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Review Article

Pharmacogenetic variants of *CYP2C9* and *CYP2C19* associated with adverse reactions induced by antiepileptic drugs used in Peru

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Abstract

Epilepsy is the most common neurological disorder with a worldwide incidence of 20% and a treatment failure rate of 25–30%. The fluctuation in serum levels, efficacy and safety of antiepileptic drugs can be attributed to single nucleotide polymorphisms of genes encoding their respective proteins involved in drug metabolism. The present study attempted to evaluate the pharmacogenetic variants of *CYP2C9* and *CYP2C19* associated with adverse reactions induced by antiepileptic drugs used in Peru. Few studies were found to significantly associate the *CYP2C9*2*, *CYP2C9*3*, *CYP2C19*2*, and *CYP2C19*3* single nucleotide polymorphisms with elevated serum levels of valproic acid and carbamazepine, and valproic acid induction of hyperammonemia, and adverse reactions cutaneous for carbamazepine. There is further evidence of a significant association of *CYP2C9*2/CYP2C9*3* with severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and epidermal necrolysis (TEN) phenytoin-induced. *CYP2C9*3* may be a pharmacogenetic biomarker for such a drug. It is proposed to reduce the dose of drugs for intermediate and poor metabolizers. No pharmacogenetic studies were found in patients with epilepsy in Peruvian populations. It is concluded that this review could help physicians in the prediction and prevention of adverse reactions induced by antiepileptic drugs, as well as to improve their pharmacotherapeutic results. It could also be used as scientific evidence to carry out pharmacogenetic and precision medicine studies in Peruvian patients with epilepsy, due to their tricontinental and Latin American ancestry.

Keywords

Antiepileptic drugs, *CYP2C9*, *CYP2C19*, pharmacogenetics, precision medicine, clinical implication

Introduction

Epilepsy is a chronic neurological disorder characterized by self-limited seizures with a high probability of recurrence within the next 10 years, which may have a genetic, acquired or idiopathic origin (Fisher et al. 2017; Thong et al. 2020; Alvarado et al. 2022a); being the second most frequent neurological condition worldwide, and according to the World Health Organization (WHO), there are some 50 million people with epilepsy worldwide; and of these, 90% are registered in developing countries, while in countries with developed economies between 40–70 new cases/day and per 100,000 people are diagnosed (Moshe et al. 2015; Burneo et al. 2017). In Peru it is estimated that the prevalence of epilepsy is 11.9–32.1 per 1000 people, which is why it is currently a national and global public health problem (Burneo et al. 2005; Burneo et al. 2017). In Peru, antiepileptic drugs (AEDs) approved in the Single National Petition for Essential Medicines are used to treat this disease, including valproic acid (VPA), carbamazepine (CBZ) and phenytoin (PHT). Most patients with epilepsy respond to standard treatment, however, between 25–30% present resistance (Sillanpaa and Schmidt 2006; Sisodiya and Marini 2009; Kwan et al. 2010), and in these cases epilepsy surgery is used as an alternative treatment, without considering the polymorphisms in the *CYP2C9* and *CYP2C19* genes of each patient, the same ones that are responsible for the metabolic phenotypes involved in the variability of the response and in the adverse reactions due to the high serum level of antiepileptic drugs (Smolarz et al. 2021; Maqbool et al. 2022). The *CYP2C9* gene is highly polymorphic, with *CYP2C9*1* being the wild type allele, *CYP2C9*2* (rs1799853, c.430C>T) and *CYP2C9*3* (rs1057910, c.1075A>C) encoding proteins of reduced function (Chaudhry et al. 2010; Saldaña-Cruz et al. 2013; Céspedes-Garro et al. 2015; Claudio-Campos et al. 2017; Alvarado et al. 2019); while the *CYP2C19* gene presents more than 35 allelic variants (Yin and Miyata 2011), of which *CYP2C19*1* the wild type allele, *CYP2C19*2* (c.681G>A) and *CYP2C19*3* (636G>A) encode non-functional proteins (Sim et al. 2006; Beitelshees et al. 2011; Saeed and Mayet 2013; Scott et al. 2013; Dehbozorgi et al. 2018; Maruf et al. 2019; Vargas and Cobar 2021); *CYP2C19*17* (g. -806 C>T) encodes proteins with greater metabolic function (Hamdy et al. 2002; Lee 2013; Skadrić and Stojković 2020). *CYP2C9*2* and *CYP2C9*3* single nucleotide polymorphisms have been reported to be significantly associated with reduced metabolism and elevated serum level of phenytoin inducing adverse reactions compared to wild-type subjects (*CYP2C9*1* and *CYP2C19*1*) (Brandolese et al. 2001; López-García et al. 2017; Liao et al. 2018); *CYP2C19*2* and *CYP2C19*3* are also associated with reduced metabolism (Makowska et al. 2021; Garg et al. 2022). *CYP2C9*3* carriers require 37% less dose of phenytoin to achieve therapeutic serum levels compared to the dose of *CYP2C9*1* carrier patients (van der Weide et al. 2001). *CYP2C9*3* is significantly associated with the occurrence of PHT-induced gingival hyperplasia in Indian (Garg et al. 2022) and Japanese patients (Hirota et al. 2013). *CYP2C19*2* and *CYP2C19*3* predict the poor metabolizer (PM) phenotype and in this group of patients an increase in the values of the area under the curve (AUC) and the maximum plasmatic concentration (C_{max}) of phenytoin is observed (Hirota et al. 2013). *CYP2C9*2*, *CYP2C9*3*, and *CYP2C19*2* have also been reported to be significantly associated with resistance to antiepileptic drugs (Seven et al. 2014).

Due to these considerations, the PubMed-Medline database on pharmacogenomic studies and precision medicine in Peru has been reviewed, with these investigations being scarce in patients with epilepsy, therefore, a review study is warranted in accordance with the new treatment approach that is postulated through precision medicine in epilepsy, which considers the pharmacogenetic profile, the serum level of the drug, ethnicity, miscegenation, and the patient's sex, to individualize the dose of the drug, which will allow maintaining serum levels within the therapeutic index and minimize the adverse reactions induced by antiepileptic drugs (Alvarado et al. 2021; Alvarado et al. 2022a, b, c; Alvarado et al. 2023). In this sense, we have addressed 4 questions that support this article: ¿What is the current status and knowledge of the subject? Worldwide, there is evidence that *CYP2C9/CYP2C19* single nucleotide polymorphisms (SNPs) are associated with an increased risk of AED-induced adverse reactions; being these studies very limited or scarce in Peru; ¿What central question did this study address? By reviewing the scientific literature, an attempt has been made to find evidence of an association between the *CYP2C9/CYP2C19* SNPs and the adverse reactions induced by the AEDs most widely used in Peru; ¿What does this study contribute to new knowledge? This review aims to inform medical specialists that patients with diplotypes predictive of intermediate and poor metabolizers who are treated with AEDs are more likely to experience adverse reactions than are normal metabolizers; ¿How can this change pharmacogenetics and precision medicine? Knowing that the *CYP2C9/CYP2C19* SNPs influence drug response, and that pharmacogenetic tests should be performed prior to treatment, will make it possible to individualize the patient's dose, which will ensure drug serum levels within the therapeutic index and, at the same time, minimize the

AED-induced adverse reactions. In addition, this review will serve to generate scientific evidence, which will encourage analytical observational studies (cases/controls and cohorts) and randomized clinical trials (RCTs), and this will promote the implementation of precision medicine in health systems of Peru. The objective was to review the available evidence on the pharmacogenetic variants of *CYP2C9* and *CYP2C19* associated with adverse reactions induced by antiepileptic drugs used in Peru and their clinical impact on medicine.

Search strategy and selection criteria

A descriptive review of articles published in PubMed/Medline and Google Scholar was carried out. The search strategy was carried out using the keywords: "*CYP2C9* gene"; "*CYP2C19* gene"; "*CYP2C9/C19* SNP"; "*CYP2C9/C19* mutation" "pharmacokinetics of antiepileptic drugs"; "pharmacokinetics of valproic acid"; "pharmacokinetics of carbamazepine"; "Pharmacokinetics of Phenytoin". Additionally, the Boolean operators AND, OR, and NOT were used to incorporate the use of *CYP2C9/19* genes and resistance, *CYP2C9/19* genes and adverse reactions, *CYP2C9/C19* enzymes that metabolize antiepileptic drugs, *CYP2C9/19* genes and clinical implication, which allowed a more refined review. No ethnic or language restriction was applied for the search and inclusion of published articles.

Pharmacokinetics of antiepileptic drugs

Pharmacokinetics of valproic acid

Valproic acid (VPA) is a short-chain branched-chain fatty acid derivative, chemically named 2-propylpentanoic acid (Doré et al. 2017; Wallenburg et al. 2017; Li et al. 2021). Due to the pKa of 4.8, it is absorbed through the gastrointestinal mucosa to obtain a bioavailability >95%, and a maximum plasma concentration (C_{max}) of 23.5–25.3 mg/L, in a maximum time (t_{max}) of 1.5 hours and an area under the curve ($AUC^{o-\infty}$) of 626–831 mg.h/L (Alvarado et al. 2022c). It has a narrow therapeutic index, therefore its serum level should be monitored during the course of therapy so that the drug exceeds the trough effective concentration (C_{mE}) of 50 mg/L (350 mM) and does not exceed the trough toxic concentration (C_{MT}) of 100 mg/L (700 mM) (Chadwick 1985; Doré et al. 2017; Alvarado et al. 2022c). After its absorption, it circulates through the blood bound to plasmatic proteins by 90%, mainly to albumin. Said binding is saturable, 93% at 50 mg/L, and 70% at 150 mg/L (Ghodke-Puranik et al. 2013; Doré et al. 2017); the free fraction of the drug (7%) crosses the blood-brain barrier, more than 30% of the free fraction of VPA can cause adverse effects (Wallenburg et al. 2017). Steady state (C_{ss}) is reached in 3 to 50 days, volume of distribution (Vd) is 0.1–0.4 L/kg in adults, 0.20–0.30 L/kg in children, half-life ($t_{1/2}$) it is 4–20 h, the same time that decreases due to the action of enzyme-inducing drugs (Alvarado et al. 2022c). 40% of the VPA dose is metabolized by phase I oxidation: CYP2C9, CYP2C19, CYP2A6 and CYP2B6 isoenzymes form 4-hydroxy valproic acid and 4-ene-VPA implicated in hepatotoxicity (Jiang et al. 2009; Ghodke-Puranik et al. 2013; Bartra et al. 2021; Alvarado et al. 2022c); while CYP2A6 generates 3-hydroxy valproic acid, and through the action of CYP2C9, CYP2A6 and CYP2B6, VPA is biotransformed into 5-hydroxy valproic acid (Ghodke-Puranik et al. 2013; Alvarado et al. 2022c; Song et al. 2022). Between 30–50% of valproic acid is metabolized by phase II conjugation, mainly by UDP-glucuronosyl transferase 2B7 (UGT2B7) and others (UGT1A3, A4, A6, A8, A9, A10; UGT2B15) that transfer the glucuronic acid group from UDP-α-D-glucuronic acid (UDPGA) to the carboxylic group of VPA to form valproyl 1-O-β-acyl glucuronide; metabolism is saturable, and metabolites are eliminated in the urine (Jin et al. 1993; Staines et al. 2004; Ghodke-Puranik et al. 2013; Doré et al. 2017; Song et al. 2022). UGT2B7**2* may be involved in the increased area under the curve of serum VPA concentrations (Chung et al. 2008). Fig. 1 summarizes the metabolic pathway of valproic acid.

It is observed that valproic acid is metabolized by phase II conjugation with the participation of UGT1B7 and others (UGT1A3, UGT1A4 and UGT1B15) forming valproyl 1-O-β-acyl glucuronide. By phase I, valproic acid is oxidized into three main metabolites: by CYP2C19 and CYP2C9 (and with CYP2A6 and CYP2B6) valproic acid is converted to 4-hydroxy valproic acid; by action of CYP2A6 it is biotransformed into 3-hydroxy valproic acid; by the action of CYP2C9, CYP2A6 and CYP2B6 it is converted to 5-hydroxy valproic acid. Figure made by the authors.

Pharmacokinetics of carbamazepine

Carbamazepine (CBZ: 5-H-dibenzazepine-5-carboxamide) is an iminostilbene-type antiepileptic (Alvarado et al. 2022b; Chbili et al. 2017), whose N of the dibenzazepine ring gives it a pKa of 2.3 and the free NH_2 group of the carboxamide generates the pKa 13.9; being a class 2 drug with low solubility and high permeability according to the Biopharmaceutical Classification System (BCS) (Alvarado et al. 2021b, c), therefore it is absorbed by simple diffusion through the gastrointestinal mucosa (Alvarado et al. 2022b). Its bioavailability is 70–85%, establishing a minimum effective plasma concentration (C_{mE}) of 4 mg/L and a minimum toxic concentration (C_{MT}) of 12 mg/L as the optimal interval (Chbili et al. 2017; Johannessen Landmark et al. 2020; Alvarado et al. 2022b); the maximum time (t_{max}) is 4–8 h, and the steady-state serum concentration (C_{ss}) is reached in 28 days. Its binding to plasma proteins is high (UP 75–85%), and its volume of distribution (Vd) is 1.4 L/kg (Aldaz et al. 2011). By phase I carbamazepine is oxidized into three metabolites: by action of CYP3A4 it is converted to 2,3-carbamazepine epoxide; 3-hydroxy

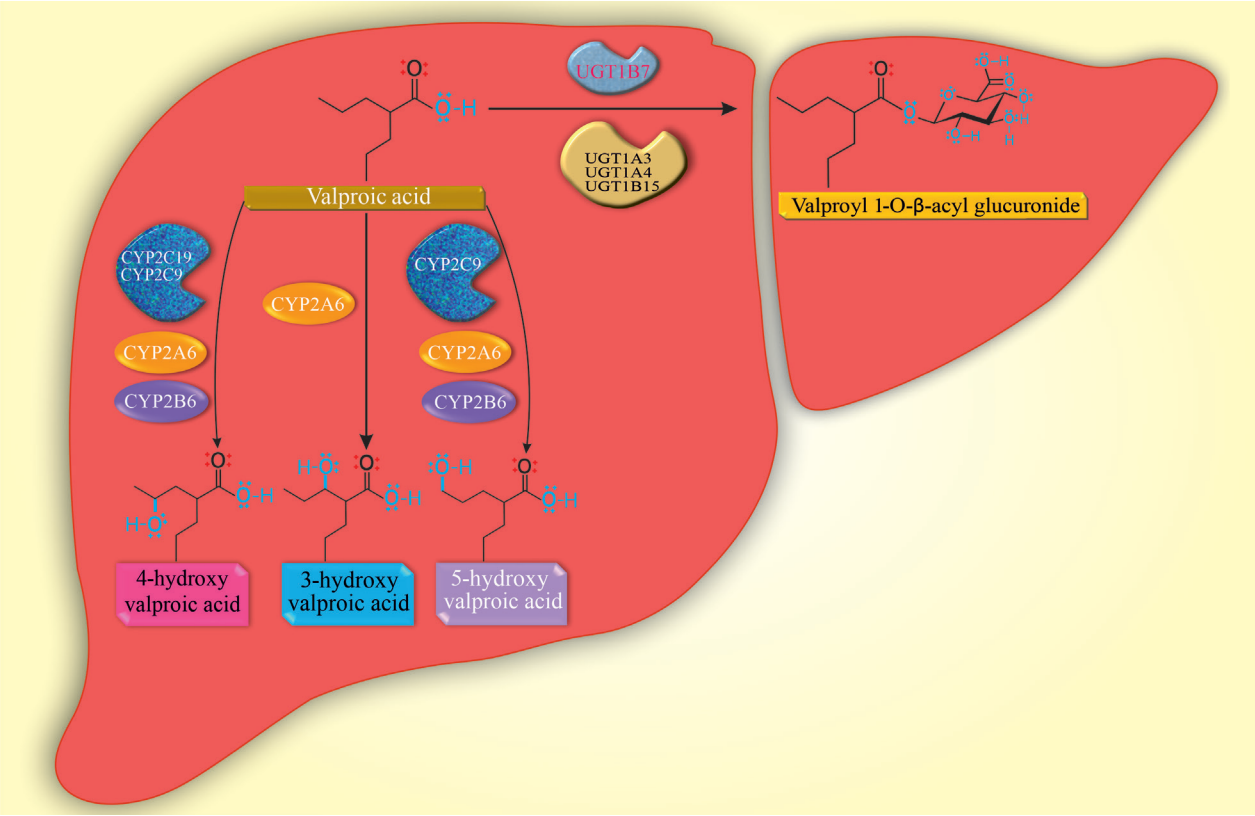

Figure 1. Metabolism of valproic acid by phase I and II.

carbamazepine is formed by CYP3A4, CYP2B6 and CYP3A7; by the action of CYP2C19, CYP2C9 and other isoenzymes (CYP2C9, CYP3A4, CYP3A5, CYP1A2, CYP1A1, CYP2A6, CYP2C8 and CYP2D6) it is biotransformed into the main metabolite carbamazepine 10,11-epoxide (Lopez-Garcia et al. 2014; Darwish et al. 2015; Gierbolini et al. 2016). Carbamazepine 10,11-epoxide undergoes two biotransformation processes: by action of UGT2B7, UGT1A6 carbamazepine 10,11-epoxide N-β-glucuronide is generated; the second reaction is by action of epoxide hydrolase forming 10,11-dihydro-10,11-trans-dihydroxy-carbamazepine (diOH-CBZ) (Darwish et al. 2015; Chbili et al. 2017); then UDP-glucuronosyl transferase 2B7, A6 and 2B (UGT2B7, UGT1A6 and UBG2B) is involved in the transfer of the glucuronic group of UDP-α-D-glucuronic acid (UDPGA) to the diOH-CBZ metabolite to generate O-β-glucuronide of carbamazepine (Darwish et al. 2015; Alvarado et al. 2022). Chronic use of carbamazepine can induce its own metabolism, inducing UGT2B7, epoxide hydrolase, CYP3A4 (Gierbolini et al. 2016), CYP2C9, CYP2C19, and CYP1A2 (Hernández and Marín 2017). The half-life time ($t_{1/2}$) in newborns is 12–64 hours, in children 10–13 hours and 8–20 hours in adults (Aldaz et al. 2011; Johannessen Landmark et al. 2020). Fig. 2 shows the metabolism of carbamazepine by phase I and II.

It is observed that carbamazepine is metabolized by three main routes: by action of CYP3A4 it is converted into 2,3-carbamazepine epoxide; by CYP3A4, CYP3A7 and CYP2B6 it is converted to 3-hydroxy-carbamazepine. By the action of CYP2C19, CYP2C9 and others (CYP3A4, CYP1A1 and CYP2D6) carbamazepine is biotransformed into carbamazepine 10,11-epoxide. The metabolite carbamazepine 10,11-epoxide is biotransformed by two routes: directly to carbamazepine 10,11-epoxide N-β-glucuronide by action of UGT2B7 and UGT1A6; By action of epoxide hydrolase, 10,11-dihydro-10,11-trans-dihydroxy-carbamazepine (diOH-CBZ) is generated, then this metabolite is conjugated by UGT2B7 forming O-β-glucuronide of carbamazepine. Figure made by the authors.

Pharmacokinetics of phenytoin

Phenytoin (PHT) is a derivative of hydantoin (5,5-diphenylimidazolidine-2,4-dione) with a pKa of 8.3;2,59,60 being class 2 (low solubility and high permeability) according to the Biopharmaceutical Classification System (BCS) (Alvarado et al. 2020), so it is absorbed in its non-ionized form through the gastrointestinal mucosa, generating a bioavailability of 80% (Milosheska et al. 2015; Guk et al. 2019; Alvarado et al. 2022a). It is another antiepileptic drug with a narrow therapeutic index, whose minimum effective plasma concentration (C_{mE}) is 10 mg/L and the minimum toxic concentration (C_{MT}) is 20 mg/L (Thaker et al. 2017). Phenytoin is metabolized by phase I oxidation, forming an intermediate metabolite 3',4'-epoxide of phenytoin by the action of the CYP2C9 isoenzymes (90%) and by CYP2C19 (10%); then said metabolite undergoes two metabolic processes: by action of epoxide hydrolase, 3',4'-dihydrodiol phenytoin is generated; and by action of CYP2C9 and CYP2C19 the main metabolite called 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) is generated. p-HPPH undergoes two metabolic processes:

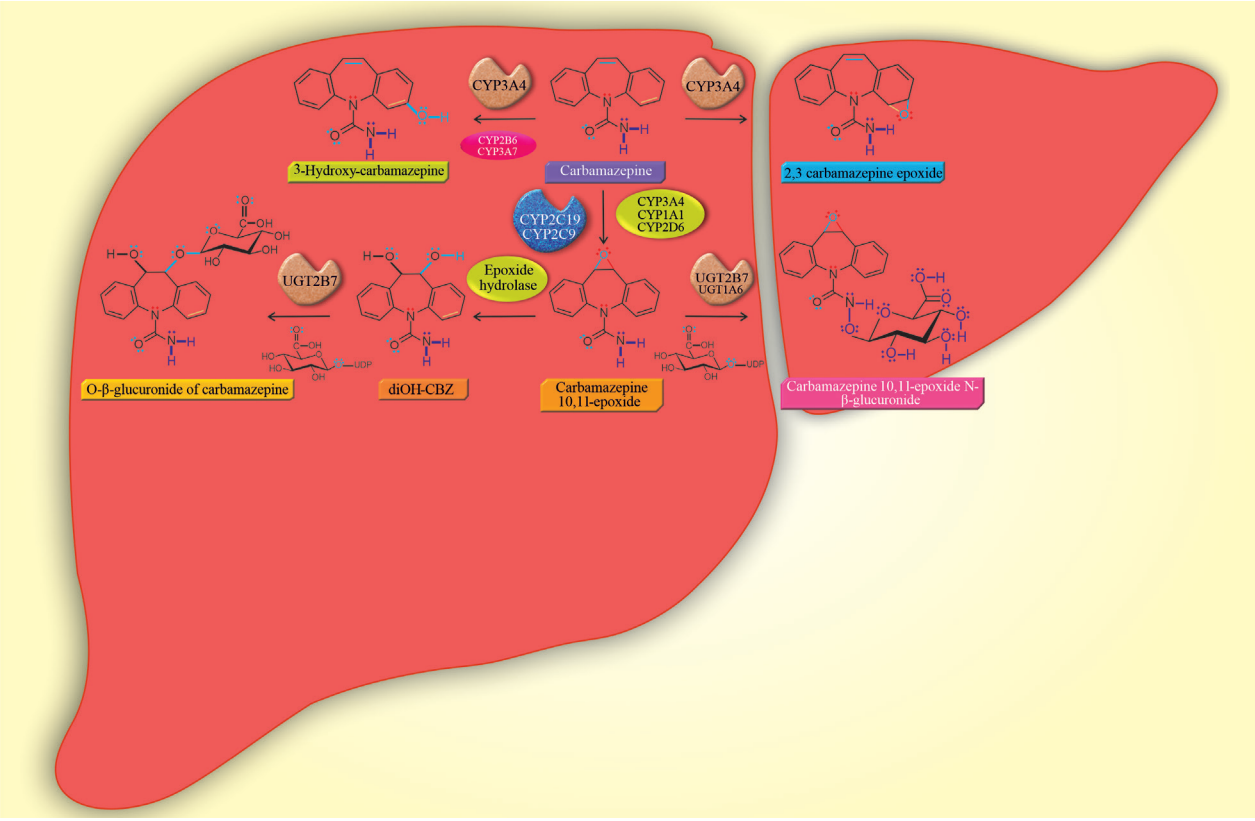

Figure 2. Metabolism of carbamazepine by phase I and II.

by action of CYP2C19 and to a lesser extent by CYP2C9, 3',4'-dihydrodiol phenytoin is generated; and by phase II conjugation, UDP-glucuronosyl transferase 1A (UGT1A) is involved in the transfer of the glucuronic group of UDP-α-D-glucuronic acid (UDPGA) to the p-HPPH metabolite to generate phenytoin O-β-glucuronide (Lopez-Garcia et al. 2014; Balestrini and Sisodiya 2018). Fig. 3 summarizes the metabolic process of phenytoin.

It is observed that phenytoin is metabolized by the action of CYP2C9 and CYP2C19 into phenytoin 3',4'-epoxide, and by the action of epoxide reductase phenytoin is regenerated. The metabolite phenytoin 3´,4´-epoxide is metabolized by two routes: by action of epoxide hydrolase it becomes 3´,4´-dihydrodiol phenytoin; by the action of CYP2C9 and CYP2C19 it is converted to 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH); then p-HPPH is converted to 3´,4´-dihydrodiol phenytoin by the action of CYP2C9 and CYP2C19; at the same time p-HPPH by action of UGT1A is converted into O-β-glucuronide of phenytoin. Figure made by the authors.

CYP2C9 and *CYP2C19* genes related to the metabolism of antiepileptic drugs

CYP2C9 gene

The *CYP2C9* gene is located on the long arm of chromosome 10 in region 24 of 500 kb (10q24) consists of 9 exons and is highly polymorphic with more than 61 allelic variants and multiple sub-alleles (Wang et al. 2004; Hirota et al. 2013; Mukai et al. 2017; Alvarado et al. 2019; Karnes et al. 2021). Of clinical interest is the wild type *CYP2C9*1* allele that encodes a protein with 100% enzymatic function and whose diplotypes predict normal metabolizers (NM) (Caudle et al. 2014; Balestrini and Sisodiya 2018); while the allelic variant *CYP2C9*2* CT (rs1799853, 430C>T) consists of three alleles *CYP2C9*2A*, **2B* and **2C34* characterized by a one nucleotide transition from cytosine (C) to thymine (T) in position 430 (c.430C>T) in exon 3 that results in the replacement of arginine (Arg) by cysteine (Cys) at position 144 of the protein (Arg144Cys) that has less interaction with its cofactor and whose function it is 12–50% compared to the wild type (Chaudhry et al. 2010; Alvarado et al. 2019; Garg et al. 2022). The allelic variant *CYP2C9*3* AC (rs1057910) is generated by a transversion of adenine (A) to cytosine (C) at base pair 1075 (c.1075A>C) in exon 7, causing an isoleucine (Ile) change to leucine (Leu) in codon 359 (Ile359Leu) of the protein, varying the binding site for the drug and whose function is 5% compared to the wild type (Chaudhry et al. 2010; Garg et al. 2022); *CYP2C9*5* (Ile359Thr) and *6 (c. delA818) that predict poor metabolizers (PM) (Fricke-Galindo et al. 2018). It has been established that an individual carrying an allele with normal function (**1*) and another with reduced function (**2* or **3*) configures a genotype or diplotype (*CYP2C9*1/*2* or *CYP2C9*1/*3*) predictor intermediate metabolism (IM) (Caudle et al. 2014; Alvarado et al. 2019); carriers of two reduced function alleles (**2* or **3*) configure diplotypes (*CYP2C9*2/*2*, *CYP2C9*2/*3*

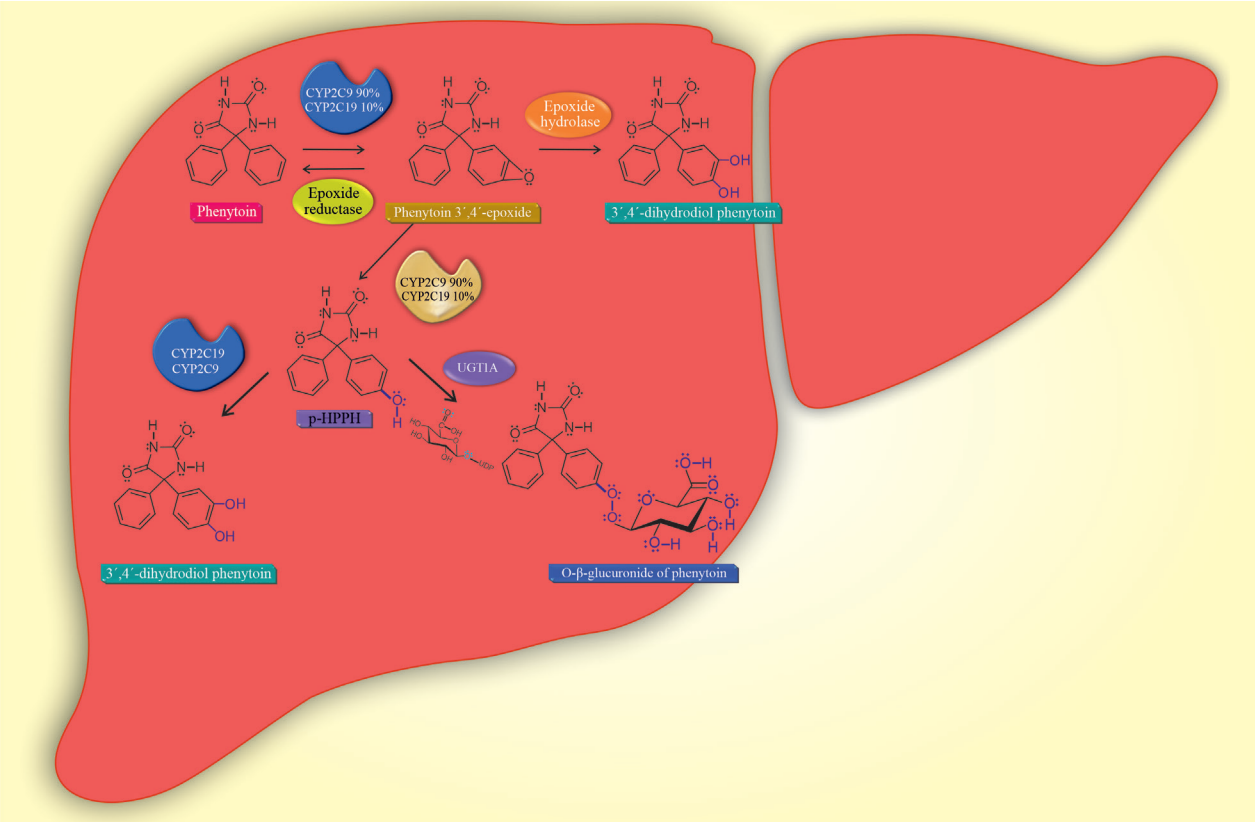

Figure 3. Metabolism of phenytoin by phase I and II.

or *CYP2C9*3/*3*) predictors of poor metabolism (PM) (Hirota et al. 2013; Caudle et al. 2014).

The *CYP2C9* enzyme (member of the mixed-function oxidase system, cytochrome P450: EC 1.14.13.48) is a 490-amino acid protein (Pinto and Dolan 2011; Hirota et al. 2013); represents 18% of the CYP proteins in liver microsomes (Pinto and Dolan 2011), and metabolizes approximately 15% of drugs, including antiepileptics, anticoagulants, antihypertensives, nonsteroidal anti-inflammatory drugs (Mukai et al. 2017), and sulfonylureas (glibenclamide) (Alvarado et al. 2021c). The frequencies of *CYP2C9*2* and *CYP2C9*3* alleles differ between ethnic groups and depend on the geographic location of a given population, being higher in Caucasians than in Africans and Asians (Caudle et al. 2014; Céspedes-Garro et al. 2015); *CYP2C9*3* is present in Caucasians with allele frequencies of 4% to 10% (Mittal et al. 2015), 4% in Asians and Indians (Henderson et al. 2019). Regarding genotypes, *CYP2C9*1/*2*, *CYP2C9*1/*3*, and *CYP2C9*2/*2* have been described in Caucasians (Fricke-Galindo et al. 2018); *CYP2C9*3/*3* in Indian (Hirota et al. 2013; Seven et al. 2014); *CYP2C9*1/*3* and *CYP2C19*1/*3* in Japanese (Mittal et al. 2015); *CYP2C9*6/*6* and *CYP2C19*1/*1* in African American populations (Fricke-Galindo et al. 2018).

CYP2C19 gene

The *CYP2C19* gene is located at locus 10q24.1 of chromosome 10 (long arm of chromosome 10 in region 24) where the coding sequence is 1473 bp, consists of 9 exons and 8 introns, encodes a protein of 490 residues of amino acids; presents more than 35 allelic variants and subvariants (Sim et al. 2006; Yin and Miyata 2011; Maruf et al. 2019); most individuals have *CYP2C19*1*, **2*, **3*, and **17* (Dehbozorgi et al. 2018). The wild type *CYP2C19*1* allele encodes the protein with 100% function; *CYP2C19*2* GA (rs4244285, 681G>A) is the most common allele that is produced by a transition from guanine (G) to adenine (A) at position 681 (c.681G>A) of exon 5, creating a site of aberrant splicing that alters the reading frame of the mRNA beginning at amino acid 215 and produces a 20 amino acid premature stop codon and non-functional protein is expressed (Sim et al. 2006; Lee 2013; Dehbozorgi et al. 2018; Maruf et al. 2019). The most important is *CYP2C19*3* (rs4986893, 683G>A) which has a point mutation (683G>A) in exon 4 resulting in a premature stop codon and therefore a non-functional protein (Hamdy et al. 2002; Saeed and Mayet 2013; Dehbozorgi et al. 2018; Bousman et al. 2019). *CYP2C19*17* (rs12248560, g. -806C>T) is a single nucleotide polymorphism of the 5' promoter region (g. -806C>T) that results in the change of Cys806Thr and the binding of region-specific nuclear proteins flanking 5'; this union increases the transcription of genes that encode proteins of greater metabolic function (Sim et al. 2006; Lee 2013; Dehbozorgi et al. 2018; Skadrić and Stojković 2020). *CYP2C19*4* (A>G in the start codon), *CYP2C19*5* (1297C>T) in the heme-binding region leading to an Arg433Trp substitution, *CYP2C19*6* (395G>A) in exon 3 generating Arg132Gln substitution, *CYP2C19*7* (T>A) at the 5' donor splice site of intron 5, *CYP2C19*8* (358T>C) in exon 3 generating Trp120Arg

substitution, *CYP2C19*16* (1324C>T) in exon 9 located near the heme binding region resulting in an Arg442Cys substitution (Lee 2013).

This gene encodes the CYP2C19 protein that metabolizes valproic acid, carbamazepine, and phenytoin; antidepressants (citalopram, escitalopram, sertraline, amitriptyline, clomipramine, doxepin, imipramine, and trimipramine), anticoagulants (clopidogrel), nonsteroidal anti-inflammatory drugs (NSAIDs), antihypertensives (propranolol), diazepam, proton pump inhibitors (PPIs), and others (Bousman et al. 2019; Skadrić and Stojković 2020). Regarding the metabolic phenotype, it is indicated that an individual who carries two alleles of normal function (**1*) inherited from mother and mother configures a genotype or diplotype (*CYP2C19*1/*1*) predictive of normal metabolism (NM) (Scott et al. 2013); carriers of the *CYP2C19*2* and *CYP2C19*3* alleles form diplotypes that are predictors of poor metabolizers (PM) (Wang et al. 2011), and the most frequent in Asians (Hamdy et al. 2002); and *CYP2C19*17* carriers configure predictive diplotypes of ultra-extensive metabolizers (URMs) (Chaudhry et al. 2008; Gawrońska-Szklarz et al. 2012).

The frequency of metabolizers, poor metabolizers (PM) for *CYP2C19* has been reported in Caucasian European populations to be 2–5% (Lim et al. 2014; Alvarado et al. 2023), 2–7% in black Africans (Scott et al. 2011), in Asians 15 -23% (Scott et al. 2011; Lim et al. 2014), specifically 15–17% Chinese, 18–23% Japanese, and 12–16% Korean; this suggests that the PM phenotype is an autosomal recessive trait that is inherited (Tabari et al. 2013). *CYP2C19*2* represents 93% in Europeans and 75% in East or East Asians (China, South Korea, and Japan) (Tabari et al. 2013; Mirzaev et al. 2017), and in Hispanics it is 12.6% (Mirzaev et al. 2017); *CYP2C19*3* represents 25% in Asians, being specific to these populations, which is why they are rare in other populations (Chen et al. 2009; Tabari et al. 2013). The frequency of *CYP2C19*17* in Europeans is 18–28%, Africans 17–18%, and 0.3–4% in Asians (Gawrońska-Szklarz et al. 2012; Saeed et al. 2013). Table 2 summarizes the polymorphisms of the *CYP2C9* and *CYP2C19* genes that

Table 1. Pharmacokinetic parameters of valproic acid, carbamazepine, and phenytoin.

Drug	F (%)	t_{max} (h)	C_{mE} (mg/L)	UP (%)	Vd (L/kg)	$t_{1/2}$ (h)	Enzyme	Reference
Valproic acid	95	1.5	50	90	0.1–0.4	4–20	*CYP2C9* *CYP2C19* *CYP2A6* *CYP2B6*	(Doré et al. 2017; Alvarado et al. 2022c)
Carbamazepine	70–85	4–8	4	75–85	1.4	8–20	*CYP2C9* *CYP2C19* *CYP3A4* *CYP2B6* *CYP3A7*	(Aldaz et al. 2011; Gierbolini et al. 2016; Alvarado et al. 2022b)
Phenytoin	80	3–12	10	90	0.6–0.7	8–60	*CYP2C9* *CYP2C19*	(Lopez-Garcia et al. 2014; Balestrini and Sisodiya 2018)

Table 2. Characteristics of the *CYP2C9* and *CYPC19* genes and their phenotypes.

Allele	Nucleotide change (cDNA)	Diplotype	Phenotype	Activity score	Reference
Gene/chromosome: *CYP2C9*/10q24					
*CYP2C9*1*	None	*CYP2C9*1/*1*	NM	2	(Karnes et al. 2021)
*CYP2C9*2*	430C>T (rs1799853)	*CYP2C9*1/*2* *CYP2C9*2/*2*	IM	1.5 1	(Karnes et al. 2021)
*CYP2C9*3*	1075A>C (rs1057910)	*CYP2C9*1/*3* *CYP2C9*2/*3* *CYP2C9*3/*3*	IM PM	1 0.5 0	(Karnes et al. 2021)
CYP2C9*5	delA818	*CYP2C9*5/*5*			(Karnes et al. 2021)
Gene/chromosome: *CYP2C19*/10q24					
*CYP2C19*1*	None	*CYP2C19*1/*1*	NM	1	(Céspedes-Garro et al. 2015; Maruf et al. 2019)
*CYP2C19*2*	681G>A (rs4244285)	*CYP2C19*1/*2*	IM	0.5	(Céspedes-Garro et al. 2015; Maruf et al. 2019)
*CYP2C19*2*	681G>A (rs4244285)	*CYP2C19*2/*2*	PM	0	(Céspedes-Garro et al. 2015; Maruf et al. 2019)
*CYP2C19*3*	636G>A (rs4986893)	*CYP2C19*3/*3*			
*CYP2C19*4*	A>G	*CYP2C19*4/*4*			
*CYP2C19*5*	1297C>T	*CYP2C19*5/*5*			
*CYP2C19*6*	395G>A	*CYP2C19*6/*6*			
*CYP2C19*7*	T>A	*CYP2C19*7/*7*			
*CYP2C19*8*	358T>C	*CYP2C19*8/*8*			
*CYP2C19*17*	-806C>T (rs12248560)	*CYP2C19*1/*17* *CYP2C19*17/*17*	UM	2	(Céspedes-Garro et al. 2015; Maruf et al. 2019)

are most relevant in the metabolism of antiepileptic drugs. Updated *CYP2C9*2/*2* diplotype (AS = 1) now predicts IM phenotype (originally predicted PM), this change is based on data from multiple substrates (celecoxib, flurbiprofen, phenytoin and warfarin) showing an effect similar to *CYP2C9*1/*3* diplotype (AS = 1) and *CYP2C9*2/*2* in metabolic ratio and dose (warfarin). In addition, *CYP2C9*3* is classified as "no function" alleles with a value of 0 for the AS calculation, this is based on the *CYP2C9*3/*3* diplotype with lowest metabolic activity and slowest pharmacokinetic clearance (Karnes et al. 2021).

Activity score and genotype: 2 an individual carrying two normal function alleles; 1.5 an individual carrying one allele of normal function plus one allele of decreased function; 1 one allele of normal function plus one allele without function or two alleles of decreased function; 0.5 an individual carrying a non-function allele plus a decreased-function allele; 0 two alleles without function.

CYP2C9 and *CYP2C19* associated with adverse reactions

Therapeutic drug monitoring is often used to adjust the dose to maintain serum concentrations within the therapeutic range, that is, the drug must exceed the minimum effective concentration (C_{mE}) to avoid therapeutic failure or resistance to treatment; but it must not exceed the minimum toxic concentration (C_{MT}), to avoid adverse reactions and toxicity of antiepileptic drugs; Therefore, therapeutic ranges of 10–20 mg/L phenytoin (PHT) have been proposed (Alvarado et al. 2022a), 4–12 mg/L carbamazepine (CBZ) (Alvarado et al. 2022b), 50–100 mg/L for valproic acid (VPA) (Alvarado et al. 2022c); the *CYP2C9* and *CYP2C19* genes are implicated in said serum levels of antiepileptic drugs. Five observational studies were evaluated, 2 case-control, 1 cohort, 8 review, and 4 systematic review and meta-analysis for the association between *CYP2C9/CYP2C19* single nucleotide polymorphisms (SNPs) and their association on plasma level and reactions adverse. In the study by Song et al. included 83 patients with epilepsy who were treated as sustained-release VPA monotherapy. The VPA concentration-dose relationship was significantly lower in *CYP2C19*1/*1* NM (3.33±1.78) compared to *CYP2C19*1/*2* IM (4.45±1.42) and *CYP2C19*3/*3* PM (6.64±1.06). An association was found between the *CYP2C19*2* and *CYP2C19*3* alleles with serum VPA concentration, whereas the *CYP2C9*13* allele had no effect on plasma VPA concentration (p = 0.809) (Song et al. 2022). In patients carrying *CYP2C9*1/*3* alleles, Tan et al. (2010) have observed in patients with Han-Chinese epilepsy an increase in the serum level of VPA compared to the wild type (3.9±0.4 μg/ml/mg dose/kg bw vs 3.4±0.4 μg/ml/ mg dose/kg bw, p = 0.0001) (Tan et al. 2010). In another study, Suvichapanich et al. analyzed the association between the *CYP2C9*3* allelic variant and PHT-induced severe skin adverse reactions (SCARs) in Thai children with epilepsy. Thirty-seven patients with antiepileptic drug-induced SCAR (n = 20 phenobarbital and n = 17 phenytoin) and 35 patients with tolerance (n = 19 phenobarbital and n = 16 phenytoin) were included. A significant association was found between *CYP2C9*3* and PHT-induced SCAR (Odds ratio, OR = 14.52; 95% confidence interval (CI) 1.18; p value = 0.044). No association was found between CYP2C9**3* and phenobarbital-induced SCARs (Suvichapanich et al. 2015). Ortega-Vazquez et al. conducted a study in 64 mestizo mexican patients with epilepsy treated with PHT monotherapy (n = 25) and combination therapy (phenytoin, carbamazepine, valproate, phenobarbital, and others; n = 39), and in 300 healthy volunteers. In multivariate models, the intronic variant IVS8-109T CYP2C9 was significantly associated with higher plasma PHT concentrations (p = 0.03); this allele was more frequent in the group with supratherapeutic serum levels compared to the subtherapeutic group (0.13 vs. 0.03, respectively; p = 0.05, Fisher's exact test). The *CYP2C19*3* allele was not identified in patients or volunteers. The results suggest that *CYP2C9* IVS8-109T may decrease the enzymatic activity of CYP2C9 in PHT. More research is needed to confirm the findings (Ortega-Vazquez et al. 2016).

Meanwhile, Yampayon et al. investigated the association of the *CYP2C9* and *CYP2C19* genes with SCAR induced by PHT. The study included 36 Thai patients (15 with Stevens-Johnson syndrome (SJS) and 21 with drug rash with eosinophilia and systemic symptoms (DRESS)/drug hypersensitivity syndrome (DHS)) and 100 PHT-tolerant controls were studied. A *CYP2C9*3* association of significant risk of SJS was found (adjusted OR 5.40, p = 0.0097) (Yampayon et al. 2017). Hikino et al. conducted a case-control study with a total of 747 Japanese patients (24 cases and 723 tolerant controls). *CYP2C9*3* carriers were found to be significantly associated with PHT-induced rashes (OD 7.05, 95% CI 2.44–20.4, p = 0.0022) (Hikino et al. 2020). Sukasem et al. conducted a retrospective study of cases (88 PHT-treated patients) and controls (70 PHT-tolerant patients) during 2008–2017. *CYP2C9*3* was found to contribute to an increased risk of PHT-induced SJS/toxic epidermal necrolysis (TEN), with the statistical association being weak (OR 4.800; 95% CI 0.960–23.990; p = 0.056) (Sukasem et al. 2020). Fohner et al. in a cohort study of multi-ethnic resources for genetic epidemiology research on adult health and aging, included 382 participants who received a prescription for PHT (at a dose of 300 mg/ day) between 2005 and 2017. Included participants self-identified as Asian (n = 21), Black (n = 18), White Hispanic (n = 29), and 308 as non-Hispanic White. The frequencies of the *CYP2C9*2* and *CYP2C9*3* alleles were 12.0% and 4.7%, respectively; 20% *CYP2C19*17*, 17% *CYP2C19*2* and 1% *CYP2C19*3*. Intermediate metabolizers carrying *CYP2C9*1/*3* or *CYP2C9*2/*2* genotypes were found to be more likely to develop cutaneous adverse reactions compared with *CYP2C9*1/*1* participant (OD 4.47; 95% CI 1.64–11.69, p < 0.01). Asian participants were 3.70 times more likely to experience a skin adverse reaction compared with non-Hispanic white participants (95% CI 0.95–12.13; p = 0.04). The association of *CYP2C19* with adverse reactions

could not be demonstrated (Fohner et al. 2020). Orsini et al. found that the *CYP2C9*2* and *CYP2C9*3* single nucleotide polymorphisms (SNPs) are involved in the expression of CYP2C9 enzymes that metabolize VPA, and whose metabolite 4-ene-VPA is associated with severe hyperammonemia and nonalcoholic fatty liver disease. Also, decreasing the dose of VPA in patients with CYP2C9 carriers has been shown to improve hyperammonemia (Orsini et al. 2018). Monostory et al. observed that the allelic variants *CYP2C9*2* or *CYP2C9*3* show a significant reduction in VPA metabolism in children, which increases serum levels of the drug and induces adverse reactions, compared to the wild-type *CYP2C9*1/*1* genotype (Monostory et al. 2019). Iannaccone et al. found that the *CYP2C19*2* and *CYP2C19*3* SNPs have been associated with SJS/TEN after CBZ administration. *CYP2C9*3* and *CYP2C9*2* carriers generate heterozygous *CYP2C9*2/*3* diplotypes that predict poor metabolizers, and in them, serum VPA levels are elevated compared to the wild-type *CYP2C9*1* allele. *CYP2C19*2* carriers require higher doses of VPA to achieve steady-state serum concentrations (Iannaccone et al. 2021). Ahmed et al. reviewed an association study between *CYP2C9*3* with a 95% reduction of PHT metabolism and the induction of SCAR. Thai patients treated with CBZ and PHT, and with *CYP2C19*2* genotype had a higher probability of developing SCAR compared with patients with wild-type *CYP2C19*; although the result was not statistically significant (OR 2.5, 95% CI 0.96–67.3; p = 0.06) (Ahmed et al. 2021). Fowler et al. reviewed the relationship of *CYP2C9* and PHT adverse reactions; it is indicated that *CYP2C9* SNPs are probably responsible for increasing the toxic arene oxide metabolites, which increase the probability of SCAR, such as SJS and TEN; consider that VPA is a CYP2C9 inhibitor, generating the same adverse reactions induced by phenytoin (Fowler et al. 2019). Chang et al. found that 97.7% of patients from Han-China with *CYP2C9*3* genotype are significantly associated with the development of PHT-induced maculopapular rash (OR 167; p = 0.007), with SJS and TEN induced by PHT (OR 30; 95% CI 8.4–109; p = 1.2 × 10–10); A significant association was also found between *CYP2C9*3* with PHT-induced SJS/TEN in Japanese patients (OR 8.9; 95% CI 2.2–35.8; p = 0.010), and in Malaysian patients (OR 8.4; 95% CI 1.5–48.5, p = 0.045). *CYP2C9*3* was found to be associated with low metabolism and high serum PHT levels (17 μg/mL), compared to drug-tolerant control patients (2.5 μg/mL) (p = 0.0002). The *CYP2C19*3* variant is associated with adverse reactions induced by PHT (OR 4.47; 95% CI 1.09–18.36; p = 0.048); no significant association was found between *CYP2C19*2* and *CYP2C19*17*, and PHT-induced adverse reactions (Chang et al. 2020). Silvado et al. showed that the maintenance dose of PHT (5–10 mg/kg/day) should be reduced by 25% in IM patients (*CYP2C9*1/*2* or **1/*3* diplotypes) and 50% in PM (*CYP2C9*2/*3* or **3/*3*) to reduce the risk of PHT-induced adverse reactions (Silvado et al. 2018). Shnayder et al. mentions that the *CYP2C9*2* and *CYP2C9*3* SNPs are associated with decreased VPA metabolism, so patients who are homozygous for *CYP2C9*2* or *CYP2C9*3* or who are heterozygous (*CYP2C9*2/*3*) have a PM phenotype and show decreased p-oxidation of VPA in liver microsomes. *CYP2C9*2/*3* catalyzed the formation of the toxic metabolites 4-ene-VPA, 4-OH-VPA, and 5-OH-VPA (Shnayder et al. 2023). While Yoon et al. found in six studies with 807 patients a significant association between CYP2C9**3* with the plasmatic concentration of VPA; said concentration was 0.70 μg/mL higher per mg/kg compared to non-carriers of the *CYP2C9*3* genotype (95% CI 0.25–1.15; p = 0.002) (Yoon et al. 2020). Wu et al. conducted a systematic review study and meta-analysis of the association of *CYP2C9*3* with SJS and TEN PHT-induced. Four studies with 117 PHT-induced SJS/TEN cases and 338 matched controls (PHT-tolerant patients) or 4231 general population controls were included. A significant association was found between *CYP2C9*3* and SJS/TEN compared with matched controls (OR 8.93; 95% CI 2.63–30.36; p = 0.0005; substantial heterogeneity I^2 46%) and control population (OR 8.88, 95% CI 5.01–15.74, p < 0.00001) (Wu et al. 2018). Su et al. performed a meta-analysis of studies that associated PHT-induced SCARs in three groups of patients from Taiwan, Thailand, and Japan. Meta-analysis of the *CYP2C9*3* allele and other genes are significantly associated with PHT-induced SCAR in three Asian populations: *CYP2C9*3* ($p = 4.66 \times 10^{-14}$, OR 10.74 for Taiwan; p = 0.04, OR 3.14 for Thailand; and p = 0.04, OR = 6.21 for Japan) (Su et al. 2019). Kanjanasilp et al. evaluated the effects of *CYP2C9* and *CYP2C19* polymorphism on PHT pharmacokinetic parameters. Eight observational studies were included, with a total of 633 Thai patients. The Michaelis-Menten constant was significantly higher in *CYP2C9* IM/*CYP2C19*NM and *CYP2C9*IM/*CYP2C19*IM carriers compared to control (*CYP2C9*NM/*CYP2C19*NM) groups at 2.16 and 1.55 mg/L (p < 0.00001, p < 0.0001). The maximum rate of action was significantly lower in control groups compared to *CYP2C9*IM/*CYP2C19*NM and *CYP2C9*IM/*CYP2C19*IM carriers at 3.10 and 3.53 mg/kg/day (p = 0.00001, <0.0001) (Kanjanasilp et al. 2021). Table 3 summarizes the type of study and the clinical importance of the genotypes involved in the adverse reactions of AEDs.

Fig. 4 summarizes the clinical implications of the *CYP2C9* and *CYP2C19* SNPs on the serum levels of valproic acid, carbamazepine, and phenytoin.

In parts A and B, it can be seen that the *CYP2C9* gene is located in locus 10q24 of chromosome 10 (long arm of chromosome 10 in region 24) and encodes its respective CYP2C9 enzyme; the curve of serum concentration vs. time of a normal metabolizer (NM) whose concentration is within the therapeutic index is observed; allelic variants *CYP2C9*2*, *CYP2C9*3*, *CYP2C19*2*, and *CYP2C19*3* are implicated in the poor metabolizer (PM) phenotype, in which case the serum valproic acid (VPA) concentration level exceeds the trough toxic concentration (CMT) of 100 mg/L and induces hyperammonemia (A); in part B it is observed that the serum level curve of phenytoin is greater than 20 mg/L; and the allelic variants *CYP2C9*2*

Table 3. Type of study associated with adverse reactions and clinical implications.

Type of study	Genotype and phenotype	Clinical implication	Reference
Observational study	*CYP2C19*2* IM *CYP2C19*3* PM	The *CYP2C19*2* and **3* SNPs are significantly associated with serum VPA levels, and the drug dose for IM and PM could be lower than for NM.	(Song et al. 2022)
	*CYP2C9*3* PM	*CYP2C9* variants may explain some of the substantial variability in VPA pharmacokinetics between different subjects	(Tan et al. 2010)
	*CYP2C9*3* PM	*CYP2C9*3* is a predictive genetic marker to anticipate and decrease serious adverse skin reactions (SCARs) induced by PHT.	(Suvichapanich et al. 2015).
	CYP2C9 IVS8-109T	Patients carrying *CYP2C9* IVS8-109 T showed significantly supratherapeutic serum PHT concentrations.	(Ortega-Vázquez et al. 2016)
	*CYP2C9*3* PM	Different genetic markers are associated with SCARs induced by PHT; It is suggested to perform genetic tests prior to treatment as predictors of SCAR induced by PHT.	(Yampayon et al. 2017)
Cases and controls study	*CYP2C9*3* PM	There is a significant association of *CYP2C9*3* with the eruption induced by PHT. The patient's genotype should be verified prior to prescription to decrease the incidence of PHT-induced rash in clinical practice.	(Hikino et al. 2020)
	*CYP2C9*3* PM	Clinical and genetic factors contributed to the risk of PHT-induced adverse reactions.	(Sukasem et al. 2020)
Cohort study	*CYP2C9*2* IM	*CYP2C9* allelic variants are associated with an increased risk of PHT-induced cutaneous adverse reactions. It is suggested to carry out pharmacogenetic tests on patients, and based on this, prescribe the correct dose and improve the safety of the drug.	(Fohner et al. 2020)
Review study	*CYP2C9*2* IM *CYP2C9*3* PM	Precision medicine is the future of antiepileptic treatment that can improve the clinical outcomes of the disease.	(Orsini et al. 2018)
	*CYP2C9*2* IM *CYP2C9*3* PM	*CYP2C9* pharmacogenetic testing is recommended as a new strategy for VPA therapy in childhood. This facilitates optimization of VPA dosing, helping to avoid adverse reactions induced by incorrect dosing, such as abnormal blood levels of ammonia and alkaline phosphatase, and improving the safety of anticonvulsant therapy in children.	(Monostory et al. 2019)
	*CYP2C9*2*/ *CYP2C19*2* IM *CYP2C9*3*/ *CYP2C19*3* PM	*CYP2C9*, *CYP2C19*, and others are potential biomarkers for VPA and CBZ therapy. More pharmacogenetic research and therapeutic drug monitoring studies are required to fully understand the impact on clinical practice.	(Iannaccone et al. 2021)
	*CYP2C9*3* PM *CYP2C19*2* IM	Dose adjustment based on *CYP2C9* genotype, especially prior to therapy, would be beneficial to reduce the risk of CBZ and PHT adverse reactions or poisoning.	(Ahmed et al. 2021)
	*CYP2C9*3* PM	High arene oxide concentrations of PHT increase the probability of SJS and NET.	(Fowler et al. 2019)
	*CYP2C9*3* PM	*CYP2C9*3* is significantly associated with higher PHT concentrations and cutaneous adverse reactions. Prescribing pharmacogenetic testing is suggested to predict PHT-induced adverse reactions and guide optimal dose selection.	(Chang et al. 2020)
	*CYP2C9*2* IM *CYP2C9*3* PM	The dose of PHT should be individualized based on the metabolic phenotype to reduce the risk of adverse reactions that could justify its withdrawal, even if it is effective.	(Silvado et al. 2018)
	*CYP2C9*2* IM *CYP2C9*3* PM	It is important to assess the risk of developing adverse reactions induced by VPA and propose its correction, according to the pharmacogenetic profile of the patient and the serum level of the drug.	(Shnayder et al. 2023)
Meta-analysis study	*CYP2C9*3* PM	The *CYP2C9*3* SNP is associated with increased serum levels of VPA. In patients with epilepsy and *CYP2C9*3* genotype, dose adjustment may be necessary to maintain a serum VPA level within the therapeutic index.	(Yoon et al. 2020)
Systematic review study and meta-analysis	*CYP2C9*3* PM	There is a significant association between *CYP2C9*3* and PHT-induced SJS/NE, especially in a Thai population. *CYP2C9*3* is a predictive genetic biomarker of SJS/NE induced by PHT.	(Wu et al. 2018)
Meta-analysis study	*CYP2C9*3* PM	Assessment of *CYP2C9* and HLA risk alleles are predictive genetic tests to prevent PHT hypersensitivity in Asians.	(Su et al. 2019)
Systematic review study and meta-analysis	*CYP2C9*2*/ *CYP2C19*2* IM	Dosage for patients with IM *CYP2C9* phenotype should be lower (2.1 to 3.4 mg/kg/day) to achieve therapeutic PHT levels.	(Kanjanasilp et al. 2021)

NM: normal metabolizer; IM: intermediate metabolizer; PM: poor metabolizer; VPA: valproic acid; CBZ: carbamazepine; PHT: phenytoin.

and *CYP2C9*3*, are associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Part C shows that the *CYP2C19* gene is located in the 10q24.1 locus of chromosome 10 and encodes its respective CYP2C19 enzyme; the curve of serum concentration vs time of a normal metabolizer (NM) and the curve of serum

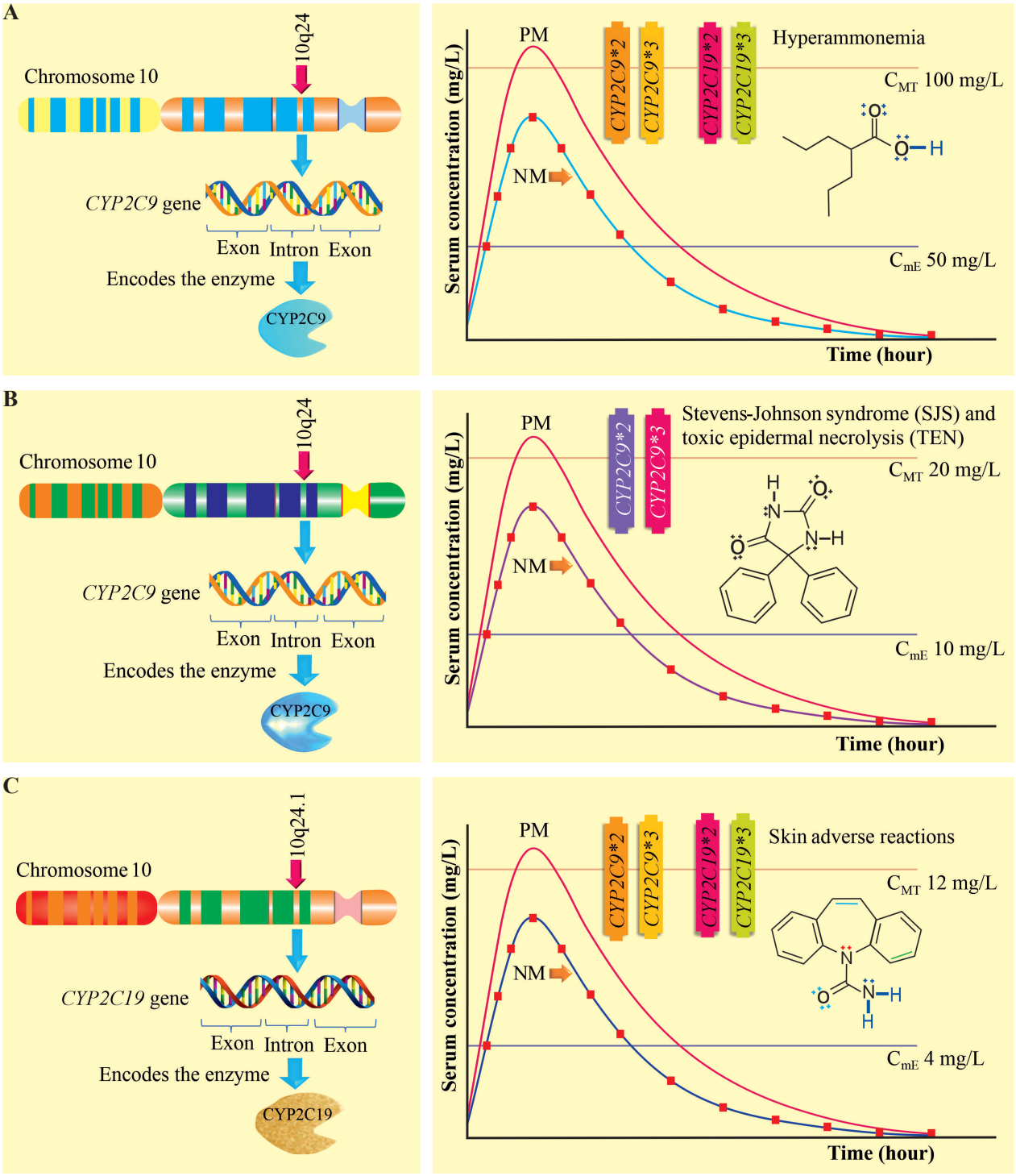

Figure 4. Location of *CYP2C9/CYP2C19* genes, allelic variants and clinical implication.

concentration vs time that exceeds the C_{MT} of 12 mg/L in a PM, and the allelic variants *CYP2C9*2*, *CYP2C9*3*, *CYP2C19*2* and *CYP2C19*3* associated with cutaneous adverse reactions induced by carbamazepine (CBZ). Figure made by the authors.

The results of this review must be considered in the context of various limitations. The main one is in the scant literature published in Peru. Other biases that can lead to confusion is to include various observational, analytical, review, systematic, and meta-analysis studies, and not only consider studies with rigorous statistical analysis; however, this review should be considered as a contribution to science and to promote studies in pharmacogenetics and precision medicine in Peru.

Conclusions and future perspectives

Based on the review of the scientific literature, it is concluded that *CYP2C9*2*, *CYP2C9*3*, *CYP2C19*2*, and *CYP2C19*3* single nucleotide polymorphisms may have

a clinical impact on valproic acid, carbamazepine, and phenytoin therapy. There is more evidence of a significant association between *CYP2C9*3* and the adverse reactions induced by phenytoin; *CYP2C9*3* being proposed as a predictive genetic biomarker of Stevens-Johnson syndrome and epidermal necrolysis induced by the aforementioned drug.

In the short term, more multicenter studies and large prospective observational studies of pharmacogenetics in patients with epilepsy are required before starting treatment, to evaluate the association between genes, high serum levels and adverse drug reactions.

The review studies will form part of the scientific evidence, so that it can be done in the future analytical observational studies (cases/controls and cohorts) and randomized clinical trials (RCTs) of pharmacogenetics will be carried out, which will allow the implementation of precision medicine in the delivery systems health of Peru and will be a routine clinical practice that contributes to improving the quality of life of patients.

Comment

We hope that this review study will be considered as a valuable tool to individualize the dose of drugs, at the same time, give sustainability to medical care and Pharmacotherapeutic Follow-up in the Clinical Pharmacy of Peru.

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