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Pharmacogenomics in Preventing Hypersensitivity Reactions Caused by Aromatic Antiseizure Medications

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ABSTRACT

Epilepsy ranks as the second most common neurological disorder worldwide, manifesting through recurrent, unprovoked, and self-limiting seizures that may have genetic, acquired, or unknown causes. This review focused on identifying pharmacogenomic markers linked to hypersensitivity reactions triggered by aromatic antiseizure medications. It addressed the pharmacokinetics and pharmacogenomics of CYP2C9 and HLA genes, explored immunopathogenic mechanisms, and discussed the clinical significance of these associations. Studies included in this review reported results using odds ratios (OR), 95% confidence intervals (95% CI), and p-values to assess links with severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Notably, CYP2C192 was associated with SCARs induced by carbamazepine, phenytoin, and phenobarbital. Five studies linked CYP2C93 to phenytoin-related SCARs, while several studies further implicated CYP2C93 and HLA alleles (HLA-B13:01, HLA-B15:02, HLA-B51:01, HLA-B55:01, HLA-B46:01, HLA-B56:02/04) in phenytoin-induced hypersensitivity. HLA-B15:02 was reported in six studies as a key risk factor for carbamazepine-induced SJS/TEN, whereas lamotrigine-induced SCARs were associated in four studies with HLA-A02:07, HLA-A24:02, HLA-A33:03, HLA-B15:02, and HLA-B44:03. Additionally, one study linked HLA-A02:01, HLA-B35:01, HLA-C04:01, and HLA-C08:01 to SCARs from lamotrigine and phenytoin, and three studies identified HLA-A02:01, HLA-A11:01, HLA-A24:02, HLA-B15:02, HLA-B38:01, HLA-B40:02, and HLA-DRB103:01 in SCARs induced by carbamazepine, lamotrigine, and phenytoin. Collectively, evidence highlights CYP2C9*3 and multiple HLA alleles as significant predictors of severe cutaneous reactions such as TEN and SJS, suggesting these variants could serve as actionable genetic biomarkers to prevent serious adverse effects from carbamazepine, phenytoin, phenobarbital, and lamotrigine, especially in Asian populations.

Keywords: Clinical implications, Pharmacogenomics, Hypersensitivity reactions, Epilepsy, Antiseizure medications

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Introduction

Epilepsy is a prevalent neurological disorder marked by recurrent, unprovoked seizures, with variable patient responses to antiseizure medications (ASMs) influenced by genetic factors. Polymorphisms in the CYP2C9, CYP2C19, and CYP3A4 genes contribute to differences in plasma drug concentrations, therapeutic outcomes, and the risk of adverse drug reactions (ADRs) [1, 2]. The CYP3A41A allele represents the wild-type, forming the CYP3A41A/1A genotype, which predicts normal metabolism [3, 4], whereas CYP3A420 and CYP3A422 alleles result in CYP3A420/20 and CYP3A422/22 genotypes, which are associated with reduced enzymatic activity [3, 5]. Similarly, CYP2C91 indicates normal metabolic function in the CYP2C91/1 genotype, while CYP2C92 and CYP2C93 alleles predict poor metabolism [6, 7]. For CYP2C19, the wild-type CYP2C191/1 genotype corresponds to normal metabolism, and CYP2C192 and CYP2C193 alleles confer poor metabolizer phenotypes, often linked to ADRs and drug toxicity [8, 9].

Human leukocyte antigen (HLA) genes, part of the major histocompatibility complex (MHC), vary across populations and influence susceptibility to drug hypersensitivity [10]. HLA-B15:02 is most common in East Asia

(6.9%), followed by Oceania (5.4%) and South/Central Asia (4.6%), but occurs at <1% in Japanese, ~2.5% in Koreans, and is absent or extremely rare in African, African American, Caucasian, Hispanic/South American, and Middle Eastern populations [10-15]. This allele strongly associates with carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [10, 11, 16-18], leading the FDA to recommend pre-treatment pharmacogenomic testing [19]. HLA-A31:01 is observed in Hispanic/South American (6%), Caucasian (3%), Japanese (8%), South Korean (5%), and South/Central Asian (2%) populations [10], and along with HLA-A24:02 has been reported in Spanish Caucasians [20]. HLA-A31:01 increases the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) and CBZ-induced SJS/TEN [10].

ADRs are unintended, harmful reactions occurring at standard doses during therapy, prophylaxis, or diagnostic procedures [21]. Cutaneous ADRs affect over 8% of the global population, with more than 10% of hospitalized patients experiencing them, though most cases are mild or self-limiting [22, 23]. ASM-induced skin reactions occur in roughly 3% of cases [22]. ADRs are categorized as Type A (dose-dependent and predictable), Type B (hypersensitivity and unpredictable), Type C (chronic), Type D (teratogenic or carcinogenic), Type E (post-discontinuation), and Type F (due to drug interactions causing therapeutic failure) [24-26]. Type A reactions, which account for over 80% of ADRs, are reversible and dose-related, while Type B reactions are genetically driven, unpredictable, and can manifest immediately (<1 h) as urticaria or anaphylaxis, or later as severe cutaneous adverse reactions (SCARs) [24, 26-30]. The main SCAR phenotypes caused by ASMs include SJS/TEN, DRESS/drug-induced hypersensitivity syndrome (DIHS), and acute generalized exanthematous pustulosis (AGEP) [28-32]. SJS and TEN involve immune-mediated epidermal, mucosal, and ocular detachment [33], with phenobarbital (15%), phenytoin (13%), carbamazepine (11%), and oxcarbazepine (<5%) showing the highest risk [22, 34-40].

The immunopathogenesis of SCARs is complex: specific HLA alleles interact with drugs or their metabolites, forming complexes that activate cytotoxic CD8+ T cells and natural killer cells. These cells release Fas ligand, TNF-α, IFN-γ, perforin, granzyme B, and granulysin, leading to keratinocyte apoptosis, necroptosis, and epidermal detachment characteristic of SJS/TEN [41-44]. SCARs are rare, with an estimated incidence of 0.4–1.2 cases per million per year [31, 45] and annual incidence of 2–7 per million [46, 47], though East Asian populations show higher prevalence [31]. Among new ASM users, SJS/TEN occurs in 0.01%–0.1% [48]. Other prevalence data include 0.32/1,000 hospitalizations in Beijing [49], ~50,000 annual cases in the UK due to aromatic ASMs [48], and 67% of severe ADRs in Koreans [50]. Mortality ranges from 1–5% for SJS and 25–30% for TEN [51]. Considering these findings, a detailed review of genes related to ASM-induced SCARs is essential. Polymorphisms in CYP2C9, CYP2C19, and HLA alleles are proposed as significant risk factors for hypersensitivity reactions, providing crucial guidance for genotype-driven personalization of ASM therapy to predict and prevent severe ADRs.

Pharmacokinetics of aromatic antiseizure medications

This section focuses on the pharmacokinetic profiles of the main antiepileptic drugs that can trigger type B hypersensitivity reactions, emphasizing their metabolic fate. Carbamazepine (CBZ; 5-H-dibenzazepine-5-carboxamide) is a widely used agent implicated in hypersensitivity, featuring an iminostilbene core derived from tricyclic antidepressants [52] and classified as a BCS class 2 compound (low solubility, high permeability) [53]. CBZ possesses two dissociation constants: pKa1 of 2.3 from the dibenzazepine nitrogen, and pKa2 of 13.9 from the free carboxamide NH_2, with the non-ionized form dominating in the intestinal mucosa, which enhances absorption but exhibits notable interpatient variability [2, 54]. Therapeutically, plasma concentrations should remain above 4 mg/L yet below 12 mg/L, reaching steady-state (Css) over 3–4 weeks, and peak concentrations occur 4–8 hours post-dose [52, 55]. After absorption, CBZ achieves 70–80% bioavailability, binds 65–85% to albumin and α1-acid glycoprotein, and shows a Vd of 1.4–1.9 L/kg, consistent with its lipophilic nature and allowing penetration into the CNS and across the placenta [2]. Hepatic metabolism involves three phase I routes: the main pathway uses CYP3A4, CYP2C19, and CYP2C9 to form 10,11-epoxycarbamazepine, which is either glucuronidated by UGT2B7/UGT1A6 to yield N-β-glucuronide-10,11-epoxycarbamazepine for renal excretion or hydrolyzed to diOH-CBZ and subsequently glucuronidated. Minor pathways include CYP3A4-mediated formation of 2,3-epoxycarbamazepine and conversion to 3-hydroxycarbamazepine via CYP3A4, CYP3A7, and CYP2B6 [2, 55, 56]. The elimination half-life varies with age: 12–64 h in neonates, 1.9 h in children, and 25–65 h in adults [2, 54].

Oxcarbazepine (OXC; 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide), another dibenzoazepine derivative, is also BCS class 2 [57] and has a pKa of 13.73, favoring intestinal absorption in its non-ionized form [58, 59]. Its bioavailability is 95% and it is unaffected by food intake [60, 61]. Therapeutic plasma concentrations should exceed 5 mg/L but remain below 30 mg/L. The active metabolite 10,11-dihydro-10-hydroxycarbamazepine (MHD) reaches steady-state within 2–3 days with twice-daily dosing, peaking at 1–3 hours, with R-(−)-MHD and S-(+)-MHD AUC values of 63.9 μmol·h/L and 241.0 μmol·h/L, respectively [58-61]. OXC and MHD bind to albumin at 59% and 40% respectively, do not bind α1-acid glycoprotein, and have a Vd of 7.8–12.5 L/kg, indicating significant CNS and placental distribution [58, 62]. Phase I metabolism converts OXC to (S)-(+)-MHD or (R)-(−)-MHD through cytosolic aryl ketone reductase, with ~4% forming the inactive 10,11-dihydro-10,11-trans-dihydroxycarbamazepine (DHD). Phase II glucuronidation via UGT2B7 produces O-β-glucuronide-MHD [59-61]. OXC has a half-life of 1–5 h, while MHD ranges from 7–20 h, shorter in children and longer in older adults. Excretion occurs primarily as MHD (27%) or MHD glucuronides (49%), with less than 1% eliminated unchanged [61].

Oxcarbazepine and its primary metabolite, MHD, display linear pharmacokinetics and do not induce their own metabolism [61]. Laboratory studies indicate that MHD is a weak UGT inducer, suggesting minimal potential for interaction with drugs such as valproic acid and lamotrigine, which are metabolized via UGT enzymes. However, coadministration with strong inducers like carbamazepine, phenytoin, or phenobarbital can lower plasma MHD concentrations by 30%–40% [60].

Phenytoin, a hydantoin derivative (5,5-diphenylhydantoin; 5,5′-diphenylimidazolidine-2,4-dione), belongs to BCS class 2 [63-66]. Its secondary amino group (R_2NH) in the aromatic ring gives a pKa of 8.3, allowing efficient intestinal absorption in the non-ionized form and bioavailability of approximately 80% [64, 67]. For seizure control, plasma concentrations must exceed 10 mg/L but remain below 20 mg/L, with steady-state levels reached over approximately 50 days. The time to peak plasma concentration (tmax) ranges from 3 to 8 hours [2, 65, 68]. Once absorbed, phenytoin binds about 90% to plasma proteins, primarily albumin, and distributes widely, with a Vd of 0.6–0.8 L/kg, facilitating CNS penetration [2, 65, 69].

Hepatic metabolism occurs via CYP2C9 and CYP2C19, forming 3′,4′-epoxide phenytoin, which is further processed either by epoxide hydrolase to 3′,4′-dihydrodiol phenytoin or via CYP2C9/CYP2C19 to 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH). p-HPPH undergoes additional phase I metabolism to dihydrodiol phenytoin and phase II glucuronidation via UGT1A to produce O-β-glucuronide-phenytoin. The elimination half-life is highly variable, ranging from 8 to 60 hours, with an average of about 22 hours [64, 66, 69, 70]. Renal excretion of unchanged drug accounts for 1%–5% of the dose. Phenytoin demonstrates first-order kinetics at low concentrations but shifts to zero-order kinetics when metabolic pathways saturate. Co-administration with enzyme inhibitors such as valproic acid, amiodarone, or fluconazole can raise plasma levels, increasing the risk of adverse effects, whereas inducers like carbamazepine or rifampicin accelerate metabolism, lowering plasma concentrations and potentially reducing efficacy [71].

Lamotrigine, a phenyltriazine derivative [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine], contains a primary amino group with a pKa of 5.7, favoring intestinal absorption in the non-ionized form. It is not affected by food and bypasses first-pass metabolism, achieving near-complete bioavailability of 98% [72-74]. Plasma concentrations rise proportionally with doses between 50 and 400 mg [74]. Therapeutic levels are maintained between 22 and 34 mg/L [75], with tmax occurring 1–5 hours post-dose [72, 74]. Approximately 55% of lamotrigine binds to plasma proteins, primarily albumin, and its Vd ranges from 0.9–1.47 L/kg, allowing distribution to the placenta, liver, kidneys, breast milk, and other tissues [74, 76]. Distribution is influenced by transporters such as P-glycoprotein (ABCB1) and hOCT1 (SLC22A1), which mediate hepatic uptake for metabolism [73, 77, 78]. Lamotrigine is metabolized mainly by phase II glucuronidation through UGT1A4, UGT1A3, and UGT2B7, forming 2-N- and 5-N-glucuronides [79, 80]. It shows no autoinduction or saturable metabolism, but plasma levels are affected by enzyme-inducing or inhibiting drugs [72, 81]. Its half-life is 24–35 hours, and less than 10% is excreted unchanged, with the majority eliminated as 2-N-glucuronide in urine [73]. Valproic acid inhibits lamotrigine metabolism, increasing plasma levels and prolonging the half-life, whereas enzyme inducers such as carbamazepine, phenytoin, and primidone enhance clearance and reduce plasma concentrations [82, 83].

Pharmacogenomics of aromatic antiseizure medication–induced scars

CYP3A4 gene and its variants

The CYP3A4 gene is located on chromosome 7q21.1 and comprises 13 exons. Its transcript includes a 5′ untranslated region (UTR) of 101 nucleotides and a 3′ UTR of 1,152 nucleotides, producing an mRNA of roughly 2 kb that encodes the 503-amino-acid CYP3A4 enzyme, which weighs approximately 57 kDa and contains a large active site. CYP3A4 is highly abundant, representing 60%–70% of the total CYP450 enzymes in liver and intestinal enterocytes, and is responsible for metabolizing 30%–60% of drugs in clinical use [3, 84-88]. The wild-type allele, CYP3A41A, corresponds to a normal metabolic phenotype, whereas several reduced-function alleles exist: CYP3A42 (15722T>C, exon 7), CYP3A43 (23181T>C), CYP3A422 (15389C>T), and CYP3A420, which involves a single adenine insertion (25898_25899insA) leading to a frameshift and premature stop codon [3, 5, 89, 90]. Individuals homozygous for CYP3A420 or CYP3A422 (i.e., CYP3A420/20 or CYP3A422/*22) are classified as poor metabolizers, exhibiting little to no CYP3A4 activity, which can result in elevated serum drug concentrations and increased risk of adverse drug reactions [89, 91].

CYP2C9 gene and its variants

CYP2C9 is mapped to chromosome 10q24, spanning approximately 500 kb and containing nine exons. The wild-type CYP2C91 allele forms the CYP2C91/1 genotype, which confers normal metabolic activity. This enzyme represents roughly 10% of the hepatic CYP450 content, making it the second most abundant CYP450 isoform [6, 9, 57, 92]. Over 61 variants have been identified, including reduced-function alleles such as CYP2C92 (3608C>T, exon 3, Arg144Cys), CYP2C93 (42614A>C, exon 7, Ile359Leu), CYP2C94 (1076T>C), CYP2C95 (42619C>G), and CYP2C96 (10601delA), which produces a truncated protein due to a frameshift caused by a splicing deletion [7, 9, 57, 93-95].

CYP2C19 gene and its variants

The CYP2C19 gene is located at chromosome 10q24.1, composed of 1,473 base pairs spanning nine exons and eight introns. Its wild-type allele, CYP2C191, produces the CYP2C191/1 genotype, predicting normal metabolic activity. The encoded CYP2C19 protein consists of 490 amino acids [9, 57, 96]. Several alleles lead to absent or reduced enzyme function, including CYP2C192 (19154G>A, exon 5) which creates an aberrant splice site and premature stop codon, CYP2C193 (17948G>A, exon 4), CYP2C194 (80161A>G), CYP2C195 (90033C>T, Arg433Trp in the heme-binding domain), CYP2C196 (12748G>A, Arg132Gln), and CYP2C19*7 (19294T>A, affecting the intron 5 donor splice site) [2, 8, 95, 97]. **Table 1** summarizes the major alleles, corresponding genotypes, and the resulting intermediate or poor metabolizer phenotypes.

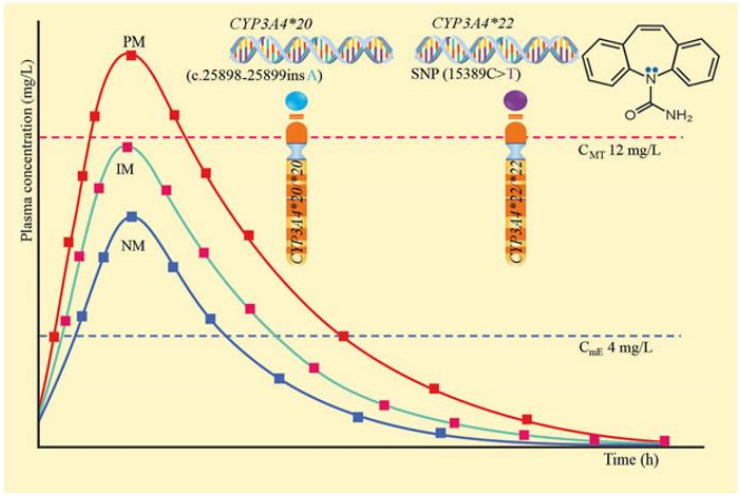
Table 1. Key genetic variants (alleles), corresponding genotypes, and their impact on metabolic phenotypes (normal, intermediate, or poor metabolizer status)

Gene (Chromosomal location)	Allele	rsID	Nucleotide change	Functional effect of the allele	Example genotype	Resulting phenotype*	Reference(s)
CYP3A4 (7q21.1)	*1A	–	No change	Normal activity	*1A/*1A	Normal metabolizer (NM)	Apellániz-Ruiz *et al.* (2015) [3]
	*2	rs55785340	15722T>C	Reduced activity	*2/*2	Intermediate (IM)	Zhou *et al.*, 2017, 2019 [5, 89]
	*3	rs4986910	23181T>C	Reduced activity	*3/*3	Poor metabolizer (PM)	–
	*20	rs67666821	25898_25899insA	Reduced activity	*20/*20	Poor metabolizer (PM)	Apellániz-Ruiz *et al.* (2015) [3]
	*22	rs35599367	15389C>T	Reduced activity	*22/*22	Poor metabolizer (PM)	Zhou *et al.*, 2017, 2019 [5, 89]
CYP2C9 (10q24)	*1	–	No change	Normal activity	*1/*1	Normal metabolizer (NM)	Skadrić and Stojković (2020) [57]

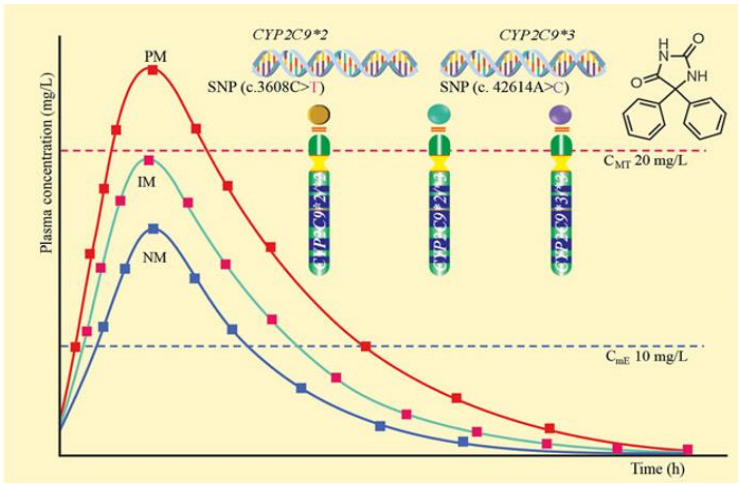
	*2	rs1799853	3608C>T	Reduced activity	*1/*2 or *2/*2	Intermediate (IM)	de Andrés *et al*. (2021) [95]
	*3	rs1057910	42614A>C	Reduced activity	*1/*3	Intermediate (IM)	de Andrés *et al*. (2021) [95]
					*2/*3 or *3/*3	Poor metabolizer (PM)	
	*5	rs28371686	42619C>G	Reduced activity	*5/*5	Poor metabolizer (PM)	Karnes *et al*. (2021) [92]
	*6	rs9332131	10601delA	Reduced activity	*6/*6	Poor metabolizer (PM)	–
CYP2C19 (10q24.1)	*1	rs3758581	80161A>G	Normal activity	*1/*1	Normal metabolizer (NM)	Maruf *et al.* (2019)[9]
	*2	rs4244285	19154G>A	Reduced activity	*1/*2	Intermediate (IM)	de Andrés *et al.* (2021) [95]
					*2/*2	Poor metabolizer (PM)	
	*3	rs4986893	17948G>A	Reduced activity	*2/*3 or *3/*3	Poor metabolizer (PM)	de Andrés *et al*. (2021) [95]
	*4	rs3758581	80161A>G	Reduced activity	*4/*4	Poor metabolizer (PM)	Lee (2013) [97]
	*5	rs56337013	90033C>T	Reduced activity	*5/*5	Poor metabolizer (PM)	Lee (2013) [97]
	*6	rs72552267	12748G>A	Reduced activity	*6/*6	Poor metabolizer (PM)	Lee (2013) [97]
	*7	rs72558186	19294T>A	Reduced activity	*7/*7	Poor metabolizer (PM)	Lee (2013) [97]

Abbreviations: MN, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer.

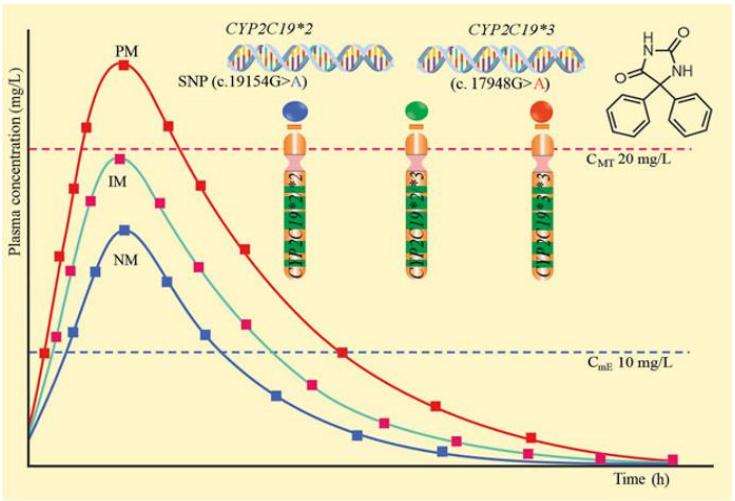
Figure 1a illustrates the CYP3A420 and CYP3A422 alleles, which give rise to the CYP3A420/20 and CYP3A422/22 genotypes, both associated with poor metabolizer (PM) status; in these patients, drug metabolism is virtually absent, leading to serum concentrations exceeding the minimum toxic level (12 mg/L) and heightening the risk of carbamazepine-induced adverse drug reactions [90, 91]. **Figure 1b** depicts the CYP2C92 and CYP2C93 alleles along with their respective CYP2C92/2, CYP2C92/3, and CYP2C93/3 genotypes, which also confer a PM phenotype and predispose individuals to phenytoin-related adverse effects [9, 57]. **Figure 1c** shows the CYP2C192 and CYP2C193 alleles forming the CYP2C19*2/2, CYP2C192/3, and CYP2C193/*3 genotypes, predicting poor metabolism, elevating plasma drug levels, and increasing the likelihood of adverse reactions [9, 57]. Plasma concentration curves for normal metabolizers (NM) and intermediate metabolizers (IM) are also presented for comparison.



a)



b)



c)

Figure 1. Plasma concentrations according to genotype and poor metabolizer phenotype. (a) CYP3A420 and CYP3A422 with their respective genotypes CYP3A420/20 and CYP3A422/22. (b) CYP2C92 and CYP2C93 with genotypes CYP2C92/2, CYP2C92/3, and CYP2C93/3. (c) CYP2C192 and CYP2C193 with genotypes CYP2C19*2/2, CYP2C192/3, and CYP2C193/*3.

Pharmacogenomics of CYP2C9/CYP2C19 and SCARs induced by aromatic antiseizure medications

The CYP2C92 allele occurs at a frequency of 3% in African Americans and between 3% and 11% in Caucasians, whereas CYP2C93 is observed in 1.3% of African Americans and 3–16% of Caucasians [95]. For CYP2C192,

frequencies are 17% in Africans, 18% in African Americans, 11% in the American population, 33% in Central/South East Asia, 30% in East Asia, and 15% in Europeans; CYP2C193 is restricted to 1% in Central/South East Asia and 7% in East Asia [98].

Understanding these allele distributions helps predict which ethnicities, admixtures, or populations are more prone to adverse reactions, including severe cutaneous adverse drug reactions (SCARs), triggered by aromatic antiseizure medications (ASMs). In Latin America, frequencies are variable due to the admixture of European, African, Asian, and Amerindian ancestries [98]. **Table 2** summarizes eleven high-quality studies that applied association statistics and identified an increased risk of SCARs linked to specific allelic variants.

Table 2. Genetic variants linked to severe cutaneous adverse reactions (SCARs) caused by aromatic antiseizure medications

Title (paraphrased)	Author & Year	Study Design	Drug(s)	Key Allelic Variant(s)	Main Findings (SJS/TEN/SCARs association with CYP alleles and aromatic ASMs)	Conclusions & Clinical Implications
Relationship between galactose deficiency testing, phenytoin metabolite levels, and CYP2C9/CYP2C19 polymorphisms in patients with long-term phenytoin treatment and gingival overgrowth	Lin *et al.* (2008) [99]	Prospective study	Phenytoin (PHT)	CYP2C9, CYP2C19	Higher plasma phenytoin levels linked to increased risk of gingival hyperplasia (OR 1.09; 95% CI 1.00–1.19). The major metabolite R-HPPH was significantly lower in CYP2C19 poor metabolizers (73.92 ± 48.14 ng/mL; p = 0.03). No direct association found between CYP2C9/CYP2C19 poor metabolizer status and gingival hyperplasia.	Elevated phenytoin concentrations due to CYP polymorphisms contribute to gingival hyperplasia in long-term users.
CYP2C19*2 allele and risk of severe cutaneous adverse reactions to phenobarbital in Thai pediatric patients	Manuyakorn *et al.* (2013) [100]	Case-control	Carbamazepine (CBZ), Phenytoin (PHT), Phenobarbital (PHB)	CYP2C19*2	CYP2C19*2 carriers had higher risk of CBZ- or PHT-induced SCARs (OR 2.5; 95% CI 0.96–67.3; p = 0.06) and significantly higher risk of phenobarbital-induced SCARs (OR 4.5; 95% CI 1.17–17.37; p < 0.03).	CYP2C19*2 may serve as a useful genetic marker to identify children at risk of phenobarbital-related severe skin reactions.

Impact of genetic and clinical factors on phenytoin-related severe skin reactions	CYP2C9*3 as a predictor of phenytoin-induced severe cutaneous adverse reactions in Thai children with epilepsy	CYP2C9*3 polymorphism and phenytoin-associated severe cutaneous adverse reactions
Yampayon *et al.* (2017) [103]	Suvichapanich *et al.* (2015) [102]	Chung *et al.* (2014) [101]
Case-control	Case-control	Case-control
Phenytoin (PHT)	Phenytoin (PHT), Phenobarbital (PHB)	Phenytoin (PHT)
CYP2C9*3*, *HLA-B*13:01, HLA-B*56:02/04*, *CYP2C19*3	CYP2C9*3	CYP2C9*3
CYP2C9*3 strongly linked to phenytoin-induced SJS (OR 10.41; 95% CI 2.06–55.42; p = 0.0042). Additional significant associations: HLA-B*13:01 (OR 13.29; p = 0.0001), HLA-B*56:02/04 (OR 56.23; p = 0.0007), CYP2C19*3 (OR 6.75; p = 0.0414).	CYP2C9*3 significantly associated with phenytoin-induced SCARs (OR 14.52; 95% CI 1.18–∞; p = 0.044). No association with phenobarbital-induced SCARs.	Strong association between CYP2C9*3 and phenytoin-induced SCARs (OR 12; 95% CI 6.6–20; $p = 1.1 \times 10^{-17}$).
Combining multiple genetic biomarkers improves prediction of phenytoin-induced SCARs.	CYP2C9*3 is a reliable predictive biomarker for phenytoin-related SCARs in Thai children.	CYP2C9*3 reduces phenytoin clearance and markedly increases the risk of severe skin reactions.

Influence of CYP2C9 and CYP2C19 variants on phenytoin-induced cutaneous adverse reactions	HLA alleles and CYP2C9*3 as predictors of phenytoin hypersensitivity in East Asian populations	CYP2C9*3 and risk of phenytoin-induced Stevens–Johnson syndrome/toxic epidermal necrolysis: systematic review and meta-analysis
Fohner *et al.* (2020) [106]	Su *et al.* (2019) [105]	Wu *et al.* (2018) [104]
Retrospective cohort	Case-control	Systematic review & meta-analysis
Phenytoin (PHT)	Phenytoin (PHT)	Phenytoin (PHT)
CYP2C9*3	CYP2C93, *HLA-B*13:01, HLA-B*15:02*, *HLA-B*51:01	CYP2C9*3
CYP2C93 *associated with higher risk of phenytoin-SCARs even without HLA-B*15:02 (OR 4.47; 95% CI 1.64–11.69; $p < 0.01$). Asians showed 3.7-fold higher SCAR risk than non-Hispanic Caucasians ($p = 0.04$).	Combined CYP2C93 *and certain HLA alleles (B*13:01, B*15:02*, *B*51:01) strongly associated with phenytoin-induced SCARs (OR 4.55; 95% CI 1.44–14.41; $p = 0.01$).	CYP2C9*3 significantly associated with PHT-induced SJS/TEN (OR 8.93; 95% CI 2.63–30.36; $p = 0.0005$ and OR 8.88; 95% CI 5.01–15.74; $p < 0.00001$). Moderate heterogeneity ($I^2 = 46\%$).
CYP2C93 *independently increases phenytoin-related skin reaction risk, particularly in populations lacking HLA-B*15:02 screening.	Joint testing of HLA risk alleles and CYP2C9*3 may help prevent phenytoin hypersensitivity in Asian patients.	CYP2C9*3 is a confirmed predictive genetic risk factor for phenytoin-induced SJS/TEN; large prospective studies still needed.

HLA-B*51:01, HLA-B*55:01, and CYP2C9*3 as risk factors for phenytoin-induced severe skin reactions in South Indian Tamil population	John *et al.* (2021) [109]	Case-control	Phenytoin (PHT)	CYP2C93, *HLA-B*51:01, HLA-B*55:01	CYP2C93 *associated with SCARs (OR 12.00; 95% CI 2.76–84.87; p = 0.03) and with maculopapular rash (OR 4.04; 95% CI 1.13–15.67; p = 0.035). HLA-B*51:01 and HLA-B*55:01 also significant risk factors.*	These genetic variants are important risk markers in South Indian Tamils; larger studies required to establish clinical utility.
Genetic and clinical predictors of phenytoin-induced cutaneous adverse reactions in Thai individuals	Sukasem *et al.* (2020) [108]	Case-control	Phenytoin (PHT)	CYP2C93, *HLA-B*46:01, HLA-B*56:02/04	CYP2C93 *borderline association with SJS/TEN (OR 4.80; 95% CI 0.96–23.99; p = 0.056). HLA-B*56:02/04 strongly linked to DRESS/DHS (OR 29.31; 95% CI 1.21–708; p = 0.038). HLA-B*46:01 also significant (OR 2.34; p = 0.032).*	These alleles contribute to phenytoin ADR risk; larger studies needed for confirmation.
HLA-B*51:01 and CYP2C93 as risk factors for phenytoin-induced rash in Japanese patients (Biobank Japan Project)	Hikino *et al.* (2020) [107]	Case-control	Phenytoin (PHT)	CYP2C93, *HLA-B*51:01	CYP2C93 *(OR 7.05; 95% CI 2.44–20.4; p = 0.0022) and HLA-B*51:01 (OR 3.19; 95% CI 1.37–7.48; p = 0.010) both associated with phenytoin-induced cutaneous eruption.*	Pre-treatment screening for CYP2C93 *and HLA-B*51:01 is recommended in Japanese patients to reduce phenytoin-related rash.

Abbreviations: ASMs = antiseizure medications; CBZ = carbamazepine; PHT = phenytoin; PHB = phenobarbital; DRESS = drug reaction with eosinophilia and systemic symptoms; DHS = drug hypersensitivity syndrome; SCARs = severe cutaneous adverse drug reactions; SJS/TEN = Stevens–Johnson syndrome/toxic epidermal necrolysis; OR = odds ratio; 95% CI = 95% confidence interval.

The significant influence of pharmacogenomic variability on AEDs-induced SCARs across different populations

The human leukocyte antigen alleles HLA-B15:02 and HLA-A31:01 serve as pharmacogenomic markers for predicting the likelihood of carbamazepine-induced hypersensitivity reactions [14]. Specifically, HLA-B15:02 is linked to Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) triggered by carbamazepine [13, 110], as well as reactions to oxcarbazepine and phenytoin [12, 111], and lamotrigine [112]. In contrast, HLA-A31:01 is associated with drug reaction with eosinophilia and systemic symptoms (DRESS), postoperative

myalgic pain syndrome (PMS), and also SJS/TEN [14]. **Table 3** provides a summary of HLA allelic variants linked to severe cutaneous adverse reactions induced by antiseizure medications.

Table 3. Human Leukocyte Antigen (HLA) alleles linked to severe cutaneous adverse reactions (SCARs) caused by antiseizure medications (ASMs)

Title (paraphrased)	**Author & Year**	**Study Design**	**Culprit Drug(s)**	**Associated HLA Allele(s)**	**Key Findings on SJS/TEN or other SCARs (with statistical data)**	**Conclusions & Clinical Implications**
HLA-A*31:01 and HLA-B*15:02 as predictors of carbamazepine hypersensitivity reactions in pediatric patients	Mehta *et al.* (2009) [113]	Case-control	Carbamazepine (CBZ)	HLA-B*15:02	Strong association between HLA-B*15:02 and CBZ-induced SJS in Indian children (OR 71.40, 95% CI 3.0–16.98, p = 0.0014)	HLA-B*15:02 is a useful genetic marker for CBZ-induced SJS in Indian pediatric patients.
Prevalence and role of HLA-B*15:02 in carbamazepine hypersensitivity among Malaysian epilepsy patients	Then *et al.* (2011) [114]	Case-control	CBZ	HLA-B*15:02	HLA-B*15:02 significantly linked to CBZ-induced SJS/TEN (p = 0.0006)	Confirmed association in Malay and Chinese Malaysian epilepsy patients.
HLA-B*15:02 association with carbamazepine-induced SJS/TEN and toxic epidermal necrolysis in a multi-ethnic Malaysian cohort	Chang *et al.* (2011) [16]	Case-control	CBZ	HLA-B*15:02	75.0% of affected Malaysian patients carried HLA-B*15:02 vs 15.7% in controls (OR 16.15, 95% CI 4.57–62.4, p = 7.87×10^{-6})	HLA-B*15:02 can serve as a reliable genetic screening marker to prevent CBZ-induced SJS/TEN in Malaysians.
Strong link between HLA-B*15:02 and carbamazepine-induced SJS/TEN in Han Chinese patients from mainland China	Zhang *et al.* (2011) [115]	Case-control	CBZ	HLA-B*15:02	94.1% of patients with CBZ-induced SJS/TEN carried HLA-B*15:02 (p < 0.01)	Clear association of HLA-B*15:02 with CBZ-induced SCARs in central and northern Han Chinese populations.

HLA-A*24:02/Cw*0102 haplotype associated with lamotrigine-induced maculopapular eruption in Koreans	HLA-A*02:01:01–B*35:01:01–C*04:01:01 haplotype linked to lamotrigine- and phenytoin-induced maculopapular exanthema in Mexican Mestizo individuals	HLA-A*31:01 and HLA-B*15:02 as markers of carbamazepine hypersensitivity in a pediatric multi-ethnic North American cohort	HLA-B*15:02 as a robust predictor of carbamazepine-induced SJS/TEN in Thai patients treated for neuropathic pain
Moon *et al*. (2015) [119]	Fricke-Galindo *et al*. (2014) [118]	Amstutz *et al.* (2013) [117]	Kulkantrakorn *et al*. (2012) [116]
Case-control	Case-control	Case-control	Case-control
LTG	Lamotrigine (LTG), Phenytoin (PHT)	CBZ	CBZ
HLA-A*24:02	HLA-A*02:01, HLA-B*35:01, HLA-C*04:01, HLA-C*08:01	HLA-B*15:02	HLA-B*15:02
HLA-A*24:02 significantly higher in LTG-induced MPR cases (OR 4.09 vs tolerant, p = 0.025; OR 3.949 vs general Korean population, p = 0.005)	HLA-C*08:01 strongly linked to PHT-induced MPR (pc = 0.0179 vs tolerant, pc < 0.0001 vs general population). Same haplotype also associated with LTG-induced MPR (pc = 0.0048 vs tolerant, pc < 0.0001 vs population)	HLA-B*15:02 significantly associated with CBZ-induced SJS/TEN (OR 38.6, p = 0.002)	Very strong association (OR 75.4, 95% CI 13.0–718.9, p < 0.001)
HLA-A*24:02 appears to be a risk factor for lamotrigine-induced maculopapular rash in the Korean population.	These HLA variants may serve as biomarkers for LTG- and PHT-induced maculopapular rash; further confirmation studies needed.	HLA-B*15:02 predicts CBZ hypersensitivity even in ethnically diverse North American children.	HLA-B*15:02 is a valuable biomarker for preventing CBZ-induced SJS/TEN in Thai patients.

Different HLA class I associations for aromatic AED-induced SJS/TEN versus DRESS in Spanish patients	HLA-A and HLA-B alleles linked to lamotrigine-induced severe cutaneous reactions in Thai patients	HLA allele distribution in 5802 Koreans and varying associations with SJS/TEN depending on the causative antiseizure drug	Meta-analysis of HLA-B*15:02 and lamotrigine-induced SJS/TEN in Han Chinese populations
Ramírez *et al.* (2017) [20]	Koomdee *et al.* (2017) [121]	Park *et al.* (2016) [120]	Zeng *et al.* (2015) [112]
Case-control	Case-control	Retrospective	Meta-analysis
CBZ, PHT, LTG	LTG	LTG	LTG
HLA-A*02:01*, *HLA-A*11:01, HLA-B*38:01	HLA-A*02:07*, *HLA-A*33:03, HLA-B*15:02*, *HLA-B*44:03	HLA-B*44:03	HLA-B*15:02 (also mentions HLA-A*24:02 in title but focus is B*15:02)
HLA-A*02:01/Cw*15:02 strongly linked to PHT-induced SJS/TEN (OR up to 27.50). HLA-B*38:01 linked to PHT- and LTG-induced SJS/TEN (OR up to 147). HLA-A*11:01 linked to CBZ-induced SJS/TEN (OR up to 63.89)	HLA-A*02:07* & *HLA-B*15:02 linked to overall LTG-SCARs (OR 7.83 & 4.89). HLA-A*33:03*, *HLA-B*15:02, and HLA-B*44:03 linked specifically to MPR (OR 8.27, 7.33, 10.29 respectively; all $p \leq 0.029$)	HLA-B*44:03 associated with LTG-induced SJS/TEN (OR 12.75, 95% CI 1.03–157.14, $p = 0.053$)	Pooled analysis showed association between HLA-B*15:02 and LTG-induced SJS/TEN (OR 4.98, 95% CI 1.43–17.28, $p < 0.05$)
Distinct HLA risk profiles for SJS/TEN vs DRESS with aromatic ASMs in Spaniards.	These four alleles are potential screening markers to prevent LTG-induced cutaneous reactions in Thai patients; larger studies warranted.	HLA-B*44:03 may be a risk allele for lamotrigine-induced SJS/TEN in Koreans.	Moderate increased risk of LTG-induced SJS/TEN in carriers of HLA-B*15:02; larger studies recommended.

HLA-A*24:02 as a shared risk factor for cutaneous adverse reactions induced by multiple aromatic antiepileptic drugs in southern Han Chinese	Shi *et al.* (2017) [122]	Case-control	CBZ, PHT, LTG	HLA-A24*:02, HLA-*B15:02	HLA-B*15:02 very strongly linked to CBZ-SJS ($p = 5.63 \times 10^{-15}$); HLA-*A24:02 linked to CBZ (p = 0.015), LTG (p = 0.005), and PHT (p = 0.027) SJS. Combined positivity: sensitivity 72.5%, specificity 69.0%	HLA-A*24:02 is a common genetic risk factor across aromatic ASMs in southern Han Chinese; pretreatment screening recommended.
Pharmacogenomic markers of severe cutaneous reactions to aromatic antiseizure medications in Iraqi patients	Ahmed *et al.* (2024) [123]	Case-control	CBZ, PHT, LTG	HLA-A*24:02, HLA-B*15:02, HLA-B*40:02, *HLA-DRB1*03:01	HLA-A*24:02 and HLA-B*15:02 increase risk of SJS (OR 3.60 and 4.41). HLA-DRB1*03:01 linked to TEN (OR 5.09). HLA-B*40:02 linked to DRESS (OR 29.33)	These alleles are promising biomarkers for personalized prevention of ASM-induced SCARs in Iraqi/Middle Eastern populations.

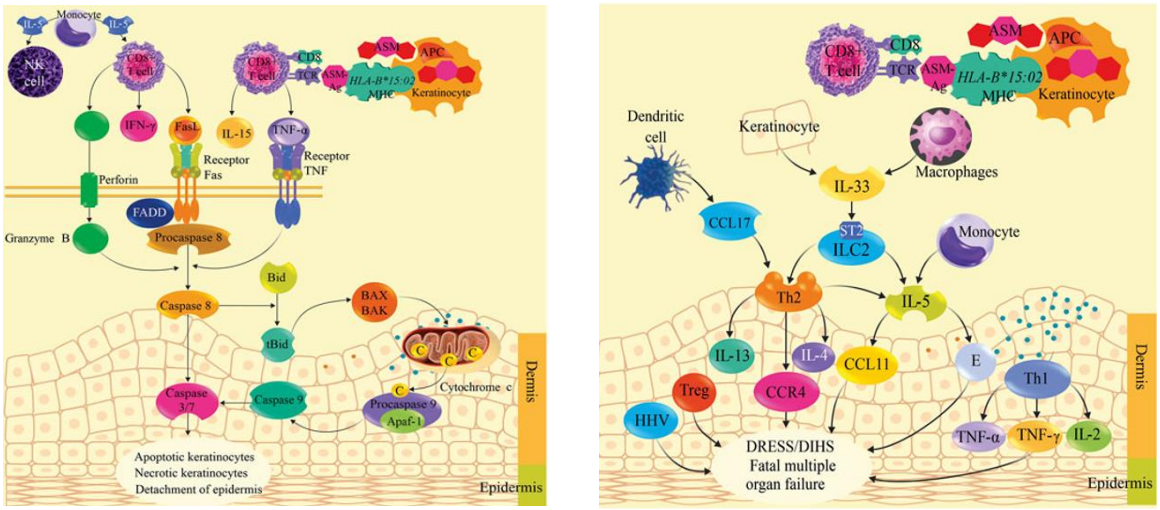
Abbreviations: ADRs, adverse drug reactions; DRESS, drug reaction with eosinophilia and systemic symptoms; SCARs, severe cutaneous adverse reactions; MPR, maculopapular rash; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; ASMs, antiseizure medications; CBZ, carbamazepine; PHT, phenytoin; LTG, lamotrigine; OR, odds ratio; 95% CI, 95% confidence interval.

Immunopathogenesis of hypersensitivity reactions

The precise mechanisms underlying the immunopathogenesis of SJS/TEN and DRESS/DIHS induced by antiseizure medications (ASMs) remain unclear, though several prominent pathways have been proposed. Aromatic ASMs and their metabolites function as haptens that are phagocytosed by keratinocyte antigen-presenting cells (APCs) and degraded into small fragments (ASM antigens, ASM-Ag). These ASM-Ags can activate the HLA-B*15:02 allele, which is part of the major histocompatibility complex (MHC) class I genes; MHC I molecules then present the ASM-Ags on the keratinocyte surface, allowing recognition by cytotoxic T cells (CD8+). This triggers extensive clonal expansion of CD8+ cells within the damaged epidermis, which release cytotoxic mediators such as perforin, granzyme B, granulysin, Fas ligand (FasL/CD95L), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) [32, 41, 42, 44, 124]. Concurrently, monocytes and other immune cells secrete IL-5, which further activates CD8+ T cells and natural killer (NK) cells [125]. TNF-α engages TNF receptors to activate procaspase-8, while perforin forms membrane pores in keratinocytes allowing granzyme B entry, which also activates procaspase-8. FasL on lymphocytes binds to the Fas receptor, recruiting procaspase-8 via FADD and forming a signaling complex that converts procaspase-8 into active caspase-8, which subsequently activates caspases-3/7. Caspase-8 also cleaves the proapoptotic protein Bid into truncated Bid (tBid), which translocates to the mitochondrial outer membrane to activate BAX and BAK; these proteins form pores in the mitochondrial membrane, releasing cytochrome c and forming the caspase-9–cytochrome c–Apaf-1 complex, leading to caspase-9 activation and subsequent stimulation of caspases-3/7. The cumulative effect of these pathways drives extensive keratinocyte apoptosis, necroptosis, and epidermal detachment [42-44, 126-128]. Additionally, reactive oxygen species (ROS) generated within keratinocytes contribute to intracellular injury [129-131].

In DRESS/DIHS, immune cell infiltration in the dermis involves CD4+ and CD8+ T cells, plasma dendritic cells (DCs), regulatory T cells (Tregs), innate lymphoid cells type 2 (ILC2), and monocytes (M) [131]. Keratinocytes and macrophages release IL-33, which binds to the ST2 receptor to activate ILC2s, while DCs secrete CC

chemokine ligand 17 (CCL17) to recruit Th2 T cells expressing chemokine receptor 4 (CCR4). Th2 cells and ILC2s produce IL-5 to activate and recruit eosinophils, and Th2 cells additionally release IL-4 and IL-13. Eosinophils secrete eotaxin-1 (CCL11), and together with IL-5, this facilitates local accumulation of cytotoxic eosinophils. Th1 cells release cytokines such as TNF-α, IFN-γ, IL-2, and IL-12. Human herpesvirus (HHV) reactivation and Treg dysregulation also occur, collectively contributing to DRESS/DIHS induced by aromatic ASMs [32, 132] and potentially leading to severe multi-organ failure [28, 133]. The immunopathogenesis of SJS/TEN is illustrated in **Figure 2a**, while the proposed pathway for DRESS is shown in **Figure 2b.**



a) b)

Figure 2. Immunopathogenic Mechanisms of Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Drug-Induced Hypersensitivity Reaction (DIHS) Triggered by Antiseizure Medications.

(a) illustrates the SJS/TEN pathway induced by aromatic ASMs. ASMs are engulfed by keratinocyte antigen-presenting cells (APCs) and broken down into ASM antigens (ASM-Ag). These antigens interact with the HLA-B*15:02 allele within MHC class I genes. The resulting MHC I–ASM-Ag complex is displayed on keratinocyte surfaces, where CD8+ cytotoxic T cells recognize it, leading to a substantial clonal expansion of CD8+ cells that infiltrate the injured epidermis. These cells release perforin, granzyme B, granulysin, Fas ligand (FasL/CD95L), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α), which collectively activate caspases, causing apoptosis, necroptosis of keratinocytes, and epidermal shedding. Monocyte-derived IL-5 further amplifies CD8+ T cell and NK cell activity. (b) depicts the immunopathogenic sequence in DRESS/DIHS. Keratinocytes and macrophages release IL-33, which engages ST2 receptors to stimulate ILC2s. Plasma dendritic cells secrete CCL17, recruiting Th2 cells expressing CCR4. Both Th2 cells and ILC2s generate IL-5, promoting eosinophil (E) activation and migration, while Th2 cells additionally release IL-4 and IL-13. Eosinophils produce CCL11 (eotaxin-1), and IL-5 together with CCL11 drives the accumulation of cytotoxic eosinophils at the affected site. Th1 cells release TNF-α, IFN-γ, IL-2, and IL-12. Concomitant HHV reactivation and Treg dysfunction contribute to the pathology. This combination of cytokines and chemokines underlies DRESS/DIHS and can precipitate severe multi-organ failure [28, 32, 132, 133].

Non-genetic factors linked to ADRs and SCARs from aromatic antiseizure medications

Several non-genetic variables influence the likelihood of ADRs and SCARs, including age, comorbidities, polytherapy, high ASM doses, alcohol consumption, sex, and viral infections [134, 135]. Aging is associated with hepatocyte structural alterations and mitochondrial dysfunction [136], as well as reduced functional glomeruli due to nephrosclerosis [137], which slows drug metabolism, prolongs half-life, and increases ASM plasma concentrations, thereby heightening ADR risk [138]. People with epilepsy exhibit higher rates of comorbid conditions—anxiety, depression, dementia, migraines, arthritis, cardiovascular disease, and peptic ulcers—up to eightfold compared to the general population [139], correlating with an elevated risk of ADRs [140, 141].

Using multiple ASMs simultaneously (polytherapy) increases ADR risk relative to monotherapy [142, 143]. Drugs such as valproic acid, stiripentol, felbamate, and rufinamide act as enzyme inhibitors, reducing the clearance

of co-administered ASMs and raising their plasma levels [89, 144]. For example, carbamazepine levels exceeding 12 mg/L can cause photosensitivity, eosinophilia, and hepatotoxicity [145, 146], whereas phenytoin above 20 mg/L can lead to neurotoxicity (dizziness, nystagmus, ataxia, sedation), as well as gingival overgrowth, hirsutism, and acne [2, 146-148].

Epileptic patients are more vulnerable to infections such as HIV, cytomegalovirus, or Epstein-Barr virus, which can sustain neuroinflammation, cause persistent brain infection, and trigger seizures in immunocompromised individuals [135]. These infections may impair hepatic enzyme function, slowing drug metabolism and leading to elevated, potentially toxic drug levels, necessitating dose adjustments or selection of ASMs metabolized independently of CYP-450 pathways [149].

Considering interactions between non-genetic factors and genetic polymorphisms (CYP2C9, CYP2C19, and HLA genes) is critical for anticipating ADRs and SCARs and implementing effective preventive strategies.

Clinical implications

This study carries significant clinical relevance by highlighting risk alleles, enabling predictive medicine to anticipate hypersensitivity reactions, facilitating preventive strategies, and supporting personalized approaches for treatment initiation, dose adjustment, or discontinuation—hallmarks of genomic or precision medicine. Pharmacogenetic testing, when prescribed by a neurologist, can detect patients carrying genetic variants associated with increased susceptibility to hypersensitivity reactions, and such testing is ideally performed prior to initiating antiseizure medication therapy.

Recognizing at-risk individuals allows neurologists to implement proactive measures to reduce the likelihood and severity of hypersensitivity reactions. Additionally, knowledge of a patient's genotype and metabolic phenotype provides the foundation for individualized dosing from the outset of treatment. Specifically, understanding the pharmacogenomic significance of allelic variants such as CYP2C192, CYP2C93, and human leukocyte antigens (HLA) is critical for making informed decisions regarding treatment discontinuation, switching to alternative antiseizure medications, or selecting safer therapeutic options for patients with epilepsy.

It is important to acknowledge the limitations of this descriptive review, which may introduce bias or limit interpretability. The main limitation is the relatively small body of published research on pharmacogene allelic variants associated with Stevens-Johnson syndrome and toxic epidermal necrolysis triggered by antiseizure medications, often with small patient cohorts and lacking statistical association analyses. Nonetheless, this review consolidates and updates current knowledge on CYP2C9, CYP2C19, and CYP3A4 pharmacogenes linked to hypersensitivity reactions induced by aromatic antiseizure medications, providing a foundation for initiating further research on epilepsy patients in Peru and across Latin America.

Conclusion

Current evidence supports that CYP2C19*2, CYP2C9*3, and various HLA alleles are strongly associated with severe cutaneous adverse reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Neurologists should consider these genetic variants as both predictive and preventive biomarkers when prescribing carbamazepine, phenytoin, phenobarbital, and lamotrigine.

Future research should involve prospective, multicenter, and observational studies with larger patient cohorts to enable robust statistical analyses of these associations. This study provides neurologists with an academic resource to apply pharmacogenomic insights in clinical practice and serves as a foundational document for developing a Pharmacogenomic Guide. Such a guide could facilitate the implementation of 4P medicine—predictive, preventive, personalized, and participatory—within health systems, enhancing the quality of life for patients with epilepsy, particularly in Peru and across Latin America.

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