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Pharmacogenomics in Gastroenterology

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1. Introduction

The prescription of drugs is an instrumental practice of modern therapeutics. According to the definition of the World Health Organization, the adequate prescription involves the selection of the correct drug, dose and duration of administration. In this sense, it is known that drugs that are prescribed for certain indications cannot produce the desired therapeutic effect in approximately 30 to 60% of the cases (Wang et al., 2011).

The pharmacological effects of most drugs depend on the result of a series of pharmacokinetic processes, which determine the amount of drug that reaches the biophase (target tissues), as well as on pharmacodynamics, involving the interaction between the drug and its site of action. These processes occur at variable levels in different individuals, and one of the major determinants of this variability is genetics. The structure, function and expression of most enzymes involved in drug transport and metabolism as well as the specific drug receptors may be affected by the presence of genetic variants, which may in turn modify the intended therapeutic effect or the appearance of adverse effects. In cases in which polymorphisms or mutations affect the structure or expression of these proteins, with corresponding implications in their function, genomic analyses can be applied to predict the patient's response prior to treatment. This concept represents the central aim of pharmacogenomics (Weinshilboum & Wang, 2006).

Importantly, pharmacogenomic analyses do not explain all of the variability in drug responses. The new paradigm of individualized therapy must combine genetic information and non-genetic factors, such as sex, age, diet, environmental factors, drug interactions, demographics and clinical observations to determine the best treatment for a patient, both in the selection of drugs and in the dosage; the aim is to optimize the

patient's therapeutic experience (Belloso & Redal, 2010). As with other areas of modern therapeutics, pharmacogenomics is gaining a place in the treatment of gastroenterological diseases.

Some gastroenterological diseases, such as gastroesophageal reflux and peptic ulcer disease, are among the most frequent and relevant pathologies in adult patients. In addition, inflammatory bowel disease, hepatitis C and postoperative or cancer-associated nausea and vomiting are conditions in which pharmacological therapy does not show a universal response. Interestingly, genetic factors may partially explain this variability of therapeutic efficacy for most drugs that are used in the treatment of these important gastroenterologic disorders.

In this chapter, we evaluate the major polymorphisms that are associated with the effectiveness or toxicity of drugs that are commonly used in gastroenterology.

2. Genes and polymorphisms

The magnitude of the expression of transporters, metabolizing enzymes and receptors depend primarily on genetic factors. Among these factors, different types of inherited genetic variants may be found, such as deletions, insertions and the multiplication or repetition of sequences, which may involve large portions of DNA. However, the most frequent variants and the most common targets of pharmacogenetic tests are the single nucleotide polymorphisms (SNPs). SNPs are modifications of a single base in the nucleotide sequence.

Studies of the human genome sequence have established that there are more than 15 million SNPs, of which only a small minority appear to have any impact on the kinetics or dynamics of drugs. Different approaches of pharmacogenomic study can range from purely genetic to the identification of those SNPs that confer clinical impacts; conversely, they can include the identification of specific sequences of nucleotides to recognize individuals with particular behaviors in relation to metabolism or drug responses (*The International HapMap Consortium: A haplotype map of the human genome*, 2005; Redon et al., 2006).

The genes that encode metabolic proteins, transporters or receptors may have different polymorphisms, and some of these polymorphisms will confer a particular impact on the magnitude of the expression of the gene products (Leucuta & Viase, 2006).

A polymorphism is considered when an allelic variant appears in more than 1% of the general population. These variants may be associated with a deficient expression or, in a minority of the cases, the overexpression of the enzyme, transporter or receptor.

For most drugs, the genotypic study of its metabolizing enzymes does not exhaust the potential sources of genetic variability. By accounting for the overall potential polymorphisms of transporters and receptors that are involved in the pharmacology of drugs, it may be possible to characterize multiple SNPs from multiple genes, which would refine our understanding of the impact of pharmacogenomics in the selection of therapeutic agents.

3. Peptic ulcer disease by *Helicobacter pylori* infection and gastroesophageal reflux disease

3.1 Clinical characteristics

Helicobacter pylori (HP) infection is associated with chronic gastritis, peptic ulcer disease, gastric mucosal associated lymphoid tissue (MALT) lymphoma and gastric cancer. The eradication of bacterial infection provides an effective means of curing or preventing these HP-associated diseases.

Gastroesophageal reflux disease (GERD) is noted by its prevalence, variety of clinical presentations and under-recognized morbidity. In general, GERD is considered for patients who demonstrate symptoms that are suggestive of reflux or complications thereof and with or without esophageal inflammation.

The most common symptoms of GERD are heartburn (or pyrosis), regurgitation and dysphagia. In addition, a variety of extraesophageal manifestations have been described including bronchospasm, laryngitis, and chronic cough.

A possible role for HP in the pathogenesis of GERD has also been suggested. However, the link between GERD and HP is complex and remains poorly defined.

3.2 Pharmacological treatment

The current treatment strategies for the cure of HP infection are based on a triple therapy that includes a proton pump inhibitor (PPI) and two antibiotics, which are usually amoxicillin and/or clarithromycin or metronidazole. These regimens are effective in 70-90% of patients. Treatment failures have been attributed to bacterial resistance to the antibiotics.

PPIs also constitute the standard treatment for GERD; in fact, the introduction of PPIs for the management of acid-peptic disorders constitutes one of the great success stories in gastroenterology because of their efficacy and safety. Nevertheless, the treatment response is not uniform, and in fact, the average response to treatment may actually hamper the identification of two different populations of patients, which include those who respond almost completely and those who have a consistently suboptimal response.

3.3 Pharmacogenomic considerations

Among the mechanisms of drug metabolism in the body, the most important is cytochrome P450. The complex enzymes that are involved in the metabolism of drugs include CYP2C19, CYP2D6, CYP2C9 and CYP3A4/5/7.

The CYP2C19 isoenzyme metabolizes all of the PPIs that are currently available, some antidepressant drugs, the antifungal voriconazole, thalidomide and the antiplatelet clopidogrel.

The gene that encodes CYP2C19 has been mapped to chromosome 10 (10q24.1-q24.3). At least 21 variants of CYP2C19, from *1 to *20, have been identified. CYP2C19*1 is the wild-type allele. The variant allele CYP2C19*2, which contains 681G>A on exon 5 that causes a splicing defect, which is the major genetic defect that is responsible for the polymorphism of S-mephenytoin metabolism in humans. CYP2C19*3 carries the 636G>A SNP, which results

in a premature stop codon in exon 4. Both *CYP2C19**2 and *3 are null alleles, which result in the absence of enzymatic activity (de Morais et al., 1994). The majority of the PMs of *CYP2C19* are due to these two variant alleles (Desta et al., 2002).

It has been described that approximately 3-5% of the Caucasian population has a total absence of enzymatic activity that is primarily associated with the gene variant *CYP2C19**2, and it is associated to a lesser extent with *CYP2C19**3. The frequency of these polymorphisms is highly variable among different populations (Goldstein et al., 1997). Likewise, the *CYP2C19* * 17 variant (I331V) was identified more recently, and it is found in ultra-rapid metabolizers (UMs) (Sim, 2006). The alleles *2 and *3, which are associated with poor metabolizers (PMs), have been found in approximately 85% of the Caucasian population and nearly 100% of the Asian population. If the alleles *4 and *6 are included, the prevalence of the PM phenotype in Caucasians is 92%.

The biotransformation of PPI occurs primarily through *CYP2C19*, and the study of polymorphisms for these drugs has a specific application. *CYP2C19* is responsible for the initial hydroxylation of omeprazole and lansoprazole and, to a lesser extent, the demethylation of pantoprazole and rabeprazole, which are the steps that produce metabolites without antacid activity (figure 1). The ability of these drugs to reduce gastric acidity depends largely on the concentration that is reached in the plasma after absorption. Therefore, those who rapidly metabolize the drugs, rapid metabolizers (RMs) have significantly lower gastric pH values than those who are "extensive metabolizers", "intermediate metabolizers" (IMs) or PMs. The PMs have inherited variations in both of the alleles and therefore cannot express the functional enzyme. The differences in the area under the curve (AUC), which is a variable that quantifies the exposure of the subject to the current drug, can be up to 13-fold higher for the PM in the case of omeprazole.

In addition, it has been observed that these pharmacokinetic and pharmacodynamic differences result in diverse clinical outcomes by using proton-pump inhibitor therapies, which are primarily used in the treatment of gastroesophageal reflux disease (GERD) and the eradication of HP (Furuta, 2005).

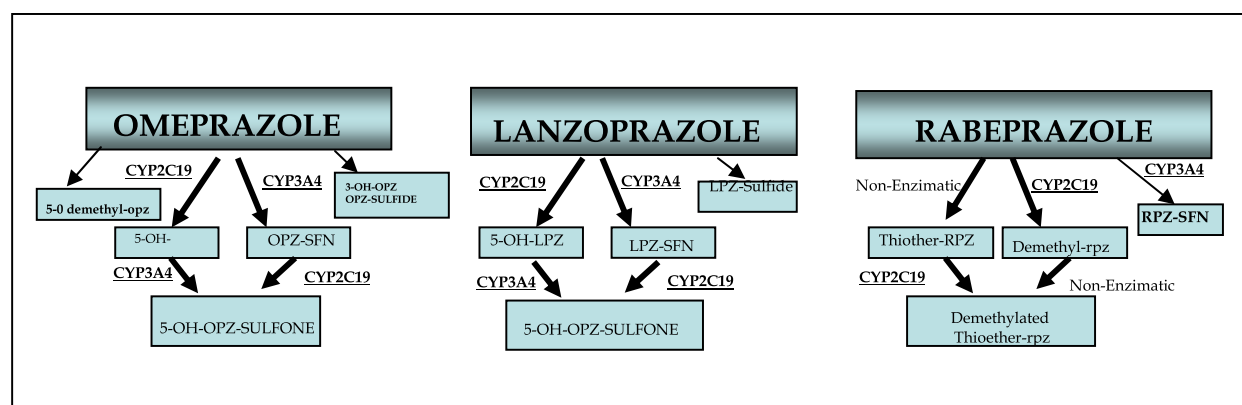


Fig. 1. Metabolism of omeprazole, lansoprazole and rabeprazole

3.4 Pharmacogenomic influences in the treatment of GERD with PPIs

In recent years, it has been established that one of the causes of GERD that is refractory to PPI therapy, which occurs in approximately 10% of patients, is related to differences in the

efficiency of the metabolism of the drug. Endoscopic cure rates are much lower in RMs than in IMs, and higher cure rates are observed in the PMs, which display a poorer outcome in relation to the severity of the injury (less than 17% for RM C or D lesions, Los Angeles classification). It was established that the genotype is also crucial for the nocturnal acid bouts, which are episodes in which the pH falls below 4 for more than an hour and are considered to be an influential factor in the treatment outcome. These intrusions are much more frequent in RMs than in the other two types of metabolizing patterns. This result suggests that patients who are refractory to standard doses of PPI should be offered an increased dose or frequency on the premise that they are RMs (Kawamura et al., 2007; Egan et al., 2003).

The safety profile of PPIs also seems to be influenced by pharmacogenetics, which is illustrated in the case of GERD treatments that require long treatment periods. There is some evidence that IMs and, to a larger extent, PMs, have a higher risk of hyperplasia of enterochromaffin-like cells, which is related to the development of carcinoid tumors, than their RM counterparts (Rosemary & Adithan, 2007). Likewise, the first two groups have higher rates of megaloblastic anemia by vitamin B12 deficiency, which arises from the neutralization of the gastric pH for extended periods; these groups also suffer from atrophic gastritis, which is especially likely if it coexists with HP infection (Kang, 2008).

3.5 Pharmacogenomic influences on the eradication of *Helicobacter pylori*

To eradicate and as a part of the therapeutic strategy for managing patients with various conditions, such as peptic ulcer disease or MALT, PPIs are a central part of the scheme that also require the addition of antibiotics. The suppression of gastric acidity is also crucial for the bioavailability and stabilization of the plasma concentration of antibiotics, which can force HP to its growth phase, which is where it is most responsive to treatment, increase the intragastric concentrations of antibiotics and provide some intrinsic actions against HP.

Response rates in the eradication of HP are also influenced by the genotype of the patient (figure 2), such that the PMs are able to achieve 100% eradication with the standard dose of PPIs and with the addition of 500 mg of amoxicillin and omeprazole four times a day for two weeks. In this scheme, the eradication rate for IMs is 60%, and that for RMs is only 30% (Kang, 2008). In addition, adequate results have been reported with dual schemes that utilize 10 mg of rabeprazole twice per day, which has a greater ability to suppress gastric acidity than omeprazole that is combined with amoxicillin, and has reached 90% eradication in both PMs and IMs (Furuta, 2005). Therefore, in a large number of cases, the use of a second antibiotic may be avoided. Moreover, in the cases of eradication failure, an attempt can be made by doubling the dose of rabeprazole with amoxicillin before a third antibiotic is added; the intention of this treatment is to achieve effectiveness in the case of RMs. This differential approach that permits the individualization of PPI treatment according to the CYP2C19 genotype constitutes a real breakthrough, and it facilitates the avoidance of the addition of clarithromycin or metronidazole, which are not exempt from adherence problems, cost, resistance and adverse effects.

The addition of clarithromycin to the regimen of PPIs and amoxicillin has a pharmacokinetic basis: clarithromycin inhibits another cytochrome, CYP3A4, which is an alternative pathway for the metabolism of PPIs. Therefore, PPI concentrations are extremely high when PMs are

exposed concomitantly to these drugs and clarithromycin, although the rise of the plasma concentration has been observed with all of the genotypes (Furuta, 1999).

This technique may represent one mechanism to increase the effectiveness of the triple scheme regardless of the CYP2C19 genotype. Nevertheless, the RMs cure rates are lower than the IMs and PMs cure rates, which is probably because the RMs receive insufficient doses of PPIs in accordance with the enzyme expression. It is believed that in the case of the triple scheme, prior knowledge of CYP2C19 genotype may help to optimize the dose of PPI to minimize the possibility of therapeutic failures. It is recommended that the dose and the dosing interval, up to four times daily, should be increased to ensure a gastric pH that is close to 7 for the majority of the day (Chaudhry & Kochhar, 2008).

Finally, in patients for whom therapy has been individualized but fails to eradicate the disease, a consideration should be made regarding the possibility of an infection by a HP strain that is resistant to clarithromycin (Furuta & Graham, 2006).

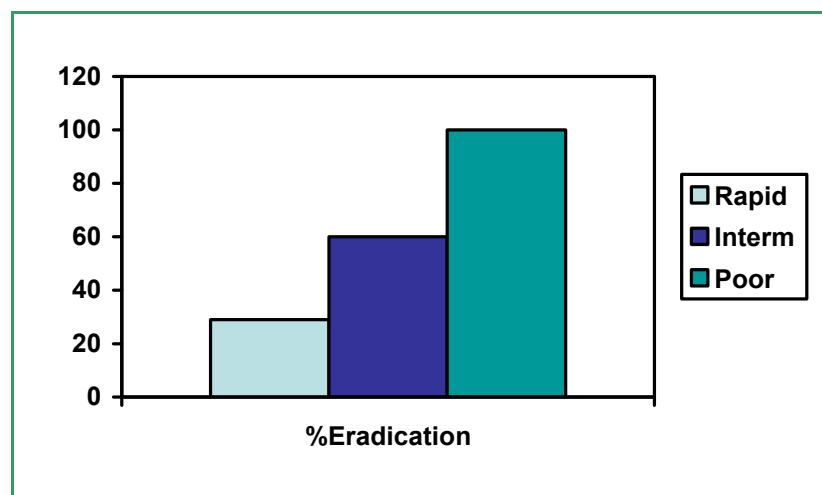


Fig. 2. Omeprazole metabolism by CYP2C19. (Furuta et al, 1998)
The percent of HP eradication is dependent upon the metabolizer phenotype.

4. Inflammatory Bowel Disease

4.1 Clinical characteristics

Inflammatory bowel disease (IBD) is a chronic, disabling disease that generally presents with flares and remissions. Ulcerative colitis (UC) and Crohn's disease constitute the most frequent forms of presentation. There are remarkable differences between both conditions regarding the clinical presentation, extension and extra-intestinal manifestations of the disease. The precise etiology of IBD is unknown, but both ambient and genetic factors may play a significant role.

4.2 Pharmacological treatment

The clinical course of this condition has changed substantially since immune modulator therapies and monoclonal antibodies were introduced to the therapeutic armamentarium; as a result, the extent of the remission periods has increased. However, a curative pharmacological approach is not yet available.

In addition, considerable variability exists regarding the efficacy and toxicity of the treatment. Multiple factors may influence the response to treatment, which include disease severity and complications; environmental factors, such as smoking; and genetic factors. It is estimated that between 20% and 95% of the variability in the toxicity and the treatment response may be explained by polymorphisms. The overall response rate to the treatment is more difficult to estimate than toxicity because there are multiple confounding factors, such as the concomitant use of other drugs, which may influence outcomes. The polymorphism of the enzyme thiopurine methyl transferase (TPMT) (figure 3) and its influence on treatment with Azathioprine (AZA) and 6-mercaptopurine (6-MP) is the best example of how genotyping can help to optimize therapy in inflammatory bowel disease (Hindorf et al., 2002), (table 1).

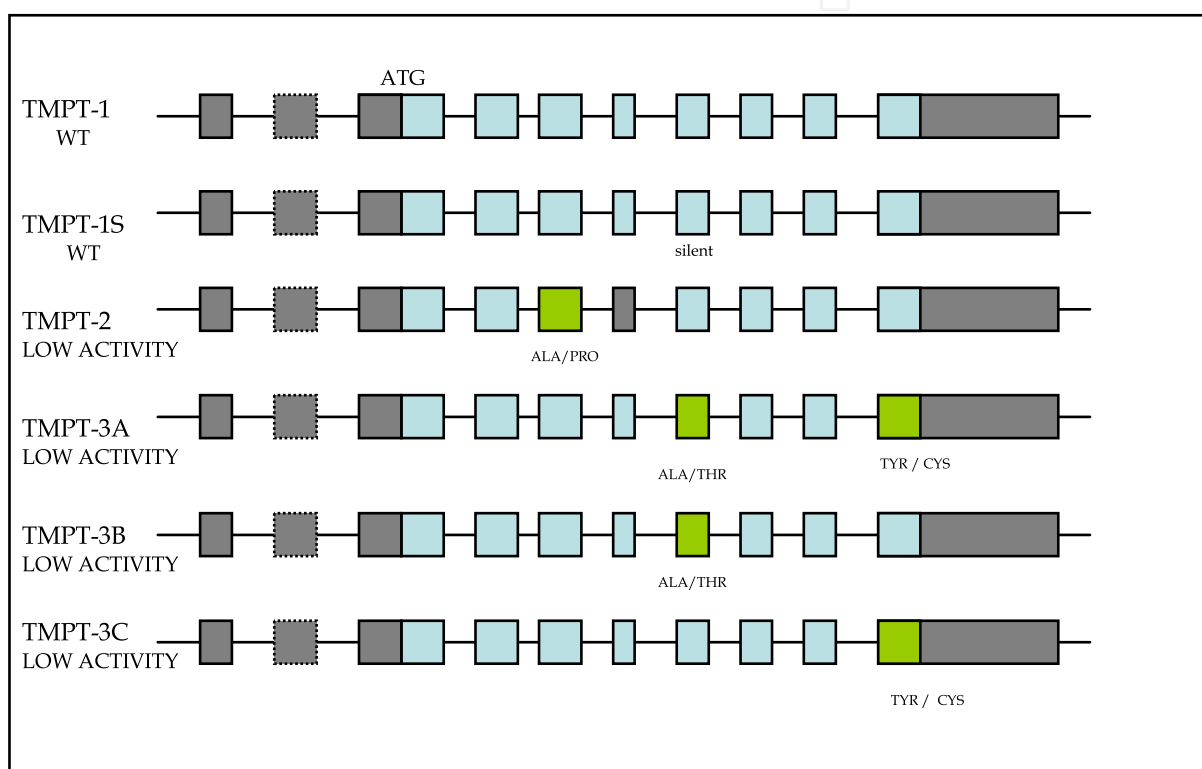


Fig. 3. Allelic variant of the TMPT locus. The boxes depict exons in the TMPT gene. The grey boxes are the untranslated region and blue boxes represent exons in the open reading frame. The green boxes are exons that contain mutations resulting in amino acid changes.

Genotype	Phenotype / Activity	AZA dose
TMPT*1/*1	High	Standard doses
TMPT*1/*2 TMPT*1/*3 (A,B or C)	Intermediate	Half dose
TMPT*2/*3 (A,B or C) TMPT*3/*3 (A,B or C)	Deficient/ Null	Avoid AZA. Alternative treatment recommended.

Table 1. Relationship between genotype and phenotype in TPMT and doses of AZA in patients with IBD

AZA is a thiopurine derivative with immunosuppressive properties that has been available on the market for almost 40 years. It is widely used in the treatment of rheumatic diseases of children and adults, transplantation and inflammatory bowel disease, and it is used in different treatment combinations. However, approximately 40% of IBD patients do not respond to AZA treatment, and 10-25% must discontinue treatment because of adverse reactions, being either major (leukopenia, pancreatitis and hepatitis) or minor (rash, nausea, flu-like syndrome and diarrhea). Adverse reactions, which include liver, gastrointestinal and bone marrow toxicity are present in approximately 15-28% of patients.

Hematologic toxicity occurs in approximately 2-9% of patients, and it can, in extreme cases, lead to death (Pierik et al., 2006).

AZA is a pro-drug that is administered orally in doses of approximately 2.5 mg/kg per day. Fifteen to sixty percent of the drug is absorbed in the intestine, and after it enters the body, it is converted to 6-MP by a non-enzymatic reaction. 6-MP is also a pro-drug that undergoes a series of enzymatic reactions to form thioguanide nucleotides (6-TGNs), which are active metabolites that antagonize the metabolism of purines; inhibit the synthesis of DNA, RNA and proteins; and may also interfere with cellular metabolism and prevent mitosis. 6-TGNs are responsible for the immunosuppressive activity and the myelosuppressive action of AZA.

The inactivation of AZA and 6-MP depend primarily on two metabolic pathways; one pathway utilizes xanthine oxidase, producing 6-thiouric acid, and the other utilizes TPMT, which converts the original drug to 6-methylmercaptopurine. Both of the metabolites are inactive.

In myelopoietic precursors, no xanthine oxidase activity is observed; therefore, TPMT expression and function are vital for the inactivation of thiopuric derivatives.

However, the accumulation of active metabolites also depends on the activity of these enzymes. In this regard, the toxicity of both AZA and 6-MP are strongly related to the TPMT activity. The decreased activity or deficiency of TPMT causes 6-MP to be preferentially metabolized to 6-TGNs, which are responsible for much of the toxicity of 6-MP.

Following the introduction of the pharmacogenetic test for TPMT, there have been major changes in the prescription patterns of AZA in the last decade. The choice to use or not use AZA in accordance with the TPMT genotype offers the possibility of a safer and more effective treatment.

Several studies have shown that 80-90% of patients who have at least one of the aforementioned variants will have to discontinue AZA treatment due to adverse effects, which primarily include neutropenia (Evans & McLeod, 2003).

4.3 Pharmagenomic considerations

Supporting evidence currently exists for the pre-treatment genetic testing of TPMT in the reduction of neutropenic episodes in patients receiving azathioprine, although the evidence regarding its contribution in increasing drug efficacy is not as strong (Lakatos, 2010). A recent survey in the UK showed that 67% of gastroenterologists used TPMT testing before

prescribing AZA (Payne et al., 2007). In 2004, the US Food and Drug Administration (FDA) approved TPMT testing in the US and made the recommendation to include this information in the drug prescription brochure; however, no formal recommendation was made for mandatory testing.

A socio-economic study of IBD has demonstrated that TPMT genotyping is a cost-effective method that can identify patients with active low/absent enzyme to avoid treatment with AZA and its subsequent severe hematologic complications (van den Akker, 2006)

It is now recommended that patients with IBD who have low or intermediate enzyme activity should receive a starting dose of 50% of the usually prescribed dose, and treatment with AZA should be avoided in patients with null enzymatic activity to prevent toxicity (Pierik et al., 2006; Lakatos, 2010)

5. Gilbert Meulengracht syndrome and irinotecan

5.1 Clinical characteristics

Gilbert syndrome is characterized by the presence of unconjugated hyperbilirubinemia, which is usually moderate, transient or intermittent; has a non-obstructive origin without liver inflammation or fibrosis; and is not associated with changes in histology.

The occurrence of this syndrome is primarily related to the genetic variability in a family of enzymes (UDP-glucuronyltransferase (UGTs)) that are part of a detoxification system against endogenous toxins and xenobiotic chemicals. These membrane enzymes catalyze the glucuronidation of different substances by making them more polar to facilitate their excretion through bile or urine.

This is a route of detoxification that is used for substances that are taken with meals, tobacco smoke, or drugs; however, this route is primarily involved in the maintenance of the homeostasis of endogenous substances, such as bilirubin, steroids, thyroid hormones and bile acids (Strassbourg, 2008).

5.2 Pharmacogenomic considerations

Different polymorphisms are associated with the variable activity of these enzymes, which affects their ability to detoxify substances. Subsequently, the glucuronidated products are recognized by transport systems for organic anions, and they are secreted in urine or bile.

From a pharmacogenetic standpoint, the primary current use of the identification of alleles of UGT1A1 is focused on the ability to adequately predict the occurrence of severe hematologic toxicity (grade 3 or 4) in cytostatic treatment combinations, which include high doses of irinotecan.

The UGT1A1 enzyme is the only enzyme that is relevant in the metabolism of bilirubin. At least 113 variants have been identified, but very few are common in the general population. One hundred ninety-five SNPs have been identified in the UGT1A1 gene. Among these, there are 11 SNPs in exons 1-5. The UGT1A1*6 (211 G>A) in exon 1 is the most common SNPs that is found in the East Asian population (15.7%), but it is not

common in the Caucasian population (0.7%) (Bernabeu et al., 2010). It has been suggested that the allele *6 contributes to the high incidence of neonatal hyperbilirubinemia in Asian children (Akaba et al., 1999). Exon 1 is unique for each member of the UGT1A1 subfamily, whereas exons 2 to 5 are common to all of the members of the subfamily. The variants in the 3'UTR of UGT1A1 in exon 5, therefore, may have distinct effects on all of the members of the UGT1A1 subfamily.

Polymorphism in the promoter region of the UGT1A1 gene is caused by variability in the number of TA repeats in the TATA-box that is located upstream of UGT1A1. The presence of seven TA repeats (UGT1A1*28) is associated with reduced UGT1A1 expression compared to the wild type allele (UGT1A1*1), which contains six TA repeats. Homozygous individuals who carry the A (TA)₇ TAA allele show significantly higher plasma levels of unconjugated bilirubin caused by a 30% reduction in the transcription of UGT1A1 (Lyer et al., 2002). There are interethnic differences in the frequency of the UGT1A1*28 allele, which has an approximate incidence of 6-12% in the Caucasian population, 0-3% in the Asian population and 16-19% in the African population (Shu-Feng Zhou et al., 2008).

However, there are other polymorphisms, such as UGT1A1*36, which contains 5 TA; UGT1A1*37, which contains 8 TA; and other polymorphisms that are not linked to the TATA-box region, such as the variant UGT1A1*7 (1456T>G, mutation in exon 1); UGT1A1*27 (686C>A), which is very rare in all of the ethnic groups that were examined; and the variant UGT1A1*62, which is found exclusively in Asians and is not present in either Caucasians or Africans.

Because haplotypes with UGT1A1 variants may coexist in the same person, the scenario is actually more complex. This may help to explain why there is hyperbilirubinemia in 5-9% of Caucasians, while 10-16% are homozygous for the UGT1A1*28 variant (Strassburg, 2010).

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves DNA torsional strain by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent the relegation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is related to double-strand DNA damage that is produced during DNA synthesis, when replication enzymes interact with the ternary complex that is formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks. The irinotecan metabolite SN-38 is conjugated by UGT1A1. The presence of seven TA repeats, rather than the wild type number of six, in the UGT1A1 promoter reduces enzyme expression and consequently the expression of SN-38; this also confers a higher chance of developing diarrhea and/or leukopenia during irinotecan therapy when compared to patients with a wild type genotype. Gilbert's syndrome is also associated with the TA₇/TA₇ genotype, and these patients may have an increased risk of irinotecan-induced toxicity (Côté et al., 2007).

In the same way, the recognition of patients with UGT1A1 deficiency may contribute to the prediction of the development of severe hyperbilirubinemia in patients with HIV infection who are treated with atazanavir, which is an enzyme blocker, and increased plasma concentrations of the integrase inhibitor raltegravir.

Irinotecan is primarily converted to its active metabolite SN-38 by liver carboxylesterases. UGT 1A1 inactivates SN-38 into the more polar SN-38 glucuronide, which is further eliminated in bile and urine (figure 4).

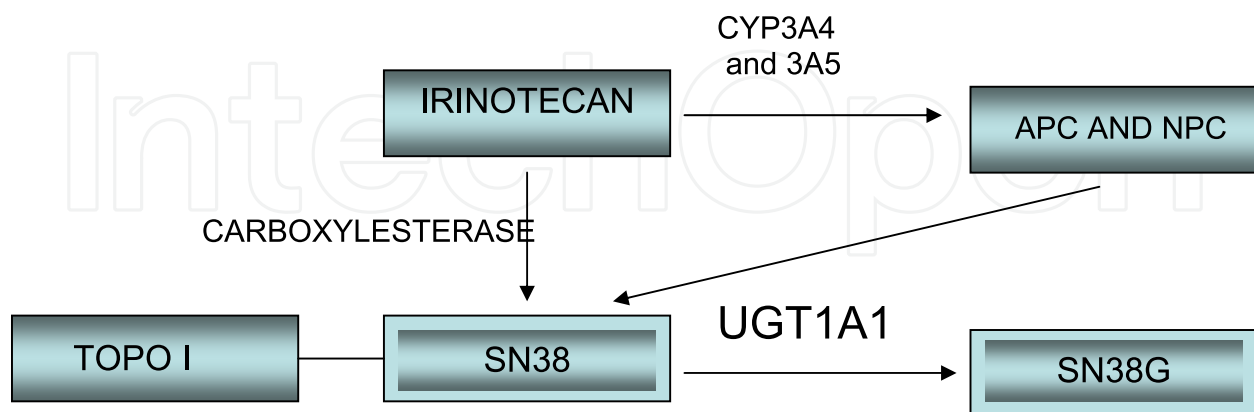


Fig. 4. Metabolic pathway of irinotecan

6. Hepatitis C infection

6.1 Clinical characteristics

The hepatitis C virus (HCV) infection affects over 170 million people worldwide; it causes chronic hepatitis, which may, in turn, lead to cirrhosis and hepatocellular carcinoma (HCC). There are six different genotypes whose prevalence varies geographically. Genotype I is responsible for most of the infections in North America, South America and Europe. Direct contact with blood (as in uncontrolled transfusions) or the use of parenteral drugs constitute the most common method of transmission, while unprotected sex is a secondary risk factor.

A patient's immune response will determine whether HCV is eventually eliminated or remains, which can produce a persistent infection; this latter outcome occurs in the majority of cases. The course of HCV infection is variable, although in most patients, it will progress toward cirrhosis.

The hepatitis C virus is a flavivirus. The HCV genome is a positive-sense RNA molecule of approximately 9500 nucleotides and encodes a polyprotein precursor of approximately 3000 amino acids.

The observation of nucleotide and amino acid mutations that are specifically segregated in groups or subgroups in almost all of the regions of the HCV genome has permitted the classification of HCV genotypes and subtypes whose sequences differ from each other by 30% and 20%, respectively. Currently, we accept the existence of at least 6 genotypes that are divided, in turn, into more than 84 subtypes. These genotypes were identified by a number (1 through 6), and the subtypes were identified by a lowercase letter in the order of their discovery (e.g., 1a, 1b, 2a, 3a, etc.).

After they bind to the cell surface, HCV particles enter the cell by receptor-mediated endocytosis. The cytosolic recognition of specific motifs in viral products induces the production of interferons and proinflammatory cytokines, which leads to the recruitment of

a signaling complex that activates transcription factors. The subsequent expression of interferon alpha regulatory factor 3 (IRF-3) target genes, and likely lambda (type III) interferons induces innate immune programs and drives the maturation of adaptive immunity for infection control. The coordinated activities of CD4+ T cells and cytotoxic CD8+ T cells, which are primed in the context of HLA class II and I alleles, respectively, on antigen presenting cells, are critically important for the control of acute HCV infection. Mutations in viral epitopes that are targeted by cytotoxic CD8+ T cells can permit the virus to escape immunomediated clearance. The up-regulation of inhibitory receptors on exhausted (functionally impaired) T cells is another mechanism of T-cell dysfunction during chronic infection.

The host immune response determines whether the HCV persists or is eradicated spontaneously.

One of the most influential factors appears to be related to certain polymorphisms of a site that is in close proximity to the IL28B gene (Thomas et al., 2009; Grebely et al., 2010).

The risk of chronic infection that follows an acute episode of hepatitis C is high. In most studies, 80% to hundred percent of patients remain HCV RNA-positive, and 60 to 80 percent have persistently elevated liver enzymes (Chu et al., 1999; Farci et al., 1991). The mechanism that is responsible for the high prevalence of chronic infection is unclear. This mechanism may be related to the genetic diversity of the virus and its tendency toward rapid mutation, which allows HCV to constantly escape immune recognition. Most patients with chronic infection are asymptomatic or have only mild, nonspecific symptoms. The most frequent complaint is fatigue; other less common manifestations include nausea, anorexia, myalgia, arthralgia, weakness, and weight loss.

Cirrhosis occurs in up to 50 percent of chronically infected patients (Tong et al., 1995; Takahashi et al., 1993; Yano et al., 1996). Complications of hepatitis C are mostly confined to patients who have developed cirrhosis. The development of cirrhosis is silent in the majority of patients in whom it occurs. The progression to fibrosis and later to cirrhosis depends on many factors, such as the duration of infection, advanced age, male sex, co-infection with other viruses (HIV or HBV), or alcohol intake. HCC in patients with hepatitis C occurs almost exclusively in those with cirrhosis, which suggests that this is the major risk factor. The deaths that are associated with chronic hepatitis C are more likely to be related to end-stage liver disease rather than hepatocellular carcinoma (HCC). However, HCV accounts for approximately one-third of HCC cases in the United States. Estimations of the risk of developing HCC after the development of cirrhosis have varied from 0 to 3 percent per year in various reports. The risk appears to be greater with genotype 1b when compared with genotype 2a/c (Fattovich et al., 1997; Hu & Tong, 1999; Planas et al., 2004; Bruno et al., 2007).

Once the complications of cirrhosis have occurred, liver transplantation is the only effective therapy. Recurrent HCV infection of the graft occurs in almost all patients, although the long-term survival following transplantation for HCV is similar to the survival that is related to other causes of hepatic failure (60 to 80 percent). Several factors may be important determinants of disease progression in individual patients; these factors include age, ethnic background, gender, HCV-specific cellular immune response, viral diversity, alcohol use, daily use of marijuana, viral coinfection, environmental factors and geography.

6.2 Pharmacological treatment

The decision to treat a patient with chronic HCV infection is based upon several factors, which include the natural history of the disease, the stage of fibrosis, and the efficacy and adverse effects that are related to the therapy. For patients with clinically significant hepatic fibrosis, there is widespread agreement that antiviral therapy is indicated because of the high risk of cirrhosis.

Currently, the standard treatment for HCV infection is ribavirin in combination with peg-interferon (INF), but unfortunately, approximately 50% of patients with genotype I do not respond to the treatment (Liapiakis & Jacobson, 2010). In contrast, 70-80% of patients with genotypes II or III have sustained virological response (SVR) that is defined as undetectable HCV RNA 6 months after the treatment. Although the treatment response rate depends on several factors, such as patient age, sex, viral genotype, viral load at the start of treatment and the liver fibrosis rate, genetic factors that may be related with the rate of response to treatment and disease progression have been recently identified (table 2).

Ribavirin is a nucleoside analogue. The mechanism by which ribavirin contributes to its clinical antiviral efficacy is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutational frequency in the genomes of several RNA viruses, and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction. Ribavirin is generally well tolerated. The major adverse effects include hemolysis, nonspecific fatigue, depression, insomnia, vertigo, anorexia, nausea, nasal congestion, and pruritus. As a result of hemolysis, ribavirin treatment may be associated with a mild reversible increase in serum bilirubin and uric acid.

Peg-INF is derived from the recombinant human interferon Alpha2a. Alpha interferons possess potent antiviral activity.

General characteristics	<ul style="list-style-type: none"> • Non I HCV Genotype • Low viral load • Caucasian descent • IL28B Genotype • Absence of fibrosis • Weight < 85kg • Age < 40 years • Female gender
Before treatment initiation	<ul style="list-style-type: none"> • Absence of insulin resistance • Absence of liver steatosis • Use of statins
During treatment	<ul style="list-style-type: none"> • Rapid virological response (at week 4 of treatment) • Adherence to treatment • Standard dose of ribavirin.

Table 2. Predictors of adequate responses to treatment with ribavirin and INF in HCV

They induce interferon-stimulated genes (ISGs) that help to establish an antiviral status milieu within cells, although the response is not virus-specific. Alpha interferons act by binding to cell surface receptors, which activates a response cascade that culminates in the expression of multiple ISGs, some of which block viral protein synthesis. Peg-IFN binds the human type I INF receptor, which leads to receptor dimerization. Receptor dimerization activates multiple intracellular signal transduction pathways that are initially mediated by the JAK/STAT signal cascade. A combination therapy with ribavirin and interferon may be associated with an increased risk of side effects (such as nausea, rash, and dyspnea) when compared to the treatment with interferon alone (table 2). However, a meta-analysis and the large studies that were discussed above have suggested that the incidence of serious side effects of these treatments are not significantly different (Schalm et al., 1997; Mc Hutchison et al., 1998).

6.3 Pharmacogenomic considerations

As aforementioned, the efficacy of INF treatment is determined by a number of factors. Among these factors, genetic variance has been established as an important predictor of treatment response and viral clearance.

Four independent genetic studies (Genome Wide Association Study (GWAS)) have identified a polymorphism in the IL28B gene on chromosome 19 that encodes IFN- λ that has a strong association with the response rate to combination therapy with peg-IFN and ribavirin (Ge et al., 2009; Suppiah et al., 2009; Tanakah et al., 2009; Rauch et al., 2010).

Using a GWAS, several investigators from the US and the UK identified a SNP on chromosome 19, rs12979860. The rs12979860 SNP is 3 kb upstream of the aforementioned IL-28B gene (Brian, 2011). Ge et al. identified rs1297960 as the variant that is most strongly associated with SVR in European-American, African-American and Hispanic populations.

Their study showed an association of the CC genotype with a greater rate of SVR than the TT genotype. The frequency of the CC genotype was 39%, 16% and 35% in European-American, African-American and Hispanic populations, respectively.

Suppiah et al. and Rauch et al. -in a European cohort- and Tanaka et al. -in Japanese patients- found the strongest association with rs8099917 (located 8 kb upstream of IL28B), which is in linkage disequilibrium with rs12979860. The TT genotype of rs8099917 was significantly associated with the presence of a sustained virological response (SVR) following treatment with peg-IFN and ribavirin in patients who were chronically infected with genotype 1, while the minor allele G is associated with the absence of the response and the increased risk of progression to chronic states.

A higher prevalence of the T allele in the HIV-negative control population was also found, which suggests that this allele may be associated with the possibility of the clearance of the hepatitis C virus (Thomas et al., 2009; Aparicio et al., 2010).

These findings may impact the prognosis and treatment of HCV infection. Furthermore, the ability to identify patients with a risk allele, particularly in homozygosity, in which the response to treatment would be very poor, would make them candidates for alternative therapies.

7. Postoperative and cancer-associated nausea and vomiting

7.1 Clinical characteristics

Postoperative nausea and vomiting is a frequent experience for patients who are subjected to surgery with general anesthesia. Twenty to forty percent of surgical patients may display this disorder, and in certain high-risk groups, the incidence is even higher (Candiotti et al., 2005). In addition, nausea and vomiting is one of the most distressful side effects of cytotoxic drugs that are administered to patients with oncologic conditions. There are multiple factors related to the individual risk of developing nausea and vomiting, such as female sex, young age, alcohol consumption, preexisting nausea, and the emetogenic potential of the chemotherapeutic agents that are used (Perwitasari et al., 2011).

7.2 Pharmacological treatment

Among the most commonly used drugs, the receptor antagonists of serotonin type 3 (5HT₃), such as ondansetron, granisetron and tropisetron, are widely used as antiemetics to primarily prevent nausea and vomiting that are associated with chemotherapy and postoperative conditions. These drugs provide a substantial contribution toward the prevention and the treatment of nausea and vomiting in these scenarios. However, 20-30% of patients do not respond to treatment with 5HT₃ antagonists.

7.3 Pharmacogenomic considerations

One reason that may explain these interindividual differences in the response to treatment is the variation in the hepatic biotransformation of the drug, which, in turn, could be genetically determined by polymorphic variants of the gene that encodes CYP2D6. All of the 5HT₃ antagonists are metabolized by the CYP450 complex, and they are primarily metabolized by the CYP2D6 isoenzyme.

The CYP2D6 gene is mapped to chromosome 22q13.1 and encompasses nine exons with an open reading frame of 1383 base pairs that encode 461 amino acids (Eichelbaum et al., 1987). More than 63 different CYP2D6 variants have been identified by the human cytochrome P450 allele nomenclature. Relative to the wild type CYP2D6 allele, different variants of the CYP2D6 gene may result in the complete absence of enzyme activity, reduced activity, normal activity or even increased activity. Null alleles of CYP2D6 do not encode a functional protein, and there is no detectable residual enzymatic activity. These null alleles are responsible for the PM phenotype when they are present in homozygosity or compound heterozygosity. The mechanisms by which these variants are leading to a total loss of function include the following: a) single-base changes or small insertions/deletions that interrupt the reading frame or interfere with the correct splicing, which leads to a prematurely terminated protein or stop codon (e.g., CYP2D6*3, *4, *6, *8, *11, *15, *19, *20, *38, *40, *42, and *44) (Kagimoto et al., 1990); b) nonfunctional full-length coded alleles (e.g., CYP2D6*5, *12, *14 and *18) (Evert. et al., 1997); and c) the deletion of the entire CYP2D6 gene as a result of large sequence deletions (e.g., CYP2D6*5, *13, and *16) (Gaedigk et al., 1991). However, extremely high CYP2D6 activity results from the gene duplication of functional alleles *1 and *2 that are fused in a head-to-tail orientation as a result of unequal crossover events and other mechanisms. This was noted by a molecular characterization of

the CYP2D6 locus in patients with extremely rapid metabolism (Bertilsson et al., 1993). Approximately 5-10% of the Caucasian population has no activity of the enzyme (PMs) and approximately 2% are UMs. These patients have two active gene copies resulting in the production of enzymes with increased activity which will rapidly decrease the plasma concentration of the substrate drug with subsequent treatment failure (Lewis et al., 2010; Ho et al., 2006; Vermiere et al., 2010).

Therefore, antiemetic treatment may be optimized through CYP2D6 genotyping prior to chemotherapy or surgical treatment by identifying the patients that will behave as PMs or UMs for these drugs; this analysis can specifically identify which patients would require a dose adjustment (Perwitasari et al., 2011).

Because the CYP2D6 polymorphism explains only a proportion of the therapeutic failures in these patients, it has been postulated that changes in both the dopamine receptor and serotonin receptor may also be related to the antiemetic treatment response (Perwitasari, 2011). Interestingly, it has also been postulated that CYP2D6 polymorphisms may be related to the predisposition to the development of dyskinesias with the use of metoclopramide, but the confirmation of these findings has not yet been provided (van der Padt et al., 2006). In summary, genetic variants may help in the individualization of drug dosing and the prediction of treatment outcome with the use of 5HT3 antagonists, although its routine use in therapeutics will require further confirmation by larger studies.

8. Resume

In table 3 major gastroenterological diseases are described as well as the drugs available for pharmacological treatment and the enzymes involved in their metabolism.

DISEASE	ENZYME	DRUGS
Peptic Ulcer	CYP2C19	Proton Pump Inhibitors
Inflammatory Bowel Disease	TMPT	Azathioprine 6-Mercaptopurine
Gilbert Meulengracht syndrome	UGT1A1	Irinotecan
Hepatitis C	IL28B	Peg-IFN
Nausea and vomiting associated with chemotherapy and postoperative states.	CYP2D6	Type 3 serotonin receptor (5HT3) antagonists

Table 3. Gastroenterological diseases, drug and associated metabolic enzyme

In table 4, the genes involved in the pharmacogenomic studies for gastroenterological diseases are summarized, as well as their effects in the enzymatic activities and phenotypic consequences.

GENE	POLIMORPHISM	EFFECT	CONSEQUENCES
CYP2C19	SNPs-Alleles: *2, *3, *4, *6	Decrease activity	Poor metabolizers
	SNPs-Allele: *17	Increase activity	Ultrarapid Metabolizers
TMPT	SNPs-Alleles: *2, *3 ^a , *3B, *3C	Decrease activity	Toxicity
UGT1A1	STRs -Short Tandem Repeats-:113 Alleles	Different activity levels	Predict the occurrence of severe hematologic toxicity with irinotecan
IL28B	SNPs: TT variant	Associated with the sustained virological response (SVR)	Impact on the prognosis and treatment of Hepatitis C with interferon
CYP2D6	SNPs: more than 50 alleles	Different activity levels	Poor to Ultrarapid Metabolizers

Table 4. The most important genes, variants and their effects on the enzymatic activities involved in pharmacological treatment of gastroenterological diseases.

9. Conclusions

In some of the most important areas of gastroenterological therapy, the relevance of pharmacogenomic analysis has been already demonstrated or is in the process of confirmation for both the identification of the proper dosage for a particular patient and the prevention of significant toxicity.

The major polymorphisms (*2 and *3) of CYP2C19 associated with the phenotype of poor metabolizers in certain drugs, can identify patients who will achieve higher plasma concentrations of the main proton-pump inhibitors with the use of standard doses. Because this particular therapeutic group has a wide therapeutic range, the presence of higher concentrations is associated with higher treatment success rates for the treatment of *Helicobacter pylori* in either peptic ulcer disease or gastroesophageal reflux disease. The knowledge of these associations is particularly useful in populations with a higher prevalence of these polymorphisms. The analysis of variants in the promoter region of the UGT1A1 enzyme coding gene facilitates the identification of patients with Gilbert Meulengracht syndrome, although its pharmacogenetic relevance is currently limited to the cytostatic irinotecan. The experience that has been gained with the use of pharmacogenomic studies in the context of inflammatory bowel disease is currently limited to the analysis of variants of the TMPT coding gene. These variants are associated with the risk of the hematologic adverse effects of azathioprine, and its analysis has resulted in favourable pharmacoeconomic evaluations.

Other polymorphisms, such as the ones in the intracellular glucocorticoid receptor, the MDR1 gene that encodes P-glycoprotein and the TNF receptor, warrant further evaluation. However, to date there is no incontrovertible evidence regarding their clinical usefulness. The identification of polymorphisms in IL28 likely represents a potential new paradigm in the treatment of Hepatitis C infection. Genetic testing for antiemetic drugs will likely show great potential are expected to be developed in the near future, although their final usefulness will only be established after the acquisition of more clinical data.

Currently, pharmacogenomics only constitutes a tool that can be utilized for personalized medicine, and it provides a concrete potential to predict therapeutic responses beyond the population level. Because it has been recently developed, it also benefits from the interest that is generated by its novelty. In the next few years, it will become more clear which aspects of this method can offer specific advantages regarding the efficacy and safety of the patients when compared to the aspects that are only of an academic interest.

However, given the fact that the therapeutic experience with the use of drugs in gastroenterology is far from satisfactory, any firm step in the direction of individualizing drug treatment will facilitate better patient care.

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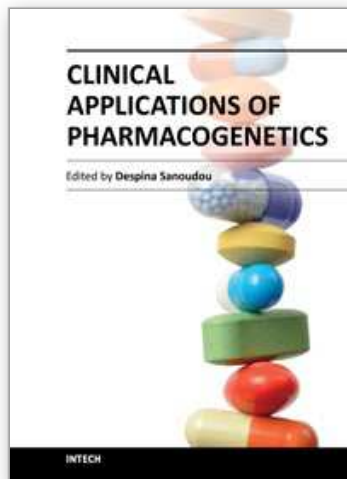
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The rapidly evolving field of Pharmacogenetics aims at identifying the genetic factors implicated in the inter-individual variation of drug response. These factors could enable patient sub-classification based on their treatment needs thus expediting drug development and promoting personalized, safer and more effective treatments. This book presents Pharmacogenetic examples from a broad spectrum of different drugs, for different diseases, which are representative of different stages of evaluation or application. It has been designed so as to serve both the unfamiliar reader through explanations of basic Pharmacogenetic concepts, the clinician with presentation of the latest developments and international guidelines, and the research scientist with examples of Pharmacogenetic applications, discussions on the limitations and an outlook on the new scientific trends in this field.

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