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Review Article

Pharmacogenomics of Pediatric Oncology: Genetic Predictors of Chemotherapy Toxicity in Children

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Abstract

Chemotherapy-induced toxicity remains a significant challenge in pediatric oncology, affecting treatment outcomes, quality of life, and long-term survival. Inter-individual variability in drug response is partly explained by genetic polymorphisms affecting drug metabolism, transport, and pharmacodynamics. This review examines recent advances in pharmacogenomics of chemotherapy-induced toxicity in pediatric cancer patients, focusing on genetic predictors of serious adverse reactions to commonly used anticancer agents. A comprehensive literature review was conducted examining pharmacogenomic studies published between 2020-2025, focusing on validated genetic markers associated with chemotherapy toxicity in pediatric populations. Significant progress has been made in identifying genetic variants that predict toxicity to thiopurines (TPMT, NUDT15), anthracyclines (SLC28A3, RARG, CBR2), vincristine (CEP72, ABCC1, SLC5A7), and platinum-based agents (ACYP2, TPMT). These variants influence drug metabolism, transport, and cellular sensitivity through various mechanisms. Meta-analyses and large international cohorts have validated several associations, with some achieving clinical implementation.Pharmacogenomic testing offers promise for personalized chemotherapy dosing in pediatric oncology. However, challenges remain regarding clinical implementation, standardization of phenotyping, and the need for validation across diverse populations. Future research should focus on multi-gene risk prediction models and integration into clinical decision-making tools.

Keywords: *Novel drug delivery systems, nanoparticles, smart delivery, stimuli-responsive, personalized medicine, bioavailability, targeted therapy*

1. Introduction

The remarkable improvement in pediatric cancer survival rates over the past five decades, now exceeding 85% for many malignancies, represents one of the most significant achievements in modern medicine [1]. This success has been largely driven by risk-stratified treatment protocols employing intensive multi-agent chemotherapy regimens. However, the use of highly cytotoxic agents at maximum tolerated doses comes at a considerable cost, with the majority of pediatric cancer survivors experiencing at least one serious treatment-related toxicity during therapy, and many developing long-term complications that significantly impact quality of life [2,3]

Chemotherapy-induced toxicities in children are particularly concerning due to several factors unique to the pediatric population. Developing organ systems may be more susceptible to damage, toxic effects can impair growth and development, and survivors face decades of potential long-term sequelae. Additionally, the inability of young children to reliably report subjective symptoms complicates early detection and management of toxicities such as peripheral neuropathy and ototoxicity [4]

Substantial inter-individual variability exists in susceptibility to chemotherapy-induced adverse effects, even among children receiving identical treatment protocols. While clinical factors such as age, cumulative drug dose, and concomitant therapies contribute to this variability, germline genetic variation has emerged as a critical determinant of individual risk [5] Pharmacogenomics, the study of how genetic variation influences drug response, offers an opportunity to identify patients at highest risk for serious toxicities before treatment initiation, enabling personalized dose modifications or alternative therapeutic strategies [6].

This review examines the current state of pharmacogenomics in predicting chemotherapy-induced toxicity in pediatric oncology, focusing on genetic markers with robust evidence from recent studies (2020-2025). We discuss validated associations for major drug classes including thiopurines, anthracyclines, vinca alkaloids, and platinum-based agents, and evaluate progress toward clinical implementation of pharmacogenomic testing.

2. Pharmacogenomics Of Thiopurine Toxicity

2.1 Thiopurine Agents in Pediatric Cancer

Thiopurine drugs, including mercaptopurine (6-MP), azathioprine, and thioguanine, are essential components of treatment protocols for acute lymphoblastic leukemia (ALL), which accounts for approximately 25% of pediatric malignancies [7]. During the maintenance phase of ALL therapy, which extends 2-3 years, thiopurines represent the backbone of treatment. However, severe myelosuppression, hepatotoxicity, and gastrointestinal toxicities necessitate dose reductions or treatment interruptions in a significant proportion of patients, potentially compromising therapeutic efficacy [8].

2.2 TPMT Pharmacogenetics

Thiopurine S-methyltransferase (TPMT) catalyses the S-methylation of thiopurine drugs, representing a major pathway of drug inactivation. Genetic polymorphisms in TPMT resulting in decreased or absent enzyme activity have been recognized as clinically actionable pharmacogenetic markers for over two decades [9]. The most common variant alleles (3A, 3B, 3C, and 2) occur with varying frequencies across ethnic populations, being more prevalent in individuals of European ancestry (5-10%) compared to Asian populations (1-3%) [10].

The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides evidence-based guidelines for TPMT genotype-directed thiopurine dosing. Patients with homozygous variant genotypes (poor metabolizers) require dose reductions of 85-90%, while heterozygous carriers (intermediate metabolizers) typically require 30-70% dose reductions to prevent life-threatening myelosuppression [11].

2.3 NUDT15 Pharmacogenetics

The discovery of NUDT15 (Nudix Hydrolase 15) as a major determinant of thiopurine tolerance in 2014 represented a breakthrough in explaining thiopurine intolerance in East Asian populations where TPMT variants are relatively rare [12]. The most common variant allele, NUDT15*3 (rs116855232, c.415C>T, p.R139C), occurs at significantly higher frequencies in Asian populations (10-20%) compared to European or African populations (<1%) [13].

Recent studies have demonstrated additive effects of TPMT and NUDT15 variants on thiopurine toxicity. A large international study across multiethnic pediatric ALL cohorts demonstrated that patients with compound intermediate metabolizer status (TPMT IM/NUDT15 IM) required greater dose reductions than single IM patients, highlighting the importance of considering both genes in clinical decision-making [14]. Updated CPIC guidelines now incorporate both TPMT and NUDT15 genotyping to optimize thiopurine dosing across diverse populations [15]. Table 1 presents the Major Pharmacogenomic Markers for Thiopurine-Induced Toxicity.

Table 1. Major Pharmacogenomic Markers for Thiopurine-Induced Toxicity

Gene	Major Variant Alleles	Frequency (Population)	Clinical Impact	CPIC Recommendation
TPMT	*3A (rs1800460 + rs1142345) *3B (rs1800460) *3C (rs1142345) *2 (rs1800462)	5-10% (European) 1-3% (Asian)	Severe myelosuppression, hepatotoxicity	IM: 30-70% dose reduction PM: 85-90% dose reduction
NUDT15	*3 (rs116855232) c.415C>T (p.R139C)	10-20% (East Asian) <1% (European, African)	Severe myelosuppression, hair loss, infections	IM: 50-70% dose reduction PM: 90% dose reduction
TPMT + NUDT15	Compound IM/IM genotype	1.2% (multiethnic cohorts)	Additive risk - more severe toxicity	Greater dose reduction required (median 25.7 mg/m²)

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; IM, intermediate metabolizer; PM, poor metabolizer.

Source*: Data compiled from references [9, 10, 11, 12, 14].*

2.4 Additional Genetic Markers

Beyond TPMT and NUDT15, several candidate genes have been investigated for associations with thiopurine toxicity. Variants in ITPA (inosine triphosphate pyrophosphatase), IL6, and CRIM1 have shown associations with myelosuppression in specific cohorts, though these require validation in larger, independent populations before clinical implementation [16,17]. Recent whole-exome sequencing studies suggest that interplay between multiple genetic variants may better explain toxicity risk in patients with wild-type TPMT and NUDT15 [18].

2. Anthracycline-Induced Cardiotoxicity

3.1 Clinical Significance

Anthracyclines, including doxorubicin, daunorubicin, and epirubicin, are critical components of treatment protocols for leukemias, lymphomas, and solid tumors in children. However, anthracycline-induced cardiotoxicity (AIC) remains a major dose-limiting toxicity, affecting 10-16% of pediatric patients and potentially manifesting decades after treatment completion [19]. The irreversible nature of anthracycline cardiomyopathy and its impact on long-term survival and quality of life underscore the critical need for risk prediction strategies [20].

3.2 SLC28A3 and Drug Transport

The most robustly replicated pharmacogenomic association with AIC involves variants in SLC28A3 (solute carrier family 28 member 3), which encodes a concentrative nucleoside transporter. A genome-wide association study followed by multi-center replication identified the synonymous variant rs7853758 (c.1383T>G, p.L461L) as protective against anthracycline-induced cardiac dysfunction, with an odds ratio of approximately 0.3-0.4 across multiple pediatric cohorts [21]. This protective effect appears to be mediated through altered expression of a nearby long non-coding RNA (SLC28A3-AS1) rather than changes in the SLC28A3 protein sequence [22].

Recent mechanistic studies using patient-derived induced pluripotent stem cell cardiomyocytes (hiPSC-CMs) have validated the cardioprotective role of this locus and identified potential therapeutic interventions, including the tricyclic antidepressant desipramine, which mimics the protective genetic effect [23].

3.3 RARG and Retinoic Acid Signalling

A candidate gene study identified rs2229774 in RARG (retinoic acid receptor gamma) as significantly associated with increased risk of AIC in children [24]. This variant results in an amino acid substitution (p.Ser427Leu) in the ligand-binding domain of the receptor. Functional studies suggest that the variant allele may alter cellular response to oxidative stress and apoptotic signalling triggered by anthracyclines [25]. Table 2 shows the Pharmacogenetic Markers in Anthracycline-Induced Cardiotoxicity

Table 2. Pharmacogenetic Markers in Anthracycline-Induced Cardiotoxicity

Gene	Variant	Function	Effect on Risk	Replication Status
SLC28A3	rs7853758 (c.1383T>G, p.L461L)	Nucleoside transporter	OR 0.3-0.4 (protective)	Multiple independent pediatric cohorts; strongest evidence
RARG	rs2229774 (p.Ser427Leu)	Retinoic acid receptor gamma	Increased risk	Replicated in multiple cohorts; functional validation
CBR3	Multiple variants	Carbonyl reductase (anthracycline metabolism)	Variable	Inconsistent across studies; requires further validation
CELF4	rs1786814	RNA-binding protein (cardiac biology)	Dose-dependent	Replicated; effect >300 mg/m² cumulative dose
GSTM1	Null deletion	Glutathione S-transferase (antioxidant defense)	Increased risk	Replicated in multiple pediatric cohorts
SULT2B1 ABCB4	Multiple variants	Sulfotransferase (SULT2B1); Drug transporter (ABCB4)	Sex-specific effects	SULT2B1 in males; ABCB4 in females

Abbreviations: OR, odds ratio.
Sources: Data compiled from references [21, 22, 23, 24, 25, 26, 27].

3.4 Additional Genetic Determinants

Multiple candidate gene studies have identified associations with variants in genes involved in anthracycline metabolism (CBR3, CBR1), antioxidant defense (GSTM1), and cardiac biology (CELF4, HAS3) [26]. A recent systematic review

identified CBR2, CELF4, GSTM1, HAS3, RARG, and SLC28A3 as genes with replicated associations in pediatric cohorts [27]. However, sex-specific effects have been noted for several variants, including SULT2B1 (males) and ABCB4 (females), suggesting complex gene-environment interactions [27]. Figure 1 shows the Mechanisms of Anthracycline-Induced Cardiotoxicity and Pharmacogenetic Modifiers.

4. Vincristine-Induced Peripheral Neuropathy

4.1 Clinical Impact

Vincristine, a microtubule-disrupting vinca alkaloid, is used in treatment protocols for ALL, lymphomas, neuroblastoma, and various solid tumors. Vincristine-induced peripheral neuropathy (VIPN) occurs in 30-78% of treated children, manifesting as sensory loss, motor weakness, and neuropathic pain [28]. Severe VIPN necessitates dose reductions or treatment delays, potentially compromising disease control. Unlike many chemotherapy toxicities, VIPN can persist for years after treatment completion, significantly impacting quality of life [29].

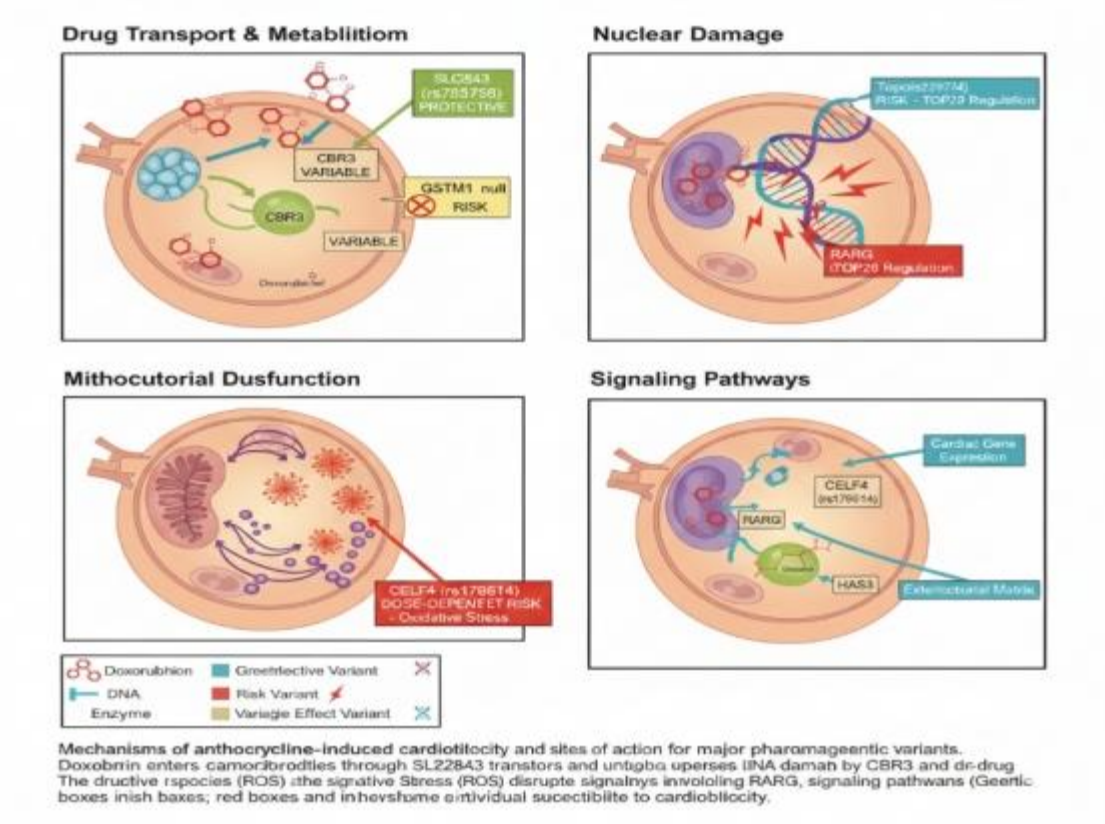
4.2 CEP72 Polymorphisms

The landmark genome-wide association study by Diouf et al. identified rs924607 in the promoter region of CEP72 (centrosomal protein 72) as significantly associated with VIPN risk [30]. The variant T allele results in decreased CEP72 expression, which sensitizes neurons to vincristine-induced damage. Functional studies demonstrated that reduced CEP72 expression compromises microtubule formation through mechanisms distinct from vincristine, essentially "lowering the threshold" for vincristine neurotoxicity [31].

This association has been replicated in multiple independent cohorts, with meta-analyses confirming odds ratios of 2-3.5 for the risk genotype [32,33]. However, the association appears most robust in patients receiving prolonged vincristine therapy during continuation treatment, with less consistent findings during induction therapy, suggesting time-dependent or cumulative dose-dependent effects [34].

4.3 Drug Transport Genes

Variants in ATP-binding cassette (ABC) transporters have shown associations with VIPN. A Canadian pharmacogenomics study identified ABCC1 rs3784867 as significantly associated with VIPN (OR 4.9), suggesting that altered vincristine efflux from neurons may modify toxicity risk[35]. Additionally, SLC5A7, which is involved in choline transport and has connections to hereditary neuropathies, showed strong association with VIPN (OR 8.6) [35]



Mechanisms of anthocycline-induced cardiotilocity and sites of action for major pharamageentic variants. Doxobrin enters camordbrodties through SL22843 transtors and untgbo uperses IINA damah by CBR3 and dr-drug The dructive rspocies (ROS) othe signative Stress (ROS) disrupte signalnys invololing RARG, signaling pathwans (Geertic boxes inish baxes; red boxes and inhevshome eirtividual sucectibilite to cardiobliocity.

Figure 1: Mechanisms of Anthracycline-Induced Cardiotoxicity and Pharmacogenetic Modifiers
Sources: Adapted from references [21,24,26,27]

Table 2. Genetic Variants Associated with Vincristine-Induced Peripheral Neuropathy

Gene	Variant (rsID)	Effect/Location	Odds Ratio (95% CI)	Proposed Mechanism
CEP72	rs924607 (T allele)	Promoter region	2.0-3.5 (meta-analysis)	Decreased CEP72 expression sensitizes neurons to vincristine; impaired microtubule formation
ABCC1	rs3784867	Coding region	4.9 (2.0-12.1)	Altered vincristine efflux from neurons
SLC5A7	rs1013940	Intronic	8.6 (1.9-39.8)	Choline transport; linked to hereditary neuropathies
NRG3	Novel variants (GWAS)	Multiple loci	HR 0.36 (protective)	Neuregulin signaling; neuronal protection
ACTN1	Novel variants (GWAS)	Multiple loci	Protective (combined with NRG3)	Alpha-actinin; cytoskeletal organization

Abbreviations: CI, confidence interval; GWAS, genome-wide association study; HR, hazard ratio. Data compiled from references [30, 31, 32, 33, 34, 35, 36].

4.4 Novel GWAS Findings

A recent genome-wide association study in over 1,100 pediatric patients identified 13 novel genomic variants associated with VIPN risk or protection [36]. Notably, protective variants in NRG3 (neuregulin 3) and ACTN1 (alpha-actinin 1) showed additive effects, with patients carrying both variants experiencing substantially reduced neuropathy incidence (HR 0.36). These findings highlight the complexity of VIPN genetics and suggest that multiple biological pathways contribute to individual susceptibility [36]. Figure 2 presents the Schematic representation of genetic variants affecting Vincristine Pharmacokinetics and Pharmacodynamics in Peripheral Neuropathy.

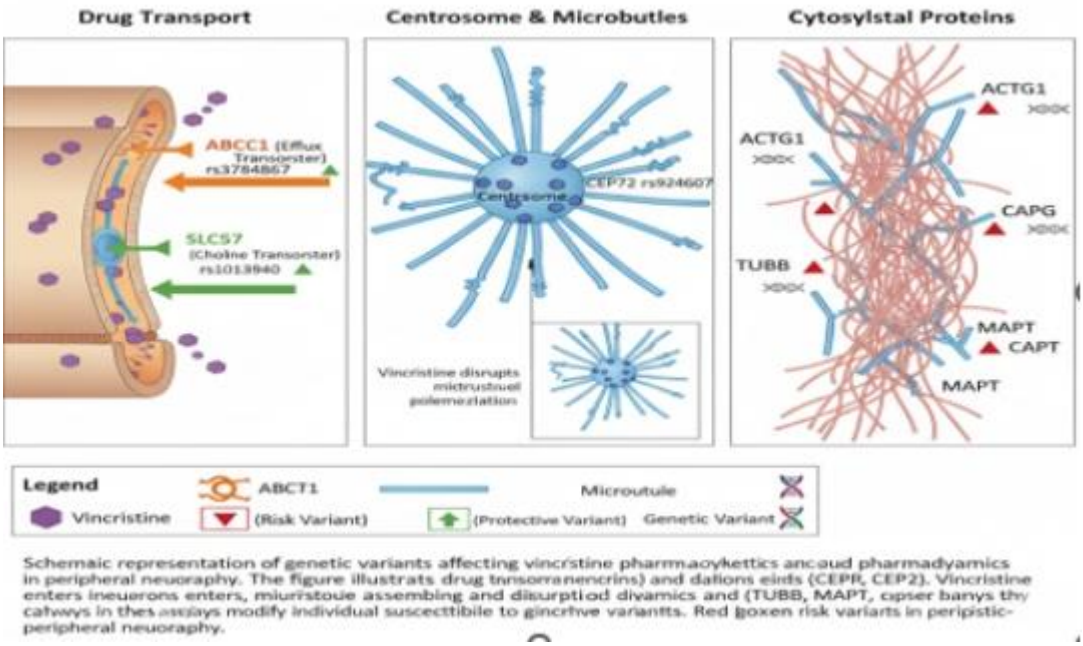


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Figure 2: Schematic representation of genetic variants affecting Vincristine Pharmacokinetics and Pharmacodynamics in Peripheral Neuropathy.

Sources: Adapted from references [30,32,35,36]

5. Platinum-Induced Ototoxicity

5.1 Cisplatin Ototoxicity

Platinum-based agents, particularly cisplatin, are essential for treating medulloblastoma, neuroblastoma, osteosarcoma, and germ cell tumors. Cisplatin-induced ototoxicity affects 40-70% of pediatric patients, manifesting as irreversible, bilateral, high-frequency sensorineural hearing loss [37]. In young children, hearing impairment during critical developmental periods can profoundly affect language acquisition, academic performance, and social development [38].

5.2 ACYP2 Polymorphisms

The ACYP2 (acylphosphatase 2) gene emerged from genome-wide association studies as a robust predictor of cisplatin ototoxicity across both pediatric and adult populations. The variant rs1872328 has been associated with significantly increased ototoxicity risk in multiple independent cohorts [39]. While the precise mechanism remains unclear, ACYP2 is expressed in cochlear tissues and may influence cellular response to cisplatin-induced damage. Recent meta-analyses have confirmed consistent associations (OR 3.9-5.9) across diverse populations [40,41].

5.3 Controversial TPMT and COMT Associations

Early candidate gene studies reported strong associations between variants in TPMT (rs12201199) and COMT (rs9332377, rs4646316) with cisplatin ototoxicity in children [42]. However, subsequent replication attempts have yielded inconsistent results, with some large studies failing to confirm these associations [43,44]. A 2023 systematic review by the Canadian Pharmacogenomics Network for Drug Safety concluded that while ACYP2 shows consistent association with ototoxicity, the evidence for TPMT remains controversial and may be population-specific or confounded by concurrent therapies [45].

5.4 Additional Genetic Factors

Variants in genes associated with Mendelian hearing loss syndromes, including WFS1, have shown associations with cisplatin ototoxicity, suggesting that baseline genetic predisposition to auditory dysfunction may modify drug-induced hearing damage [46]. Additionally, variants in drug transport genes (SLC22A2/OCT2) and DNA repair genes (ERCC2, XPC, GSTP1) have been implicated, though

require validation in adequately powered cohorts [47,48]. Figure 3 shows the Schematic illustration of the Major Pharmacogenomic variants and Chemotherapy toxicities.

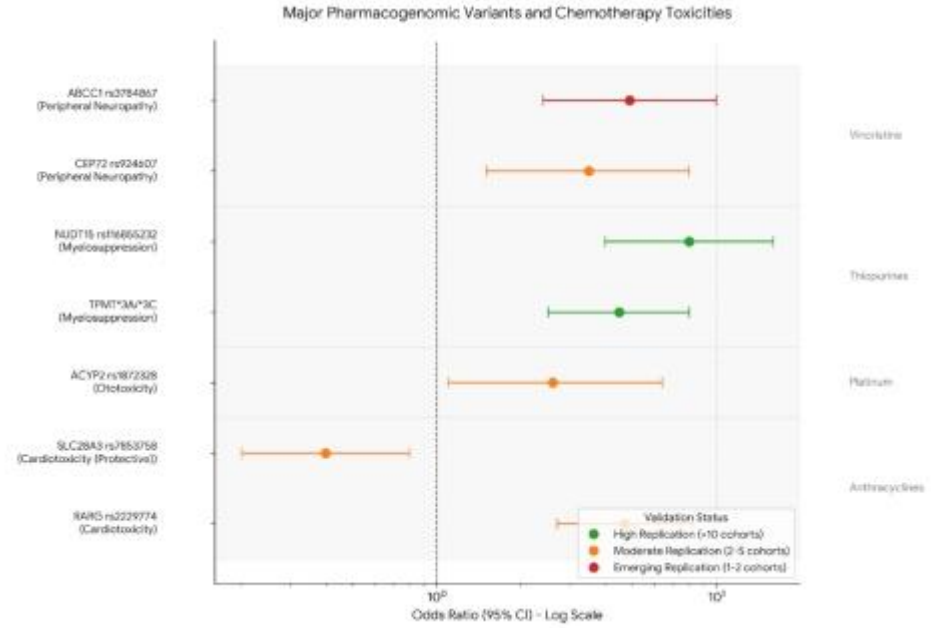

Figure 3: A Schematic illustration of the Major Pharmacogenomic variants and Chemotherapy toxicities. Sources: Authors illustration compiled from references [11,14,21,32,40]

6. Clinical Implementation and Challenges

6.1 Current State of Clinical Implementation

Despite substantial pharmacogenomic evidence, clinical implementation remains limited. TPMT genotyping prior to thiopurine therapy represents one of the few widely adopted pharmacogenetic tests in pediatric oncology, with many centers routinely testing patients before initiating mercaptopurine [49]. The recent addition of NUDT15 to CPIC guidelines has prompted expanded testing panels, particularly in centers serving diverse patient populations [50].

Preemptive pharmacogenomic testing panels that include TPMT, NUDT15, and other actionable variants are being piloted at several major pediatric cancer centers. Cost-effectiveness analyses suggest that combined TPMT/NUDT15 testing provides substantial cost savings by preventing severe myelosuppression and associated hospitalizations [51].

6.2 Barriers to Implementation

Several challenges impede broader clinical adoption of pharmacogenomics in pediatric oncology. First, inconsistency in study results, often due to small sample sizes, heterogeneous phenotype definitions, and population differences, limits confidence in many gene-drug associations. Second, for most toxicities, no validated multi-gene risk prediction models exist that integrate genetic and clinical risk factors. Third, the actionability of genetic information varies considerably—while dose adjustments are well-established for TPMT/NUDT15, appropriate interventions for other genetic risks remain unclear. Finally, implementation requires integration of genetic testing into clinical workflows, development of clinical decision support tools, and education of healthcare providers [52].

6.3 Ethical Considerations

Pharmacogenomic testing in pediatric populations raises unique ethical considerations. Since most genetic variants represent germline polymorphisms, testing generates information with potential implications beyond cancer therapy. Parents and patients should be informed about the scope and limitations of testing, including uncertainty in risk prediction and limited options for risk mitigation for many variants. Additionally, equitable access to testing and concerns about health disparities must be addressed, as many pharmacogenomic studies have been conducted primarily in populations of European ancestry [53].

7. Future Directions

7.1 Multi-Gene Risk Models

Future research should focus on developing and validating multi-gene risk prediction models that integrate multiple genetic variants with clinical risk factors. Machine learning approaches may prove useful in identifying complex gene-gene and gene-environment interactions. Recent studies have

demonstrated proof-of-concept for multi-marker models predicting anthracycline cardiotoxicity and thiopurine myelosuppression [54].

7.2 Functional Validation

Mechanistic understanding of genetic associations through functional studies is essential for moving beyond statistical associations to biological understanding. Patient-derived induced pluripotent stem cells, CRISPR-based gene editing, and other emerging technologies offer powerful tools for validating and characterizing genetic variants [23]. Such functional validation can inform therapeutic strategies, as demonstrated by the identification of desipramine as a potential cardioprotective agent based on SLC28A3 pharmacogenomics [23].

7.3 Implementation Science

Research is needed to develop effective strategies for implementing pharmacogenomic testing in routine clinical practice. This includes developing clinical decision support tools, establishing standardized protocols for result interpretation and clinical action, and demonstrating clinical utility and cost-effectiveness. Collaborative efforts such as the implementing GeNomics In pracTicE (IGNITE) network are addressing these challenges [55].

7.4 Health Disparities

Most pharmacogenomic studies have been conducted in populations of European ancestry, limiting generalizability to other populations. Substantial differences in allele frequencies across populations are well-documented for TPMT, NUDT15, and other pharmacogenes. Future studies must include diverse populations to ensure equitable benefit from precision medicine approaches. Additionally, research is needed to understand how genetic ancestry interacts with social determinants of health in influencing treatment outcomes [56].

8. Conclusion

Pharmacogenomics holds substantial promise for personalizing cancer therapy in children by identifying those at highest risk for serious treatment-related toxicities. Genetic variants in TPMT and NUDT15 (thiopurine toxicity), SLC28A3 and RARG (anthracycline cardiotoxicity), CEP72 and ABCC1 (vincristine neuropathy), and ACYP2 (cisplatin ototoxicity) have achieved varying levels of validation and clinical implementation. While TPMT genotyping has become standard practice in many centers, implementation of other pharmacogenetic tests remains limited.

Key challenges include the need for larger validation studies in diverse populations, development of multi-gene risk prediction models, demonstration of clinical utility beyond risk prediction, and addressing implementation barriers. As genomic technologies become more accessible and affordable, integration of preemptive pharmacogenomic testing into routine pediatric oncology care becomes increasingly feasible. Ultimately, the goal is to achieve optimal balance between treatment efficacy and toxicity for each individual patient, maximizing cure rates while minimizing both acute and long-term treatment-related morbidity.

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Author Contributions

The author has significantly contributed to the study's conception, design, data collection, analysis, and interpretation. All authors were involved in writing the manuscript or critically reviewing it for its intellectual value. They have reviewed and approved the final version for submission and publication and accept full responsibility for the content and integrity of the work.

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Conflicts of Interest

The authors state that there are no financial, personal, or professional conflicts of interest associated with this research.

Ethical Approvals

This research did not involve the use of human participants or animal subjects and therefore did not require ethical clearance

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