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Pharmacokinetic Polymorphisms

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Synonyms

Cytochrome P450 (CYP); Cytochrome P450 isozymes; Cytochrome P450 monooxygenases; Mixed-function oxidases; Personalized medicine; Precision medicine

Definition

A polymorphism is a genetic variant that leads to at least two non-rare phenotypes with a frequency of 1% or greater in a population. When the variant is in a gene that codifies proteins involved in drug absorption, distribution, metabolism, or excretion (ADME), it is a pharmacokinetic polymorphism.

A pharmacokinetic polymorphism can alter the plasmatic level of medication and therefore alter the response. Depending on the type of variant and the pharmacokinetic process involved, a polymorphism could conduce to different security profiles of drugs or modify the therapeutic effectiveness.

Pharmacokinetics

Pharmacokinetics is the relationship between the administered dose and the plasma concentration of a drug, which implies studying the different processes of absorption, distribution, metabolism, and excretion, in short "what the organism does with the drug." Pharmacokinetics determines the concentration of drugs in the drug-exposed subject and contributes to the observed response's intensity. Modifications in pharmacokinetics can explain different responses among different individuals, where different physiological situations may be found, including short or advanced age, organic failure (renal, hepatic), hypo-/hypervolemia, and others. Pharmacokinetic parameters vary among subjects and also depending on the route of administration [1].

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The ADME Process

From the administration of a drug until it is finally excreted from the organism, different processes occur. These encompass the processes of absorption, distribution, metabolism, and excretion (abbreviated: ADME). Although some drugs exert their effect without entering systemic circulation (creams that serve as a barrier, some laxatives, and others), most of them must enter the organism via enteral or parenteral absorption to be transported by the blood to the target organ, where they will cross cell membranes and finally reach the molecular target. Therefore, the body is a nonhomogeneous compartment in which the drug is distributed. Subsequently, the drug molecules are processed by enzymes of phase I (cytochrome P450 [CYP450], epoxide hydrolase, and others) and phase II (glutathione-*S*-transferases, UDP glucuronosyltransferases, sulfotransferases, and others), which have evolved to biotransform endogenous and exogenous compounds. Thus, depending on phase I and II enzyme activity, the drug level varies, increasing or decreasing the therapeutic response. The activity of metabolism enzymes may vary depending on genetics and also by interaction with other molecules. Finally, urinary or biliary excretion are the main (but not the only) excretion routes to remove drugs [1].

Figure 1 shows the plasma concentration versus time curve for different administration routes. Notice that the intravenous route does not have an absorption process, reaching the peak immediately after the infusion. The other routes all have absorption, distribution, metabolism, and excretion. Metabolism and excretion are represented mainly in the descendent part of the curve. However, both processes can start at the beginning of the pharmacokinetic process. Thus, if a patient has a variant that implies a lower metabolism, it can reach higher and earlier plasmatic peaks, in addition to a slighter decrease in plasmatic concentration.

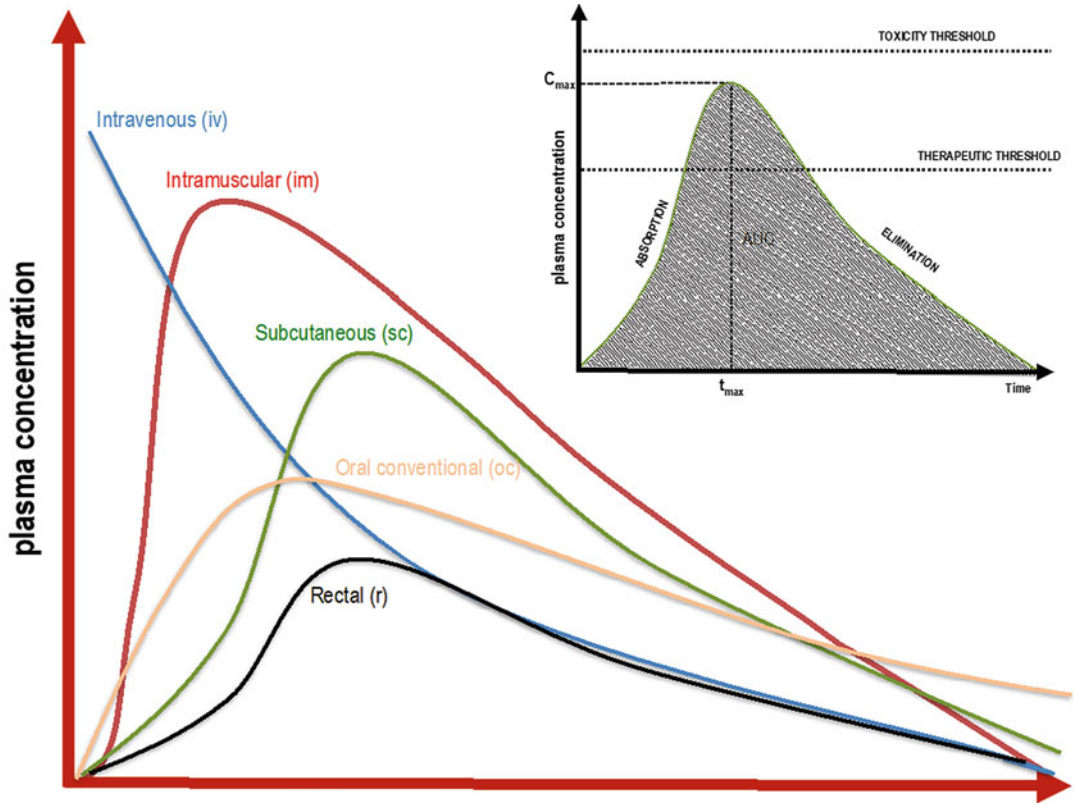
Relationship Between Genetics and Proteins Involved in Pharmacokinetic Processes

It is known that DNA contains the instruction to building proteins that allow all the cellular functions. It is also known that the genetic code is redundant, i.e., different combinations of nucleotides (DNA) can codify for the same amino acid (protein). Nevertheless, sometimes a change in DNA implies changes in the amino acid codification, changing the protein structure and possibly the function. A nucleotide change can also affect the regulatory zone, changing the protein's expression (amount). The last scenario we can found is a nucleotide change in an intronic splice zone. That can generate alternative splicing, altering the protein structure and function.

Phase I Enzymes

The CYP450 superfamily contains the main phase I enzymes. It is the most relevant metabolizing system responsible for the oxidation of numerous endogenous (endobiotic) and exogenous (xenobiotic) compounds. It is expressed in many tissues, being more abundant in the liver. Based on similarities in amino acid sequences [2], it is classified into families, subfamilies, and isoforms. In humans, 18 CYP families and 43 subfamilies have been identified. Of these, 57 genes and 59 pseudogenes have been sequenced. These enzymes' nomenclature and their variants are widely agreed though it is continuously updated (http://drnelson.utmem.edu/CytochromeP450.html).

CYP450 superfamily catalyzes phase I metabolism, generally introducing or exposing a hydrophilic group in drugs. These enzymes are very polymorphic, and their relationships with drug response have been described widely in the scientific literature [3–5]. Generally, one CYP enzyme metabolizes more than one drug, and a drug is metabolized by more than one CYP enzyme.



Pharmacokinetic Polymorphisms, Fig. 1 Pharmacokinetics curves of several routes of administration. In the right superior box, the main basic pharmacokinetic parameters are shown [32]

Besides drug detoxification, CYP enzymes participate in the bio-activation of prodrugs, and if these enzymes are less functional, the therapeutic effect will be minor due to less transformation to the active drug [6].

Several studies suggest that differences in basal levels of CYP constitute one of the primary sources of interindividual variability in response to xenobiotics. Among all CYP families, the most studied are 1, 2, and 3 families, all of them polymorphic. In this respect, polymorphisms are usually named with the number of the enzyme followed by a star and then the number of the variant (for example, CYP3A4*1B), but the best way to name them when the variant corresponds to an SNP is using the "rs number," a unique number assigned by NCBI dbSNP to each single nucleotide polymorphism [7–9].

In the CYP450 superfamily, there is a broad spectrum of relevant polymorphisms. There are SNPs related to a higher activity of the enzyme, such as CYP1A1*2C, an amino acid change near the active site, and has been linked to a rising in the enzymatic capacity. Other SNPs are related to a higher level of genetic expression, for example, CYP1A1*2A, which is a substitution in the 3′ region of polyadenylation. Moreover, a polymorphism could be related to suppressing the activity, for example, CYP3A4*26, which is a nonsense substitution; therefore, the protein has no activity [10].

Phase II Enzymes

This phase of the metabolism is associated with conjugation with hydrophilic molecules to favor eliminating a drug. After this stage, drugs are generally inactive, and their final fate is urinary or fecal excretion. In a few cases, after phase II, a chemical

compound could acquire toxic activity. For example, the nephrotoxicity of hydroquinone and bromobenzene is mediated via quinone-glutathione conjugates. Gene-related deficiency in phase II enzymes is related to an increased risk of toxicity, and the clinical recommendations when a drug metabolized by these enzymes is administered to a patient with such deficiency are focused on avoiding adverse effects and improving safety in patients [11]. In drug metabolism, glutathione-S-transferases (GST) and uridine 5′-diphosphate (UDP)-glucuronosyltransferases (UGT) metabolize half of the drugs approximately.

Human glutathione-S-transferase is a family of multi genes of soluble dimeric enzymes [12], which include alpha (α), mu (μ), pi (π), zeta (ζ), sigma (σ), kappa (κ), omega (ω), and theta (τ), with a broad subcellular distribution and partial superposition of specificities. Its principal function is to detoxify pollutants, carcinogens, and mutagens by conjugation with glutathione (GSH). They also play a role in protecting tissues against reactive oxygen species (ROS) and lipid hydroperoxides during oxidative stress [13, 14].

A relevant polymorphism in GST is the null genotype, and it corresponds to a deletion of a portion of the gen, so it is impossible to create the protein. That polymorphism has been associated with drug toxicity due to a slower metabolism and cancer risk due to the lack of detoxification of potentially carcinogenic compounds [15–17]. UGT is related to bilirubin metabolism. Its deficiency generates Gilbert's syndrome characterized by jaundice, so it is also associated with hepatic damage after administration of atazanavir, a drug used in HIV patients, due to reduced conjugation and elimination.

Human UGT contains four members of genes, UGT1, UGT2, UGT3, and UGT8, and the function is to conjugate a broad spectrum of molecules with glycosyl groups [18]. In drug metabolism, the primary reaction catalyzed by UGT is the conjugation with glucuronic acid, and therapeutic substrates of this process include analgesics, nonsteroidal anti-inflammatory agents, anticonvulsants, antipsychotics, antivirals, and benzodiazepines [19].

The polymorphism UGT1A1*28 implies a lower metabolism of some drug, for example, irinotecan, a drug used to treat colorectal cancer, thus causing a high risk of toxicity to chemotherapy [20]. The Pharmacogenomics Knowledge Database (PharmGKB) highlighted the relevance of UGT1A1 in the biotransformation process and remarked the UGT1A1*28 polymorphism as one of the most relevant because it implies the insertion of TA nucleotides in the promoter, decreasing the expression of the enzyme and, as a consequence, decreasing the drug metabolism [21].

Another relevant phase II enzymes are sulfotransferases (SULTs), N-acetyltransferases (NATs), and thiopurine S-methyltransferase (TPMT).

TPMT participates in the metabolism of mercaptopurine and thioguanine, drugs used to treat acute lymphoblastic leukemia. Its deficiency is associated with the risk of myelosuppression depending on metabolizer type. Poor and intermediate metabolizers are at higher risk than extensive metabolizers. There is currently a clinical guideline that allows taking actions in dosing regarding the genotype of patients [22].

NATs are enzymes related to the metabolism of antituberculosis drugs, and their deficiency has been related to more frequent adverse drug reactions [23]. On the other hand, SULTs enzymes are related to biotransformation of a broad spectrum of xenobiotics, including many therapeutic agents and also endogenous steroids [24].

Drug Transporters

Drug transporters participate in many pharmacokinetic processes: absorption, distribution, and excretion. Therefore, their dysfunction could affect the therapeutic goals related to suboptimal or supraoptimal plasmatic levels [1].

There are two families of essential drug transporters: ATP-binding cassette (ABC) and solute linking carriers (SLC), each of them having different functions. They could act as efflux or influx transporters. They appear in enterocytes affecting drug absorption, in renal tubules and hepatocytes impacting the urinary or biliary excretion of their substrates or the risk of organ damage, and at the brain-blood barrier affecting drug distribution to

the brain. The ABC family comprises a widespread type of transporters in different species, and they possess a well-conserved nucleotide-binding domain where ATP is hydrolyzed. ABC transporters are expressed predominantly in the liver, intestine, blood-brain barrier, blood-testis barrier, placenta, and kidney. ABC proteins transport many endogenous substrates, including inorganic anions, metal ions, peptides, amino acids, sugars, and also drugs. A well-studied member of this family is ABCB1 (ATP binding cassette subfamily B member 1) or P-glycoprotein (P-gp), which can contribute to drug elimination, affect drug absorption and distribution to the therapeutic target. It can be inhibited or upregulated by drug interactions [25].

SLC family is a very diverse family, including the SLC22 subfamily, the organic cation transporters (OCTs), organic zwitterion/cation transporters (OCTNs), organic anion transporters (OATs), and others such as the human SLC6 family members serotonin, norepinephrine, and dopamine transporters (SERT, NET, and DAT, respectively), among others [26].

SLC21A6 or SLCO1B1 gene (solute carrier organic anion transporter family member 1) encodes the organic anion transporter polypeptide OATP1B1. This protein is found in liver cells; it transports compounds from the blood into the liver to be cleared from the body. As an example, the rs4149056 C allele is related to decreased activity of the transporter **in vitro** [27, 28] and reduced clearance of some drugs **in vivo** [29, 30], and it has been associated with an increased risk to develop myopathy after administration of simvastatin, a drug used for hypercholesterolemia, due to a decreased arrival to the liver [31].

Relationship Between Pharmacogenetics and ADME Processes

Every pharmacokinetic process could be affected by pharmacogenetics, and the effect can be monitored through drug plasmatic levels. Figure 2 shows plasmatic concentration versus time curves for three patients who received the same dose of the same medication per os. The therapeutic threshold (the minimum level that must be reached to have a pharmacological effect) is not reached by patient A. Therefore, the treatment will fail. The toxicity threshold (the minimum level at which there is a probability to get adverse effects) is reached by patient C. Thus, the treatment could fail due to a toxic event. The range between therapeutic and toxicity thresholds is called the therapeutic range. Drug plasma concentrations should be within this range to reach clinical goals.

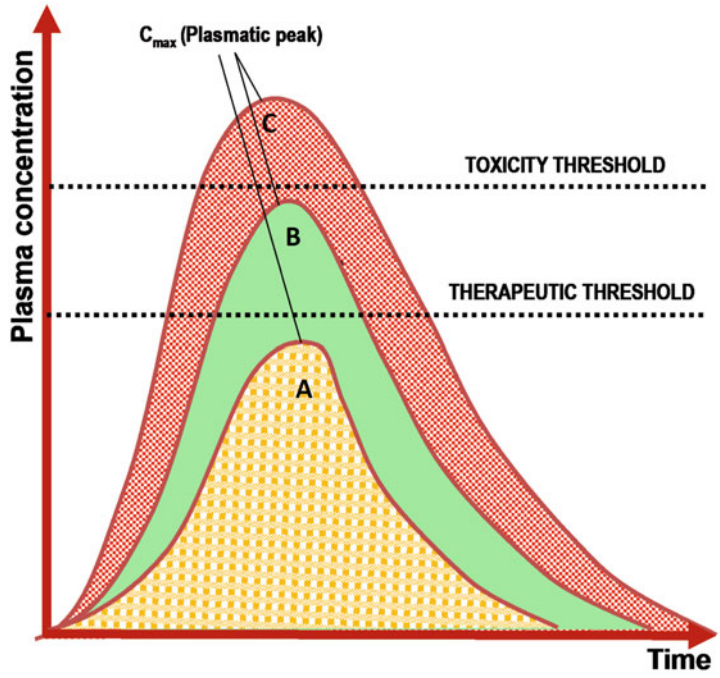
In the next subsections, we have assumed that we are treating subjects with polymorphisms affecting absorption, distribution, metabolism, or excretion-related genes exclusively, and the correspondent impact on pharmacokinetic profiles is discussed [32].

Absorption

The activity of the transporter P-gp is very variable. It could vary due to inducers or inhibitors of this protein or genetic differences in the encoding gene (*MDR1*). A less functional P-gp will increase the drug's absorbed fraction due to a decrease in the drug's return to the intestinal lumen. On the other hand, an overexpressed P-gp will decrease the absorbed drug [25, 33]. Figure 2 represents pharmacokinetic curves for three patients differing only in P-gp polymorphism. Patient A carries the *MDR1* Ser893 polymorphism, a variation that promotes a higher activity of P-gp in enterocytes. Patient B has a "wild-type" gene, and finally, patient C is homozygous for the SNP C3435T, a variant that negatively affects the expression of the gene, so there is a lower amount of P-gp in the cell surface, decreasing the efflux.

Patient A does not reach the therapeutic threshold, and patient C is exposed to drug levels above the toxicity threshold. The absorption rate is different in each patient, being the highest in patient C. The ascendant phase slope is higher in patient C than patient A or B, but the elimination rate is similar in every patient (parallel curves in the elimination phase).

Another critical point to highlight is the plasmatic peak. In patient C, the peak (C_{max}) is higher



Pharmacokinetic Polymorphisms, Fig. 2 Scheme of plasma concentration versus time curve in patients with different genotypes of P-gp, affecting absorption of drugs [32]

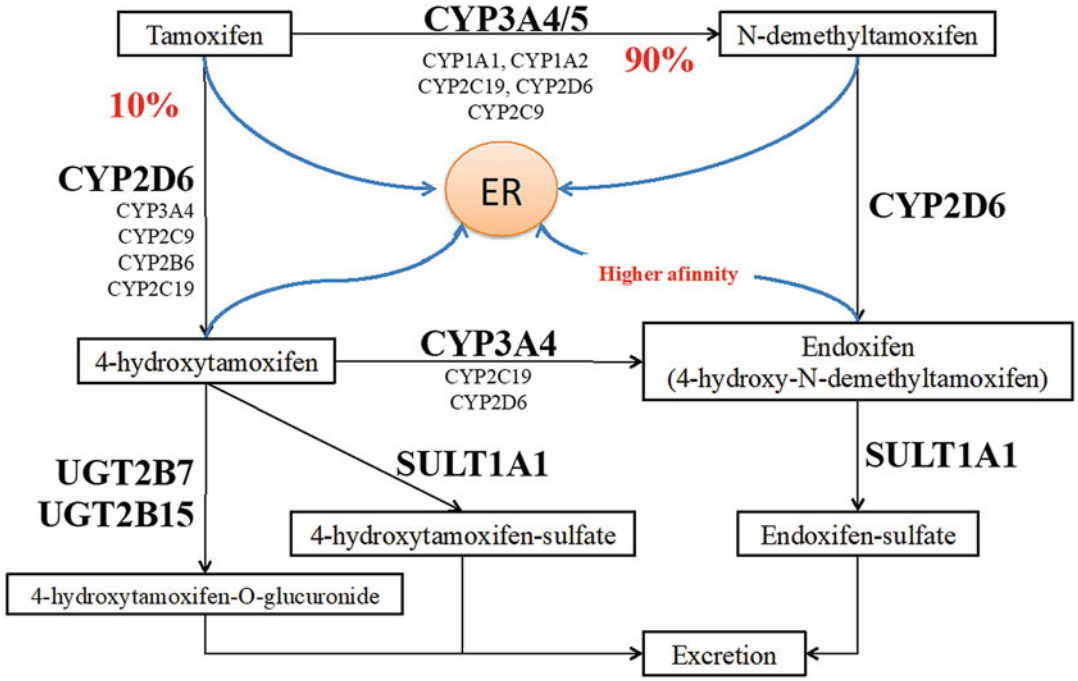
and occurs earlier than in the wild-type patient and the patient with underexpression of P-gp.

However, contrary to this hypothetical example, it is well known that several transporters are involved in the absorption phase of some drugs, with some transporters favoring drug uptake and others favoring efflux. Therefore, it is necessary to know which specific transporters impact the absorption of a given drug to predict the effect of a polymorphic variant on the drug pharmacokinetics.

Distribution

Polymorphisms in plasma proteins have not been extensively described yet. Let us assume a hypothetical situation where we found a polymorphism in albumin affecting drug binding sites linked to a reduced bound fraction in plasma. Thus, if we study a drug with a high protein binding, for example, warfarin, and remembering that the free drug is the therapeutically active entity, we will have more therapeutically active warfarin, reaching a therapeutic threshold with a relatively low dose compared to wild-type carrier subjects. Furthermore, the toxicity threshold will be reached more quickly. Therefore, this patient should receive lower doses than a wild-type one, mainly to prevent hemorrhagic episodes [32].

Some transporters could affect the distribution of drugs, thus affecting pharmacological success. For example, the overexpression of the abovementioned P-gp protein, which is also expressed in the blood-brain barrier, could decrease active drugs' entrance to the central nervous system. Other transporters such as MRP3 and MRP4 (encoded by ABCC2 and ABCC4 genes, respectively) are expressed in the liver. Polymorphisms rs12762549 in MRP2 and rs11568658 in MRP4 decrease transporters' activity and decrease the arrival of drugs to this organ, affecting both distribution and metabolism [32].



Pharmacokinetic Polymorphisms, Fig. 3 Metabolic pathways of tamoxifen. (Adapted from Miranda 2017). ER, estrogen receptor; CYP, cytochrome P450; UGT, UDP-glucuronosyltransferase; SULT, sulfotransferase [32]

Drug Metabolism (Biotransformation)

Drug metabolism is the most studied area in pharmacogenetics and pharmacogenomics. Variations in phase I and phase II enzymes have a proven relationship with therapeutic response, and the effect of a rapid or slow metabolism can be easily studied through the plasmatic level of a drug [32].

At this level, we have two different scenarios: The most common is an active drug in a rapid or ultrarapid metabolizer, where the medication will be eliminated faster than in an extensive metabolizer, making it challenging to reach efficacy. The other frequent scenario involves a patient with poor metabolism, for whom the drug will stay longer in the organism, thus favoring the incidence of adverse reactions.

Another relevant situation to be analyzed is when the administered drug is not active, but its metabolite is (as in the case of prodrugs). In that scenario, poor metabolism is associated with lower bio-activation and, consequently, to a lower or no therapeutic effect.

In other cases, for example, tamoxifen, both the drug and its metabolites (4-hydroxytamoxifen, N-desmethyltamoxifen, and endoxifen) have therapeutic activity even though it is suggested that endoxifen is more active than tamoxifen (Fig. 3) [34].

Excretion

Drug excretion may be a relevant pharmacogenetics process whenever the drug is not widely metabolized, and the elimination involves glomerular filtration and active secretion in the renal tubule. For example, β-lactam antibiotics, as penicillin and cephalosporins, are poorly metabolized, so their excretion is principally performed by excretion of the unaltered drug, to which transporters do contribute [1].

In the proximal renal tubule, there are three transporters implied in the active secretion of β-lactam

drugs, belonging to the family of organic anion transporter (OAT): OAT1, encoded by *SLC22A6* and located in the basolateral membrane together with OAT3, encoded by *SLC22A8*, and in the apical membrane OAT4, encoded by *SLC22A11* gene [32].

It has been described that all these genes have SNPs affecting the normal activity of transporters. The most studied SNPs are rs11568626 (149C>T) in OAT1, rs11568482 in OAT3 (62763264T>A), and rs11231809 (64302950T>A) in OAT4. In patients carrying some of these polymorphic alleles, the elimination process will be slower, favoring the incidence of adverse effects. On the other hand, overexpression of genes encoding these excretion transporters will result in lower drug plasma levels, and the therapeutic effect would be reduced. For example, the elimination from the body of cefotaxime (a 3rd-generation cephalosporin antibiotic) is mediated by OAT3. Hepatic excretion can also be altered by genetics. The transporter ABCC4 is expressed in the liver and participates in the excretion of diverse compounds, including conjugated bilirubin and other conjugated substances. The SNP rs11568658 in ABCC4 has been associated with cholestasis due to a lack of elimination of the compound [35]. This polymorphism has also been associated with reduced ABCC4-dependent drug resistance because the protein can be found in different cell types, and the polymorphism implies less transport through ABCC4, so the medication can easily carry out its action [36].

Conclusions

- Pharmacokinetics in patients varies due to genetic factors, and every stage in the ADME process is potentially susceptible to be modified by them, giving rise to variable therapeutic responses.
- Pharmacogenetic and pharmacogenomic tools can help to improve the clinical outcome of drug therapy, considering both drug efficacy and safety, and should be considered at the beginning of patient treatment.
- Not only ADME processes-related polymorphisms should be associated with drug selection. Factors as HLA-B, related to immune response, and others should be considered to improve efficacy and prevent adverse drug reactions.
- Genetic factors must be considered together with clinical and demographic factors to choose the correct medication and dosage.
- As pharmacogenetics is a discipline in current development, new studies must be carried out to increase the knowledge of relationships between genetic variants and pharmacological response, particularly in mixed populations. Clinical trials considering genotypes will be useful to favor the application in daily clinical practice in health centers.

References

1. Brunton LL, Hilal R, Knollmann BC. Goodman & Gilman's the pharmacological basis of therapeutics. McGraw Hill Medical; 2018.
2. Orellana M, Guajardo V. Cytochrome P450 activity and its alteration in different diseases. Rev Med Chil. 2004;132(1):85–94.
3. Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. Trends Pharmacol Sci. 2004;25(4):193–200.
4. Kirchheiner J, Seeringer A. Clinical implications of pharmacogenetics of cytochrome P450 drug metabolizing enzymes. Biochim Biophys Acta (BBA)-General Subjects. 2007;1770(3):489–94.
5. Rogers JF, Nafziger AN, Bertino JS Jr. Pharmacogenetics affects dosing, efficacy, and toxicity of cytochrome P450–metabolized drugs. Am J Med. 2002;113(9):746–50.
6. Zhou S-F, Liu J-P, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metab Rev. 2009;41(2):89–295.
7. Lin JH, Lu AY. Interindividual variability in inhibition and induction of cytochrome P450 enzymes. Annu Rev Pharmacol Toxicol. 2001;41(1):535–67.
8. Fujikura K, Ingelman-Sundberg M, Lauschke VM. Genetic variation in the human cytochrome P450 supergene family. Pharmacogenet Genomics. 2015;25(12):584–94.
9. Quiñones L, Rosero M, Roco Á, Moreno I, Sasso J, Varela N, et al. Papel de las enzimas citocromo p450 en el metabolismo de fármacos antineoplásicos: Situación actual y perspectivas terapéuticas. Rev Med Chil. 2008;136(10):1327–35.
10. Preissner SC, Hoffmann MF, Preissner R, Dunkel M, Gewiess A, Preissner S. Polymorphic cytochrome P450 enzymes (CYPs) and their role in personalized therapy. PLoS One. 2013;8(12):e82562.

11. Jancova P, Anzenbacher P, Anzenbacherova E. Phase II drug metabolizing enzymes. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2010;154(2): 103–16.
12. Strange RC, Spiteri MA, Ramachandran S, Fryer AA. Glutathione-*S*-transferase family of enzymes. Mutat Res. 2001;482(1–2):21–6.
13. Hayes JD, Strange RC. Invited commentary potential contribution of the glutathione S-transferase supergene family to resistance to oxidative stress. Free Radic Res. 1995;22(3):193–207.
14. Gallagher EP, Gardner JL, Barber DS. Several glutathione *S*-transferase isozymes that protect against oxidative injury are expressed in human liver mitochondria. Biochem Pharmacol. 2006;71(11): 1619–28.
15. Alshabeeb MA, Aithal GP, Daly AK. Investigation of oxidative stress-related candidate genes as risk factors for drug-induced liver injury due to co-amoxiclav. DNA Cell Biol. 2020;39(3):349–54.
16. Wang LI, Giovannucci EL, Hunter D, Neuberg D, Su L, Christiani DC. Dietary intake of cruciferous vegetables, glutathione *S*-transferase (GST) polymorphisms and lung cancer risk in a Caucasian population. Cancer Causes Control. 2004;15(10):977–85.
17. Hung RJ, Boffetta P, Brennan P, Malaveille C, Hautefeuille A, Donato F, et al. GST, NAT, SULT1A1, CYP1B1 genetic polymorphisms, interactions with environmental exposures and bladder cancer risk in a high-risk population. Int J Cancer. 2004;110(4):598–604.
18. Mackenzie PI, Bock KW, Burchell B, Guillemette C, Ikushiro S-I, Iyanagi T, et al. Nomenclature update for the mammalian UDP glycosyltransferase (UGT) gene superfamily. Pharmacogenet Genomics. 2005;15(10): 677–85.
19. Rowland A, Miners JO, Mackenzie PI. The UDP-glucuronosyltransferases: their role in drug metabolism and detoxification. Int J Biochem Cell Biol. 2013;45(6):1121–32.
20. Shulman K, Cohen I, Barnett-Griness O, Kuten A, Gruber SB, Lejbkowicz F, et al. Clinical implications of UGT1A1* 28 genotype testing in colorectal cancer patients. Cancer. 2011;117(14):3156–62.
21. Barbarino JM, Haidar CE, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for UGT1A1. Pharmacogenet Genomics. 2014;24(3):177.
22. Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT 15 genotypes: 2018 update. Clin Pharmacol Ther. 2019;105(5):1095–105.
23. Sim E, Abuhammad A, Ryan A. Arylamine *N*-acetyltransferases: from drug metabolism and pharmacogenetics to drug discovery. Br J Pharmacol. 2014;171(11):2705–25.
24. Nowell S, Falany C. Pharmacogenetics of human cytosolic sulfotransferases. Oncogene. 2006;25(11): 1673–8.
25. Fromm MF. The influence of MDR1 polymorphisms on P-glycoprotein expression and function in humans. Adv Drug Deliv Rev. 2002;54(10):1295–310.
26. Colas C, Ung PM-U, Schlessinger A. SLC transporters: structure, function, and drug discovery. Medchemcomm. 2016;7(6):1069–81.
27. Kameyama Y, Yamashita K, Kobayashi K, Hosokawa M, Chiba K. Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1* 5, SLCO1B1* 15 and SLCO1B1* 15+ C1007G, by using transient expression systems of HeLa and HEK293 cells. Pharmacogenet Genomics. 2005;15(7):513–22.
28. Tirona RG, Leake BF, Merino G, Kim RB. Polymorphisms in OATP-C identification of multiple allelic variants associated with altered transport activity among European-and African-Americans. J Biol Chem. 2001;276(38):35669–75.
29. Niemi M, Schaeffeler E, Lang T, Fromm MF, Neuvonen M, Kyrklund C, et al. High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). Pharmacogenet Genomics. 2004;14(7):429–40.
30. Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther. 2007;82(6):726–33.
31. Group SC. SLCO1B1 variants and statin-induced myopathy – a genomewide study. N Engl J Med. 2008;359(8):789–99.
32. Martínez MF, Quiñones LA. Relationship between pharmacokinetics and pharmacogenomics and its impact on drug choice and dose regimens. In: ADME processes in pharmaceutical sciences. Springer; 2018. p. 169–202.
33. Hoffmeyer S, Burk O, Von Richter O, Arnold HP, Brockmöller J, Johne A, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci. 2000;97(7):3473–8.
34. Miranda C. Estudio de la asociación entre polimorfismos genéticos y la respuesta clínica a Tamoxifeno en pacientes con Cáncer de Mama. Santiago: Universidad de Chile; 2016.
35. Gradhand U, Lang T, Schaeffeler E, Glaeser H, Tegude H, Klein K, et al. Variability in human hepatic MRP4 expression: influence of cholestasis and genotype. Pharmacogenomics J. 2008;8(1):42–52.
36. Tsukamoto M, Yamashita M, Nishi T, Nakagawa H. A human ABC transporter ABCC4 gene SNP (rs11568658, 559 G> T, G187W) reduces ABCC4-dependent drug resistance. Cell. 2019;8(1):39.