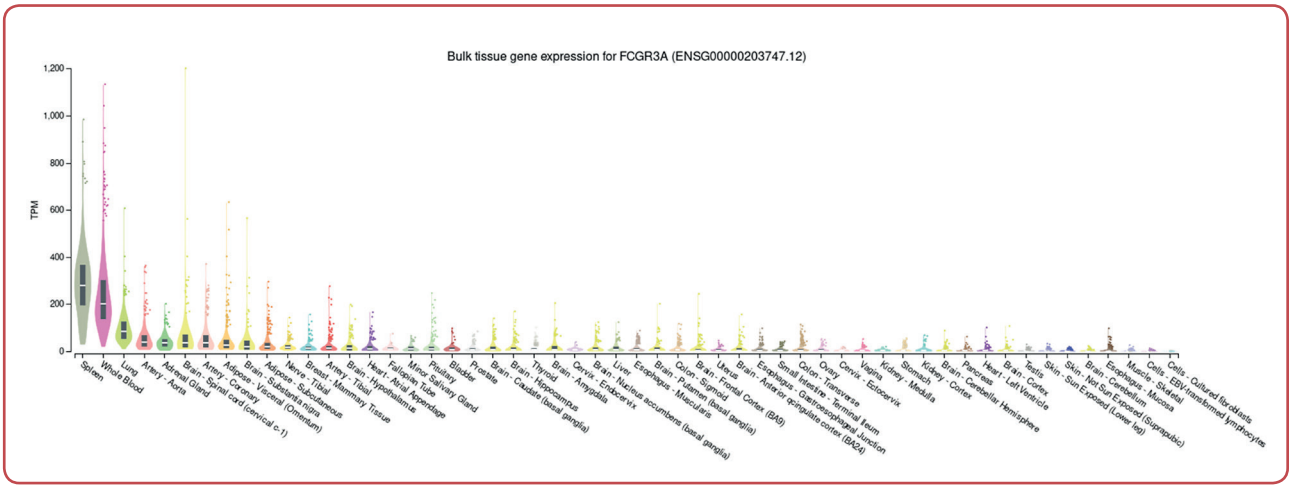


Figure 2: *Bulk tissue gene expression for FCGR3A (ENSG00000203747.12)*

showed that the highest expression levels were found in lymphocytes and lymphatic tissues, reflecting the major role of *FCGR3A* in the modulation of immune responses, especially in the activation of natural killer (NK) cells and phagocytes through the mechanism of antibody-dependent cellular cytotoxicity (ADCC). Expression was also detected in tissues such as lung and liver, albeit at a lower intensity. This expression pattern strengthens the understanding that *FCGR3A* has an important contribution in the body's immune defense function, as well as potential as a biomarker in the study of cancer diseases and autoimmune disorders involving immune cell activity in lymphatic tissues.[17, 18]

Expression analysis of the *GSTA1* gene showed that it is highly expressed in metabolic tissues, especially the liver (Figure 3). Violin plot images show that the highest expression levels were consistently found in liver tissue, reflecting the major role of *GSTA1* during xenobiotic detoxification and oxidative stress protection by means of its glutathione S-transferase enzyme activity. Expression was also detected in other tissues such as the terminal ileum of the small intestine, pancreas and kidney, albeit in lower levels. Meanwhile, most other tissues, including brain tissue, skeletal muscle and the reproductive system, showed very low to undetectable expression. This expression pattern supports the under-

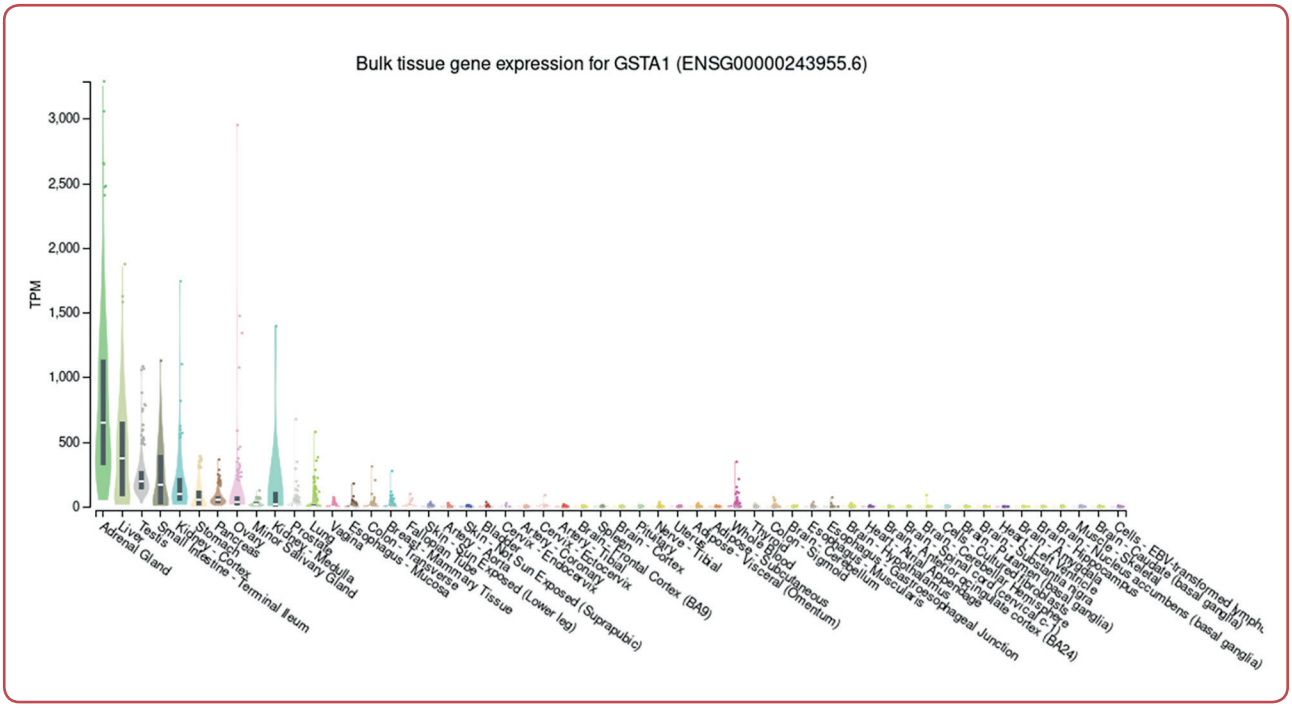
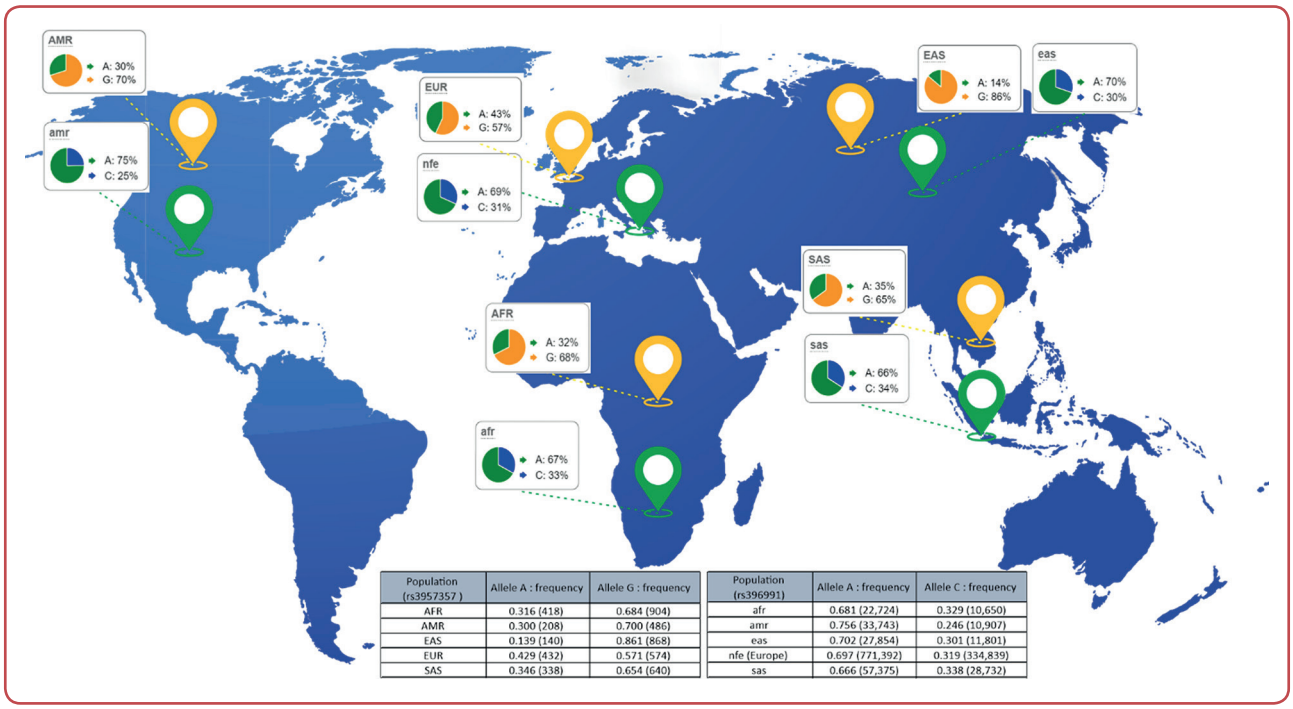


Figure 3: *Bulk tissue gene expression for GSTA1 (ENSG00000243955.6)*



Population (rs3957357)	Allele A : frequency	Allele G : frequency
AFR	0.316 (418)	0.684 (904)
AMR	0.300 (208)	0.700 (486)
EAS	0.139 (140)	0.861 (868)
EUR	0.429 (432)	0.571 (574)
SAS	0.346 (338)	0.654 (640)

Population (rs396991)	Allele A : frequency	Allele C : frequency
afr	0.681 (22,724)	0.329 (10,650)
amr	0.756 (33,743)	0.246 (10,907)
eas	0.702 (27,854)	0.301 (11,801)
nfe (Europe)	0.697 (771,392)	0.319 (334,839)
sas	0.666 (57,375)	0.338 (28,732)

Figure 4: Allele frequencies of FCGR3A and GSTA1 gene variants in various populations

standing that *GSTA1* plays an important role in the metabolic and detoxification functions of organs, particularly the liver and may have potential as a biomarker in the study of liver disease, toxin exposure, or metabolic disorders related to oxidative stress.[13, 19]

Genetic allele frequency analysis of *FCGR3A* (rs396991) showed significant variation among global populations (Figure 4). The A allele was the dominant allele in all populations observed, with the highest frequency found in African populations (AFR) at 75 % in the America (AMR) and 67 % in Africa. Other populations such as Europe (EUR), East Asia (EAS) and South Asia (SAS) showed A allele frequencies of 69 %, 70 % and 66 %, respectively, while the C allele had relatively lower frequencies, ranging from 25 % to 34 %. This distribution pattern indicates that *FCGR3A* allelic variants had a wide but uneven distribution, which may be related to natural selection, immunological adaptation to the environment, or human migration history. This allelic variation is important in the context of immune response, as SNP rs396991 in *FCGR3A* is known to affect Fcγ-RIIIa receptor activity, which impacts the efficiency of ADCC mechanisms, as well as sensitivity to antibody-based therapies such as rituximab.

Genetic allele frequency analysis of *GSTA1* (rs3957357) showed considerable variation among global populations. The G allele was the dominant allele in almost all populations observed, with the highest frequency found in EAS populations at 86 %, followed by AFR at 68 % and AMR at 70 %. On the other hand, populations such as EUR and SAS showed lower frequencies of the G allele at 57 % and 65 %, respectively. In contrast, the A allele has a higher frequency in certain populations such as the AMR with a frequency of 75 % and the AFR at 67 %, suggesting a difference in frequency between subpopulation groups within a region. EUR and SAS populations showed A allele frequencies of 69 % and 66 % respectively, while in EAS populations, the A allele was minor with a frequency of only 14 %. This variation is important to note because the rs3957357 allele in *GSTA1* is known to play a role in regulating the expression of the *GSTA1* gene, which has an important function in the hepatic detoxification process through the glutathione pathway. Therefore, this difference in allele frequency may have an impact on an individual's response to drug exposure.

Discussion

Genetic variations in the *FCGR3A* and *GSTA1* genes have a significant influence on an individual's response to drug therapy used to treat NHL. This can be seen in Figure 5.

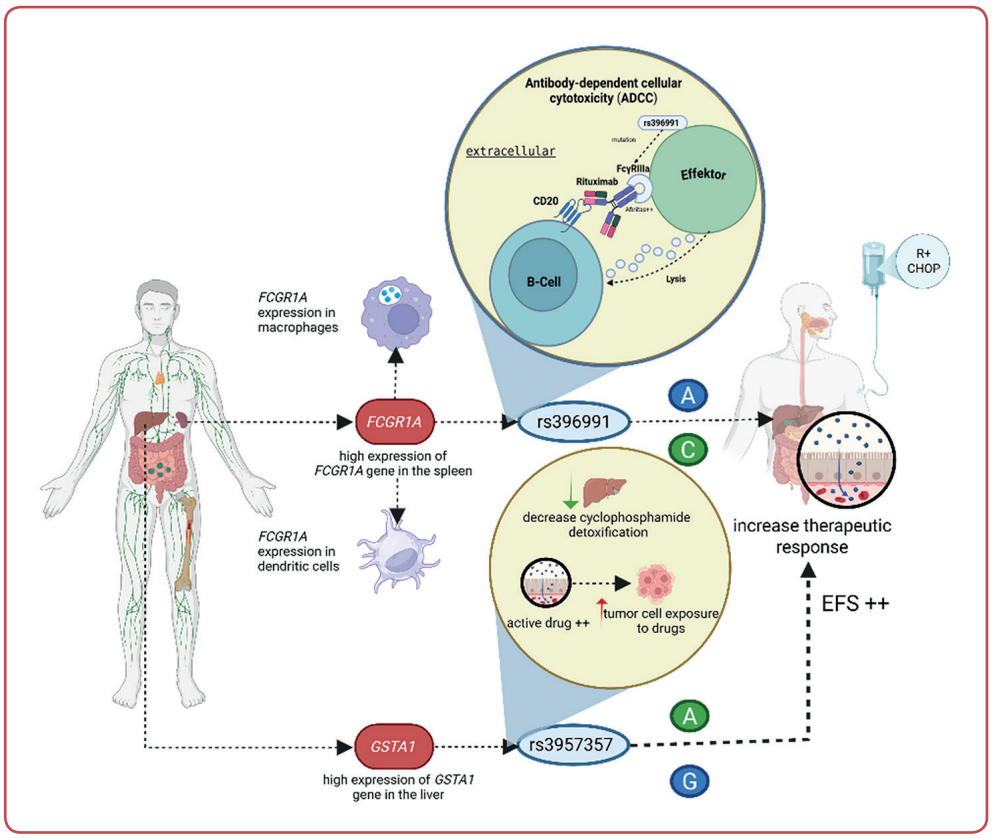


Figure 5: The mechanism of FCGR3A and GSTA1 genes affecting the effectiveness of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) regimen

FCGR3A

The Fc division of IgG is bound to the Fc gamma receptor, which is abbreviated as FcγR.[20] Every member of the immunoglobulin superfamily is an FcγR. FcγRs play a significant role in several effector activities of the immune system, including opsonised phagocytosis, release of inflammatory mediators and cellular cytotoxicity that is reliant on antibodies. Based on their affinity, three distinct types of FcγRs have been identified. There are other types of FcγRs, including FcγRI (CD64), FcγRII (CD32) and FcγRIII (CD16), which are classified as low-affinity receptors. There is a highly conserved region outside of cells that all three types of FcγRs share. Only macrophages, NK cells, myeloid precursor cells, neutrophil cell lines and macrophage cell lines include the Fc gamma receptor III (CD16). The gamma Fc III receptor's expression on macrophages is controlled by IFN-γ. The gamma Fc III receptor is responsible for mediating ADCC, which is antigen-dependent cellular cytotoxicity.[21]

Individual differences in the FCGR3A gene greatly impact the efficacy of pharmacological treatment for NHL. As seen in Figure 4, researchers found that individuals with diffuse large B-cell lymphoma (DLBCL) who had the C allele were more likely to have a full response to rituximab treatment than those with the A allele. This lends credence to the idea that the clinical response to immunochemotherapy treatments like R-CHOP (which includes rituximab) is heavily influenced by genetic variables and more specifically by certain allelic variations. There is still much mystery around the precise mechanism of action of R-CHOP therapy in the treatment of DLBCL.

The monoclonal antibody rituximab binds to cancerous B cells by recognising and eliminating their CD20 antigen.[22, 23] The ADCC pathway, which is triggered by effector cells via the FcR of immunoglobulin G (IgG) fragment, is responsible for the mechanism of action.[24, 25] Inheritance differences in the FcγR, which is implicated in the ADCC pathway, are anticipated to impact Rituximab's efficacy. Because these genetic variants may influence the affinity of rituximab for ADCC effector cells,[9] they explain how FcR polymorphisms influence responsiveness to R-CHOP treatment for DLBCL.

In NHL cancer therapy rituximab, an anti-CD20 monoclonal antibody, works by targeting B lymphoma cells and triggering ADCC through in-

teraction with FcγRIIIa receptors on immune effector cells.[26] The rs396991 mutation in the *FCGR3A* gene affects the affinity of Fc receptors to rituximab, thus contributing to differences in patient response to therapy. Individuals with the C allele have a higher binding affinity to IgG1 (rituximab antibody class), which increases the effectiveness of ADCC and therapeutic response. This is consistent with study Kim et al,[9] that the *FCGR3A* gene variant had a significant impact on improving faster complete response (CR) in NHL patients undergoing R-CHOP therapy (p = 0.022; HR: 1.654; 95 % CI: 1.076-2.542). In addition, a low IPI score was identified as a favourable prognostic factor for both overall survival (OS) (P = 0.007; HR: 0.199; 95 % CI: 0.061-0.646) and event-free survival (EFS) (p < 0.001; HR: 0.107; 95 % CI: 0.042-0.271). Therefore, genetic variation in *FCGR3A* is an important factor in the prediction of patient response to rituximab and can be used in personalised medicine approaches for optimisation of NHL therapy.[9]

GSTA1

This gene produces a protein that belongs to an enzyme family involved in attaching electrophilic compounds, including as carcinogens, medicines, environmental contaminants and oxidative stress byproducts, to glutathione. This mechanism plays a key role in neutralising and eliminating these harmful compounds. A specific subgroup of this enzyme family contributes significantly to cellular defence against reactive oxygen species and lipid peroxidation byproducts. Genetic polymorphisms in this gene may influence an individual's capacity to process various drugs. It is found within a genomic region that includes related genes and pseudogenes on chromosome 6. Additionally, alternative splicing of this gene generates multiple transcript variants.[26]

When it comes to patients with DLBCL, the clinical success of the R-CHOP chemotherapy regimen is heavily influenced by the rs3957357 mutation in the *GSTA1* gene. Researchers have shown that GG genotype patients had a shorter event-free survival (EFS) time after receiving R-CHOP compared to AA or AG genotype patients. This improved outcome suggests a potential pharmacogenomic advantage associated with the presence of the A allele. The longer EFS observed in patients with the AA or AG genotype could be attributed to differences in the expression or activity of the *GSTA1* enzyme, which is involved in the detoxification pathway. Increased enzyme activity in these genotypes may lead to more efficient metabolism and clearance of chemotherapeutic agents, resulting in lower toxicity and better therapeutic outcomes. In contrast, individuals with the GG genotype are associated with shorter EFS in the same treatment, possibly due to reduced *GSTA1* activity. This may lead to less optimal drug metabolism, higher systemic toxicity or lower drug efficacy, ultimately affecting the overall response to chemotherapy.[26]

GSTA1 an enzyme encoded by this gene, is involved in the detoxification of drugs such as cyclophosphamide and its active metabolites by conjugating them with glutathione.[27] As a result, the medicine is more soluble in water and may be eliminated from the body more quickly. But the rs3957357 mutation is linked to *GSTA1* enzyme downregulation, which means alkylating drugs like cyclophosphamide are less effectively detoxified. Consequently, the amount of time that tumor cells spend exposed to medicines increases. A lower risk of events (HR: 0.38; 95 % CI: 0.20-0.72; p = 0.003) was associated with the *GSTA1* rs3957357 genotype in DLBCL patients undergoing R-CHOP, which is in agreement with a research by Rossi et al.[28] Presented results support *GSTA1* rs3957357's role as a possible NHL predictive biomarker.

This study was limited by the exclusive use of secondary data from public databases. The SNP associations observed may also be confounded by population stratification, linkage disequilibrium with other variants, or environmental exposures. To strengthen the findings, future studies should include prospective validation using genotyped NHL patient samples with detailed clinical response data. Functional assays are also needed to confirm the biological impact of these SNPs on protein expression and drug interaction. Integration with epigenetic and transcriptomic data may further refine the role of these variants in treatment outcomes.

Conclusion

This study successfully identified two important genetic variants that have the potential to improve the effectiveness of NHL thera-

py, namely rs396991 in the *FCGR3A* gene and rs3957357 in the *GSTA1* gene. The rs396991 variant (allele C) in the *FCGR3A* gene is known to increase affinity to IgG1, thus strengthening the ADCC mechanism which is key to the effectiveness of rituximab therapy in the R-CHOP regimen. Meanwhile, the rs3957357 variant in the *GSTA1* gene plays a role in the detoxification process of chemotherapy drugs, where AA or AG genotypes are associated with better event-free survival (EFS) than GG genotypes. These findings suggest that genetic variation plays an important role as a predictive biomarker of therapeutic effectiveness, opening up opportunities for the application of personalised medicine in the clinical management of NHL.

Ethics

This study did not involve human or animal subjects directly, but was conducted using publicly available secondary data from databases. Therefore, no additional ethical approval from a research ethics committee was required. All data used have been anonymised and are freely accessible for scientific research purposes. This study was conducted in accordance with the principles of scientific research ethics and does not violate the privacy or confidentiality of individual data.

Acknowledgement

We would like to express our sincere gratitude to the "Program Penelitian dan Pengabdian kepada Masyarakat Tahun Anggaran 2025 Republik Indonesia No 0419/C3/DT.05.00/2025" for their valuable support of our study.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

Community Service, Directorate General of Research and Development, Ministry of Higher Education, Science, and Technology of the Republic of Indonesia for their support of this study under grant numbers 126/C3/DT.05.00/PL/2025, 0498.12/ll5 INT/AL.04/2025, 72/PTM/LPPM.UAD/V/2025.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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