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REVIEW ARTICLE

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Pharmacogenetics for severe adverse drug reactions induced by molecular-targeted therapy

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Abstract

Molecular-targeted drugs specifically interfere with molecules that are frequently overexpressed or mutated in cancer cells. As such, these drugs are generally considered to precisely attack cancer cells, thereby inducing fewer adverse drug reactions (ADRs). However, molecular-targeted drugs can still cause characteristic ADRs that, although rarely severe, can be life-threatening. Therefore, it is becoming increasingly important to be able to predict which patients are at risk of developing ADRs after treatment with molecular-targeted therapy. The emerging field of pharmacogenetics aims to better distinguish the genetic variants associated with drug toxicity and efficacy to improve the selection of therapeutic strategies for each genetic profile. Here, we provide an overview of the current reports on the relationship between genetic variants and molecular-targeted drug-induced severe ADRs in oncology.

KEYWORDS

adverse drug reaction, molecular-targeted drug, pharmacogenetics, polymorphism, precision medicine

1 | INTRODUCTION

The medical field is becoming inundated with a rapidly growing selection of tools to treat cancer, including the new suite of cytotoxic drugs, molecular-targeted drugs, and immune checkpoint inhibitors used to complement chemotherapy and radiotherapy. Although chemotherapy regimens have improved considerably in recent years and remain a mainstay treatment choice, there is still large variability in the efficacy and toxicity of these regimens among individual patients, along with physical and mental distress, decreased patient quality of life (QOL), and a varied set of typical adverse drug reactions (ADRs).[1,2] While it is of course preferable to select drugs that produce the maximum therapeutic effect with minimal ADR, such stratified treatment for patients with cancer is still rudimentary, and tailoring therapy to each individual patient, in what is commonly referred to as "personalized or precision medicine," is still somewhat based on trial and error.

In recent years, there has been significant progress in the field of pharmacogenetics, which aims to identify the genetic variants associated with toxicity and drug response. This, in turn, allows physicians to select a more targeted therapeutic strategy to suit the genetic profile of each patient (Figure 1).[3] Pharmacogenetics follows 2 main approaches: (1) the candidate gene approach and (2) the genome-wide approach. In the candidate gene approach, genetic association studies are carried out on specific genes that are thought to be related to drug metabolism (pharmacokinetics: PK) or drug response (pharmacodynamics: PD). These genes of interest are precisely targeted, with assays conducted to ascertain the involvement of these genes in particular disease states or phenotypes. The genome-wide approach, conversely, is much less specific, with various

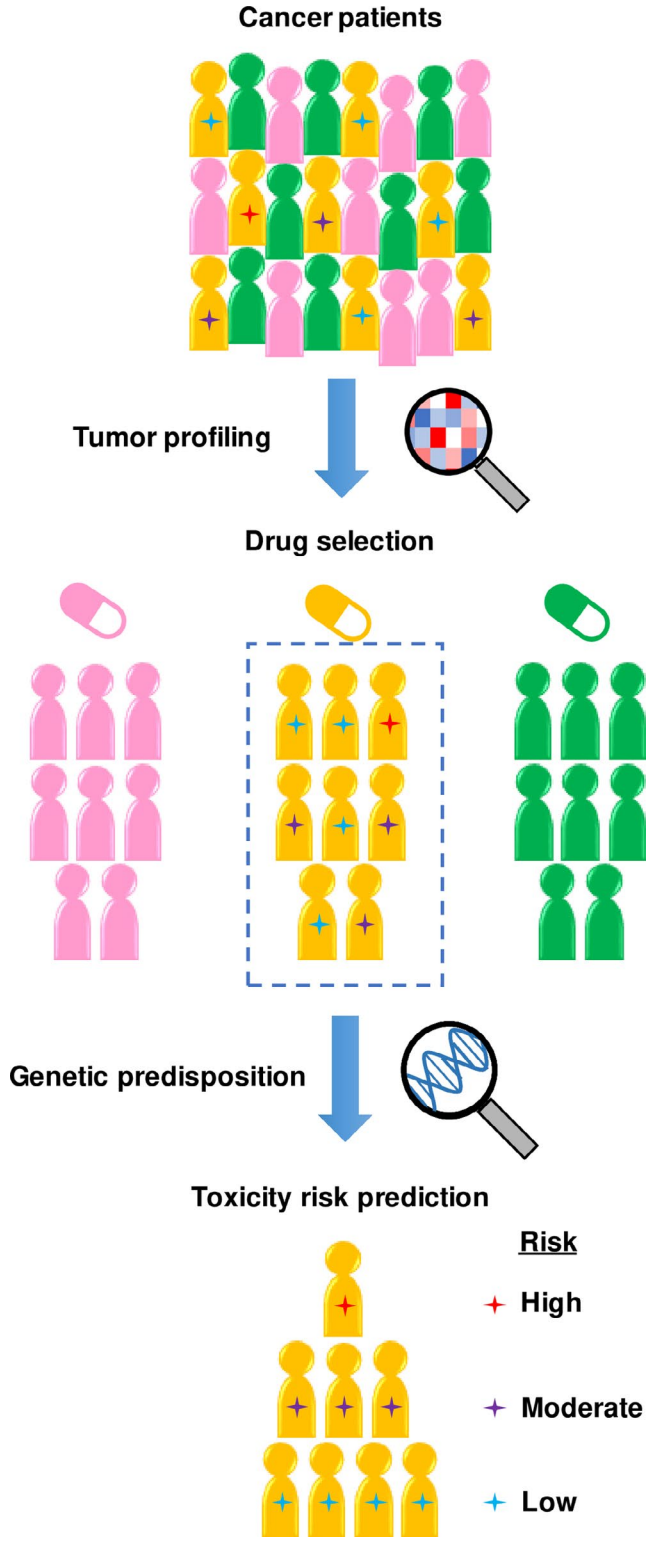

FIGURE 1 Schematic representation of the use of genetic profiles for personalized therapy. Pharmacogenetics contributes to select a more targeted and low-risk therapeutic strategy

genomic interrogative tools, such as whole-exome or whole-genome sequencing, used to scan the genome to identify genetic variants, such as single nucleotide polymorphisms (SNPs), insertions/deletions, or copy number variations, that may be linked with various conditions.[4,5] These genome-wide investigations tend to be large-scale studies, whereas the candidate gene approach tends to hone in on a few genes involved in a specific pathway or cellular mechanism. Both approaches, however, provide insight into the genetic basis of drug efficacy and toxicity; albeit, the results, at times, can be unpredictable and often overlap.

One recent notable result was the association between a germline polymorphism in uridine glucuronosyltransferase 1A1 (*UGT1A1*) and irinotecan-induced neutropenia.[6] Irinotecan is used to treat various cancers, such as lung, gastric, and colorectal cancers. Through detailed genetic analyses, it was revealed that patients harboring *UGT1A1*28/*28*, *UGT1A1*28/*6* or *UGT1A1*6/*6* genotypes were likely to develop neutropenia if treated with irinotecan.[7] Neutropenia, defined as an abnormally low count of a type of neutrophil, can lead to a higher risk of infection. This knowledge thus allows for the appropriate selection of patients without these genotypes for irinotecan treatment. Similar associations have been shown for various other drug-gene combinations. For example, a germline polymorphism in nudix hydrolase 15 (*NUDT15*) is associated with severe leukopenia or alopecia totalis in Asian persons, which are induced by thiopurine drugs: purine antimetabolites that are used to treat types of leukemia and other autoimmune diseases.[8,9]

The use of pharmacogenetic testing in the clinical setting is still limited to a few drugs, but genetic testing is covered by insurance in the USA, Japan, and some other countries.[7,10,11] In Japan, only the aforementioned 2 genetic tests (*UGT1A1* and *NUDT15*) are covered by insurance to avoid or predict the likelihood of the patient developing severe ADRs in response to cancer treatment. At present, none of the genetic tests for molecular-targeted drug-induced severe ADRs are covered by insurance. Therefore, it is becoming increasingly important to identify variants associated with drug response and toxicity for the plethora of clinically available drugs to improve treatment safety and to help physicians select the best treatment strategy in medical decision making. This review summarizes the current reports on the relation between genetic variants and molecular-targeted drug-induced severe ADRs in oncology.

2 | MOLECULAR-TARGETED THERAPY AND ADVERSE DRUG REACTIONS IN ONCOLOGY

Molecular-targeted drugs are a newer type of anticancer drug that have been used to treat cancer since the late 1990s.[12] The more recently developed molecular-targeted drugs are based on tumor molecular profiling, and this has led to a marked change in the concept of treatment selection among patients with cancer.[13] These drugs are designed to interfere with the expression of genes (proteins) that are frequently overexpressed or mutated in cancer cells, and thus these drugs are considered to attack cancer cells specifically, thereby leading to fewer ADRs.[14] However, in some cases, there are specific ADRs that depend on drug-targeted molecules and signaling pathways. Severe ADRs, such as cardiotoxicity and interstitial lung

TABLE 1 Genetic variants associated or potentially associated with trastuzumab-induced cardiotoxicity

Reference	Ethnicity	N	Approach	Gene	Variant	Alleles	Odds ratio (95%CI)	*P*-value	Definition of cardiotoxicity	Effect on PK/PD for trastuzumab
Beauclair et al[18]	White	61	Candidate gene	*ERBB2*[a]	rs1136201	A > G (Ile655Val)	NA	5.80E−03	Decrease in LVEF (≥20% reduction)	NR
Roca et al[19]	White	132	Candidate gene	*ERBB2*[a]	rs1136201	A > G (Ile655Val)	3.83 (1.11-13.18)	2.50E−02	Decrease of LVEF below 50% at least once during the treatment, and/or loss of mean LVEF, which was defined as a relative reduction from baseline of more than 15% at the last follow-up evaluation compared to the baseline, or discontinuation of trastuzumab if the patient decides to stop treatment, in case of cardiac toxicity or other clinical intolerance (at the discretion of the investigator) or patient's decision	NR
Lemieux et al[20]	White	73	Candidate gene	*ERBB2*[a]	rs1136201	A > G (Ile655Val)	5.87 (1.33-25.82)	2.00E−02	Decrease of at least 10% from baseline with a resulting LVEF < 50% at follow-up or any decrease resulting in LVEF < 45%	NR
Stanton et al[21]	White	140	Candidate gene	*ERBB2*[a]	rs1058808	C > G (Pro1170Ala)	2.60 (1.02-6.62)	4.60E-02	Either symptomatic congested heart failure or a decline in LVEF of 15% (or if the LVEF < 55%, a decline in LVEF of 10%) that resulted in at least temporary discontinuation of trastuzumab	NR
Boekhout et al[22]	White	206	Candidate gene	*ERBB2*[a]	rs1058808	C > G (Pro1170Ala)	0.09 (0.02-0.45)	3.00E−03	Decrease in LVEF of more than 15% compared with baseline or a decrease to an absolute value of LVEF below 45%	NR
Serie et al[25]	White	800	GWAS	*LDB2*	rs55756123	C > T	NA	8.93E−08	Linear regression was used for change in LVEF (lowest recorded LVEF−baseline LVEF)	NR
				BRINP1	rs10117876	T > C	NA	5.86E−07		NR
				Intergenic	rs4305714	C > T	NA	1.39E−06		NR
				RAB22A	rs707557	C > T	NA	5.62E−06		NR
				TRPC6	rs77679196	G > A	NA	7.72E−06		NR
				LINC01060	rs7698718	C > A	NA	7.73E−06		NR

(Continues)

TABLE 1 (Continued)

Reference	Ethnicity	N	Approach	Gene	Variant	Alleles	Odds ratio (95%CI)	*P*-value	Definition of cardiotoxicity	Effect on PK/PD for trastuzumab
Nakano et al[24]	Japanese	481	GWAS	Intergenic	rs9316695	C > A	4.46 (2.30-8.47)	6.00E−06	LVEF < 45% or LVEF < 50% with an absolute decrease of 10% from baseline	NR
				Intergenic	rs28415722	G > A	5.48 (2.21-13.69)	8.88E−05		NR
				Intergenic	rs7406710	C > T	6.64 (2.19-27.01)	1.07E−04		NR
				Intergenic	rs11932853	T > C	3.20 (1.70-6.23)	1.42E−04		NR
				Intergenic	rs8032978	A > G	5.83 (2.30-13.51)	1.60E−04		NR
Udagawa et al[23]	Japanese	243	WES	*EYS*	rs139944387	T > C	13.73 (4.27-44.21)	5.60E−04	≥10% decrease of LVEF compared with before trastuzumab treatment	NR

Abbreviations: GWAS, genome-wide association study; LVEF, left ventricular ejection fraction; NR, not reported; PK/PD, pharmacokinetic/pharmacodynamic; WES, whole-exome sequencing.
[a]Target molecule of trastuzumab.

disease (ILD), although not as common, can be life-threatening, and it is important to be able to predict which patients have a high-risk of developing such complications before commencing therapy by identifying how these drugs lead to ADRs through pharmacogenetic and pharmacodynamic analyses. Next, we focus on the pharmacogenetic associations established to date for some of the more frequently used anticancer agents.

3 | PHARMACOGENETICS OF ADRS

3.1 | HER2 inhibitor: Trastuzumab

Trastuzumab (Herceptin) is a humanized monoclonal antibody that is used to treat human epidermal growth factor receptor (EGFR) type 2 (HER2)-positive cancers. Trastuzumab binds to the extracellular domain of HER2, and prevents the activation of HER2 signaling, inducing antibody-dependent cellular cytotoxicity (ADCC).[15,16] However, one of the most serious side effects of trastuzumab is cardiotoxicity, with approximately 5% of patients developing left ventricular ejection fraction decline.[17] As a result, there has been significant focus on the gene encoding HER2, Erb-b2 receptor tyrosine kinase 2 (*ERBB2*), as a means to identify polymorphisms associated with trastuzumab-induced cardiotoxicity. In particular, the germline Ile655Val polymorphism is associated with trastuzumab-induced cardiotoxicity in White patients.[18-20] Cells expressing the Ile655Val polymorphism show higher growth capacity and increased sensitivity to trastuzumab in vitro.[18] Similarly, the germline polymorphism Pro1170Ala in *ERBB2* is also a predictor of trastuzumab-induced cardiotoxicity.[21,22] However, these particular SNP-based associations remain contentious among White populations, and have not been confirmed in Japanese patients.[23,24] This discrepancy may be in part due to differences in the definition of cardiotoxicity among studies (Table 1) or interethnic differences in allele frequency.[23]

A genome-wide association study (GWAS) in a White population identified germline SNPs in numerous other genes as potential genetic markers of trastuzumab-induced cardiotoxicity: rs55756123 in LIM domain binding 2 (*LDB2*); rs10117876 in BMP/retinoic acid-inducible neural-specific 1 (*BRINP1*); rs707557 in RAB22A, member RAS oncogene family (*RAB22A*); rs77679196 in transient receptor potential cation channel subfamily C member 6 (*TRPC6*); rs7698718 in long intergenic non-protein coding RNA 1060 (*LINC01060*); and rs4305714 in intergenic region on chromosome 6p22.3 ($P = 8.93 \times 10^{-8}$ to 7.73×10^{-6}).[25] In another GWAS study, 5 germline loci (rs9316695 on chr13q14.3, rs28415722 on chr15q26.3, rs7406710 on chr17q25.3, rs11932853 on chr4q25, and rs8032978 on chr15q26.3) were associated with trastuzumab-induced cardiotoxicity among a Japanese cohort ($P = 6.00 \times 10^{-6}$ to 1.60×10^{-4}; odds ratio (OR) = 3.20 to 6.64). Using these 5 SNPs, a predictive scoring system was designed and shown to be capable of predicting the risk of cardiotoxicity prior to trastuzumab therapy ($P = 7.82 \times 10^{-15}$).[24]

Finally, some rare germline genetic variants have been analyzed in a Japanese population following treatment with trastuzumab, and a possible association between trastuzumab-induced cardiotoxicity and rs139944387 in Eyes shut homologs (*EYS*) has been reported ($P = 5.60 \times 10^{-4}$, OR = 13.73).[23]

3.2 | EGFR inhibitor: Gefitinib and erlotinib

EGFR is a cell-membrane receptor tyrosine kinase. EGFR signaling is frequently activated in cancer through somatic mutations in the coding sequence of the *EGFR* gene or following overexpressing of the receptor.[26] Thus, EGFR has long been an attractive target for cancer treatment, and has incited the development of a range of antibodies and inhibitors. Gefitinib (Iressa) and erlotinib (Tarceva) are 2 well characterized drugs that selectively inhibit EGFR tyrosine kinase.[27,28] However, EGFR is also expressed in normal tissues and plays an important role in cell proliferation, differentiation, and other aspects of tissue development.[29] As such, EGFR tyrosine kinase inhibitors (TKIs) also result in ADRs in treated patients.

Several studies have sought to investigate associations between germline genetic polymorphisms in *EGFR* and the typical ADRs that develop in response to EGFR-TKI treatment. The simple sequence CA repeat in intron-1 of the *EGFR* gene is associated with *EGFR* mRNA expression and protein levels[26,30] and patient responses to gefitinib (eg, patients harboring shorter lengths of germline CA repeat showed improved progression-free survival).[31,32] However, there have been no reports of a significant association between this polymorphism and skin or gastrointestinal toxicity.[29,33-35] In contrast, in an Italian cohort, 3 different EGFR germline polymorphisms, −216G > T, −191C > A, and R497K, were associated with gefitinib-induced grade ≥ 2 diarrhea ($P < .01$; $P < .001$; and $P = .02$, respectively) but not with grade ≥ 2 skin rash ($P = .31$, .99, and .99, respectively).[33]

Various other studies have explored the pharmacogenomics of EGFR inhibitors with genes involved in drug transport and metabolism. Whereas the germline polymorphism rs2231137 in ATP binding cassette subfamily G member 2 (*ABCG2*) was significantly associated with skin rashes ($P = .046$) in a Japanese population, both germline polymorphisms rs1045642 in *ABCB1* and rs2231142 in *ABCG2* were not.[36] In a Chinese population, associations were found between erlotinib-induced ADRs (eg, skin rash and/or digestive tract injury) and the germline polymorphisms rs1064796 in cytochrome P450 family 4 subfamily F member 11 (*CYP4F11*) and rs10045685 in UDP glycosyltransferase family 3 member A1 (*UGT3A1*) ($P = .003$ and .017, respectively).[37]

One of the most severe ADRs is drug-induced ILD (DIILD), with an extremely high mortality rate.[38] Although pharmacogenetic studies for EGFR-TKI-induced ILD are limited, interethnic differences in its frequency exist between Japanese (1.6% to 4.3%) and non-Japanese (0.3% to 1.0%) populations.[38] Such interethnic differences may indicate that, although a drug regime will work for 1 cohort, it may not work or may work differently in another cohort, potentially resulting in unpredictable ADRs.[39] In a case-control association study, whole-genome sequencing was performed on germline DNA samples from 13 Japanese patients with lung cancer and EGFR-TKI-induced ILD (compared with population controls).[40] Although 7 single nucleotide variants (SNVs) (rs75399069, rs417168, rs442281, rs17690253, rs184448987, rs10165147, and rs1348851) showed possible associations with ILD ($P = 2.39 \times 10^{-6}$ to 8.59×10^{-6}, OR = 6.06 to 154.04) (Table 2), no SNVs reached a significance level because the sample size was too small.

3.3 | Multikinase inhibitor: Sunitinib

Sunitinib (Sutent) is a small-molecule multikinase inhibitor that targets a range of receptor tyrosine kinases, including vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), platelet-derived growth factor receptors (PDGFRα and PDGFRβ), Kit receptor, Fms-like tyrosine kinase-3 receptor (FLT3), and the receptor encoded by the ret proto-oncogene (*RET*).[41] Multikinase inhibitors like sunitinib are known to cause diverse ADRs, including liver injury, hypertension, diarrhea, mucositis, myelotoxicity, and hand-foot syndrome.[42] These ADRs can lead to treatment delays (38% of patients), dose reduction (32%), and treatment discontinuation (8%).[43] Asian patients have been noted to have a higher incidence of severe sunitinib-induced toxicities compared with White patients.[44,45]

Several previous studies have reported associations between SNPs in various genes that are related to the PK and PD of sunitinib, and sunitinib-induced ADRs (Table 3).[46-52] In particular, in Japanese patients with severe ADRs, the germline polymorphism rs2231142 in *ABCG2* is significantly associated with grade ≥ 3 thrombocytopenia ($P = 8.41 \times 10^{-3}$, OR = 1.86)[53]; whereas, in Korean patients with severe ADRs, the same germline polymorphism is associated with grade ≥ 3 thrombocytopenia ($P = .04$, OR = 9.90), grade ≥ 3 neutropenia ($P = .02$, OR = 18.20), and grade ≥ 3 hand-foot syndrome ($P = .01$, OR = 28.46) (Table 3).[54] Two studies with White patients found associations between the germline polymorphism rs4646437 in *CYP3A4* and grade ≥ 3 hypertension ($P = .021$, OR = 2.43)[55] and any toxicity at grade ≥ 3 ($P = .03$, OR = 0.27).[56]

3.4 | Vascular endothelial growth factor (VEGF) inhibitor: Bevacizumab

Bevacizumab (Avastin) is a humanized monoclonal antibody that targets VEGF and blocks VEGF binding to its receptors.[57] VEGF is a key factor that induces vascular endothelial cell proliferation and migration, and tumor neovascularization. Whereas VEGF inhibition primarily affects angiogenesis of tumor cells leading to tumor cell death, it can also result in ADRs. Regardless of grade, ADRs associated with bevacizumab treatment include hypertension, hemorrhage, and proteinuria.[58] Severe ADRs, such as hemorrhage and gastrointestinal perforation, can result in death. Pharmacogenetic studies performed to date have mainly focused on the association

TABLE 2 Genetic variants associated or potentially associated with EGFR-TKI-induced toxicity

Reference	Drug	Ethnicity	N	Approach	Toxicity	Gene	Variant	Alleles	Odds ratio (95%CI)	*P*-value	Effect on PK/PD for EGFR-TKI
Giovannetti et al[33]	Gefitinib	White	85	Candidate gene	Diarrhea (grade ≥ 2)	*EGFR*[a]	rs712830	C > A	NA	<.001	NR
						EGFR[a]	rs712829	G > T	NA	<.01	NR
						EGFR[a]	rs2227983	G > A (R497K)	NA	2.00E−02	NR
Tamura et al[36]	Gefitinib	Japanese	83	Candidate gene	Skin rash (grade ≥ 2)	*ABCG2*	rs2231137	G > A	NA	4.60E−02	NR
Wang et al[37]	Erlotinib	Chinese	51	Candidate gene	ADR (eg, skin rash and/or digestive tract injury)	*CYP4F11*	rs1064796	G > C	4.13 (1.54-11.12)	3.50E−03	NR
						UGT3A1	rs10045685	A > G	0.31 (0.12-0.83)	1.68E−02	NR
Udagawa et al	Gefitinib, Erlotinib	Japanese	13	WGS	Interstitial lung disease	Intergenic	rs75399069	A > C	14.91 (6.19-35.94)	2.39E−06	NR
						SLC25A48	rs417168	T > C	154.04 (36.31-653.49)	3.58E−06	NR
						SLC25A48	rs442281	G > A	154.04 (36.31-653.49)	3.58E−06	NR
						Intergenic	rs17690253	T > G	12.70 (5.28-30.54)	6.53E−06	NR
						Intergenic	rs184448987	C > A	22.91 (8.41-62.40)	7.61E−06	NR
						Intergenic	rs10165147	C > G	6.06 (2.70-13.63)	8.22E−06	NR
						Intergenic	rs1348851	A > G	15.60 (6.17-39.47)	8.59E−06	NR

Abbreviations: EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NR, not reported; PK/PD, pharmacokinetic/pharmacodynamic; WGS, whole-genome sequencing.

[a]Target molecule of EGFR-TKI (gefitinib and erlotinib).

TABLE 3 Genetic variants associated or potentially associated with sunitinib-induced toxicity

Reference	Ethnicity	N	Approach	Toxicity	Gene	Variant	Alleles	Odds ratio (95%CI)	*P*-value	Effect on PK/PD for sunitinib
van Erp et al[46]	White	188	Candidate gene	Leukopenia (grade ≥ 3)	*FLT3*[a]	rs1933437	T > C	0.36 (0.17-0.77)	8.00E−03	NR
		188		Leukopenia (grade ≥ 3)	*CYP1A1*	rs1048943	A > G	6.24 (1.20-32.42)	2.90E−02	NR
		188		Leukopenia (grade ≥ 3)	*NR1I3*[b]	Haplotype (rs2307424, rs2307418, and rs4073054)	CAG > Other	1.74 (1.02-2.96)	4.10E−02	NR
		183		Any toxicity (grade ≥ 3)	*ABCG2*	Haplotype (−15622 and rs2622604)	TT > Other	0.38 (0.17-0.83)	1.60E−02	NR
		183		Any toxicity (grade ≥ 3)	*KDR*[a]	rs2305948	C > T	2.39 (1.02-5.60)	4.60E−02	NR
		193		Mucosal inflammation (grade ≥ 3)	*CYP1A1*	rs1048943	A > G	4.03 (1.24-13.09)	2.10E−02	NR
		182		Hand-foot syndrome (grade ≥ 3)	*ABCB1*	Haplotype (rs1045642, rs1128503, and rs2032582)	TTT > Other	0.39 (0.16-0.94)	3.50E−02	NR
Mizuno et al[47]	Japanese	19	Candidate gene	Thrombocytopenia (grade ≥ 2)	*ABCG2*	rs2231142	C > A	NA	2.10E−01	Higher exposure to sunitinib
Kim et al[48]	White	63	Candidate gene	Hypertension (systolic pressure ≥ 150 mmHg and/or diastolic pressure ≥ 90 mmHg)	*VEGFA*[c]	rs699947	C > A	NA	3.00E−02	NR
				Hypertension (systolic pressure ≥ 150 mmHg and/or diastolic pressure ≥ 90 mmHg)	*VEGFA*[c]	rs2010963	C > G	NA	3.00E−02	NR
				Hypertension (systolic pressure ≥ 150 mmHg and/or diastolic pressure ≥ 90 mmHg)	*VEGFA*[c]	rs833061	T > C	NA	3.00E−02	NR
Chu et al[49]	Asian	95	Candidate gene	Diarrhea	*ABCB1*	rs1128503	C > T	0.04 (0.0-0.2)	5.00E−04	Higher plasmatic sunitinib clearance
		95		Diarrhea	*ABCB1*	rs1045642	C > T	0.3 (0.1-0.8)	2.00E−02	NR
		88		Neutropenia (<2000/μL)	*ABCB1*	rs1045642	C > T	0.1 (0.0-0.4)	1.00E−02	NR
		88		Neutropenia (<2000/μL)	*ABCB1*	rs1128503	C > T	0.3 (0.1-0.9)	3.00E−02	Higher plasmatic sunitinib clearance
		88		Neutropenia (<2000/μL)	*ABCB1*	Haplotype (rs1045642, rs1128503, rs2032582)	Other > TTT	0.1 (0.0-0.5)	3.00E−02	NR

(Continues)

TABLE 3 (Continued)

Reference	Ethnicity	N	Approach	Toxicity	Gene	Variant	Alleles	Odds ratio (95%CI)	*P*-value	Effect on PK/PD for sunitinib
		88		Neutropenia (<2000/μL)	*ABCG2*	rs2231142	C > A	0.3 (0.1-0.9)	3.00E−02	Higher exposure to sunitinib
		88		Neutropenia (<2000/μL)	*ABCB1*	rs2032582	G > T, A	0.4 (0.1-0.9)	4.00E−02	Higher plasmatic sunitinib clearance
		88		Neutropenia (<2000/μL)	*FLT3*[a]	rs1933437	C > T	2.7 (1.1-7.2)	4.00E−02	NR
		85		Leucopenia (<3000/μL)	*FLT3*[a]	rs1933437	C > T	8.0 (1.3-51.0)	3.00E−02	NR
Diekstra et al[50]	White	333	Candidate gene	Any toxicity (grade ≥ 3)	*NR1I3*[b]	rs2307424	G > A	0.46 (0.27-0.80)	6.00E−03	NR
				Any toxicity (grade ≥ 3)	*FLT3*[a]	rs1933437	C > T	3.36 (1.08-10.5)	3.70E−02	NR
				Any toxicity (grade ≥ 3)	*CYP1A1*	rs1048943	A > G	3.65 (1.04-12.8)	4.30E−02	NR
				Any toxicity (grade ≥ 3)	*NR1I3*[b]	Haplotype (rs2307424, rs2307418, and rs4073054)	Other > CAT	0.60 (0.36-0.99)	4.50E−02	NR
				Hypertension grades	*CYP3A5*	rs776746	C > T	4.70 (1.47-15.0)	9.00E−03	NR
				Hypertension grades	*ABCG2*	rs2231142	C > A	0.03 (0.001-0.85)	4.00E−02	Higher exposure to sunitinib
				Mucosal inflammation (grade ≥ 3)	*NR1I3*[b]	rs2307418	T > G	8.09 (1.55-42.3)	1.30E−02	NR
				Mucosal inflammation (grade ≥ 3)	*ABCB1*	rs1128503	C > T	0.19 (0.04-0.83)	2.80E−02	Higher plasmatic sunitinib clearance
				Mucosal inflammation (grade ≥ 3)	*ABCB1*	rs2032582	G > T, A	0.22 (0.05-0.98)	4.80E−02	Higher plasmatic sunitinib clearance
				Leukopenia (grade ≥ 3)	*VEGFA*[c]	rs3025039	C > T	5.42 (1.25-23.5)	2.40E−02	NR
				Hand-foot syndrome (grade ≥ 3)	*KDR*[a]	rs2305948	C > T	2.84 (1.09-7.38)	3.20E−02	NR
				Hand-foot syndrome (grade ≥ 3)	*FLT3*[a]	rs1933437	C > T	5.33 (1.10-25.79)	3.70E−02	NR
Diekstra et al[51]	White	374	Candidate gene	Leukopenia (grade ≥ 3)	*IL13*	rs1800925	C > T	6.76 (1.35-33.9)	2.00E−02	NR
				Hypertension (grade ≥ 3)	*IL8*	rs1126647	A > T	1.69 (1.07-2.67)	2.40E−02	NR
				Any toxicity (grade ≥ 3)	*IL13*	rs1800925	C > T	1.75 (1.06-2.88)	2.80E−02	NR
Ravegnini et al[52]	White	49	Candidate gene	Adverse events (grade ≥ 3)	*VEGFA*[c]	rs3025039	C > T	15.3 (2.2-102.1)	5.00E−03	NR
Low et al[53]	Japanese	219	Candidate gene	Thrombocytopenia (grade ≥ 3)	*ABCG2*	rs2231142	C > A	1.86 (1.17-2.94)	8.41E−03	Higher exposure to sunitinib

(Continues)

TABLE 3 (Continued)

Reference	Ethnicity	N	Approach	Toxicity	Gene	Variant	Alleles	Odds ratio (95%CI)	*P*-value	Effect on PK/PD for sunitinib
Kim et al[54]	Korean	65	Candidate gene	Hand-foot syndrome (grade ≥ 3)	*ABCG2*	rs2231142	C > A	28.46 (2.22-364.94)	1.00E−02	Higher exposure to sunitinib
				Neutropenia (grade ≥ 3)	*ABCG2*	rs2231142	C > A	18.20 (1.49-222.09)	2.00E−02	Higher exposure to sunitinib
				Thrombocytopenia (grade ≥ 3)	*ABCG2*	rs2231142	C > A	9.90 (1.16-Infinity)	4.00E−02	Higher exposure to sunitinib
Diekstra et al[55]	White	287	Candidate gene	Hypertension (grade ≥ 3)	*CYP3A4*[d]	rs4646437	G > A	2.43 (1.14-5.18)	2.10E−02	NR
Velasco et al[56]	White	159	Candidate gene	Adverse events (grade ≥ 3)	*CYP3A4*[d]	rs4646437	G > A	0.27 (0.08-0.88)	3.00E−02	NR

Abbreviations: NR, not reported; PK/PD, pharmacokinetic/pharmacodynamic.

[a]Target molecule of sunitinib.

[b]NR1I3 regulates multiple drug detoxification genes including *CYP3A4*.

[c]Ligand for the target molecule of sunitinib. rs699947 and rs2010963 have been associated with serum VEGF level.

[d]Sunitinib is primarily metabolized by CYP3A4. Although rs4646437 has been reported to be associated with blood concentration of other drugs, there is no report concerning the relationship between rs4646437 and PK/PD of sunitinib.

of bevacizumab with hypertension, which is considered the most common bevacizumab-induced ADR. The germline polymorphism rs2010963 in *VEGFA*, which encodes for VEGF, has been linked with thrombo-hemorrhagic events ($P = .0044$, risk allele: C),[59] any toxicity at grade ≥ 1 ($P = .012$, risk allele: C),[60] and grade ≥ 3 hypertension ($P = .031$, risk allele: G).[61] However, the risk alleles of these studies are inconsistent, and the underlying mechanisms of the association between rs2010963 polymorphism and bevacizumab-induced ADRs remain unknown.

Germline polymorphisms rs1799983 and rs2070744 in nitric oxide synthase 3 (*NOS3*) are associated with grade ≥ 3 hypertension and proteinuria ($P = .0002$),[62] and grade ≥ 1 proteinuria ($P = .004$),[63] respectively. These 2 SNPs are known to be related to nitric oxide (NO) production, which plays an important role in the regulation of vascular tone, and therefore might be associated with bevacizumab-induced ADRs through the inter-individual differences of NO production. In other candidate gene studies, the germline polymorphism rs1129660 in RB1-inducible coiled-coil 1 (*RB1CC1*), an autophagy-related gene, and the germline polymorphisms rs9381299 and rs834576 found upstream of the heat shock protein 90 alpha family class B member 1 (*HSP90AB1*)—a NO signaling related gene—have been reported as hypertension-related genes for bevacizumab ($P = .001$ to $.03$).[64,65] Finally, in a GWAS, a germline polymorphism rs6453204 in synaptic vesicle glycoprotein 2C (*SV2C*) was identified and validated to be associated with grade ≥ 3 hypertension ($P = 6.00 \times 10^{-8}$ to 3.70×10^{-2}, OR = 2.2 to 3.3)[66] (Table 4) in response to bevacizumab treatment.

3.5 | Immune checkpoint inhibitor: Nivolumab

The anticancer mechanism and ADRs of immune checkpoint inhibitors (ICIs) obviously differ from those of cytotoxic anticancer drugs or other molecular-targeted drugs. ICIs are relatively new drugs, and thus pharmacogenetic studies that characterize immune-related adverse events (irAEs) for ICIs are few. One example is nivolumab (Opdivo), an ICI that targets programmed cell death protein 1 (PD-1), which is expressed on the surface of T lymphocytes. Nivolumab binds to the PD-1 receptor and blocks its interaction with the ligand, thereby enhancing T cell responses against cancer cells.[67] A later study showed that a germline polymorphism rs2227981 in programmed cell death 1 (*PDCD1*), the gene that encodes for PD-1, was potentially associated with any grade irAEs in the exploration cohort, however these findings were not validated in another cohort.[68] Recently, there has been an interest in the relationship between patient human leucocyte antigen (HLA) type and the appearance of irAEs. In 1 case-control association study, HLA typing was performed on germline DNA samples from 11 patients receiving nivolumab or other ICIs (pembrolizumab or ipilimumab) who presented with pituitary irAEs (as compared with population controls). The authors showed that HLA-DR15, B52 and Cw12 were associated with pituitary irAEs ($P = .0014$, $.0026$, and $.0013$, respectively).[69] Finally, case reports have alluded to a relationship between

TABLE 4 Genetic variants associated or potentially associated with bevacizumab-induced toxicity

Reference	Ethnicity	N	Approach	Toxicity	Gene	Variant	Alleles	Odds ratio (95%CI)	*P*-value	Effect on PK/PD for bevacizumab
Stefano et al[59]	White	225	Candidate gene	Thrombo-hemorrhagic events	*VEGFA*[a]	rs2010963	C > G	NA	4.40E−03	NR
Etienne-Grimaldi et al[60]	White	137	Candidate gene	Any toxicity (grade ≥ 1)	*VEGFA*[a]	rs2010963	C > G	NA	1.20E−02	NR
Gampenrieder et al[61]	White	163	Candidate gene	Hypertension (grade ≥ 3)	*VEGFA*[a]	rs2010963	C > G	NA	3.10E−02	NR
Salvatore et al[62]	White	120	Candidate gene	Hypertension and proteinuria (grade ≥ 3)	*NOS3*	rs1799983	T > G	NA	2.00E−04	NR
Crucitta et al[63]	White	73	Candidate gene	Proteinuria (grade ≥ 1)	*NOS3*	rs2070744	C > T	NA	4.00E−03	NR
Berger et al[64]	White	449	Candidate gene	Hypertension (grade ≥ 2)	*RB1CC1*	rs1129660	A > G	0.29 (0.12-0.66)	1.00E−03	NR
Li et al	White	415	Candidate region	Early hypertension (grade ≥ 3)	Intergenic	rs9381299	T > C	2.4 (1.2-4.9)	1.00E−02	NR
		430		Systolic blood pressure > 180 mmHg	Intergenic	rs9381299	T > C	2.1 (1.1-3.7)	2.00E−02	NR
		415		Early hypertension (grade ≥ 3)	Intergenic	rs834576	C > A	2.9 (1.0-7.6)	3.00E−02	NR
Schneider et al[66]	White	582	GWAS	Systolic blood pressure > 160 mmHg	*SV2C*	rs6453204	A > G	3.3	6.00E−08	NR
		564	GWAS	Hypertension (grade ≥ 3)	*SV2C*	rs6453204	A > G	2.2	3.00E−04	NR
		185	Candidate gene	Hypertension (grade ≥ 3)	*SV2C*	rs6453204	A > G	2.4	3.70E−02	NR

Abbreviations: GWAS, genome-wide association study.

[a]Target molecule of bevacizumab. rs2010963 has been reported to affect circulating VEGF level.

HLA type and ICI-induced type 1 diabetes mellitus (T1DM)[70-73]: patients who developed ICI-induced T1DM tended to have HLA types (eg, DRB01*03 or 04, and DR3-DQ2; DR4-DQ8) that increase the risk of T1DM in the general population.[70,71] However, these relationships remain contentious and further study is warranted.[72,73]

4 | CONCLUSION

Candidate gene- and genome-wide association studies have significantly contributed to the identification of genetic variants that could be biomarkers for severe ADRs. However, the current evidence surrounding the potential use of ADR-related biomarkers in cancer therapy is inconsistent, and there is a need to validate and confirm the relationships between these genetic variants and ADRs. Furthermore, the identification of ethnic-specific biomarkers for drug response is imperative. In addition to the severe ADRs reviewed in this article, there are numerous other relatively common reactions for which pharmacogenetic reports are limited or lacking. In conclusion, we believe that pharmacogenetic studies for severe ADRs induced by molecular-targeted therapy are essential to provide advanced precision medicine.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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