Pharmacogenetics in Cardiovascular Antithrombotic Therapy

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Thrombosis is the most important underlying mechanism of coronary artery disease and embolic stroke. Hence, antithrombotic therapy is widely used in these scenarios. However, not all patients achieve the same degree of benefit from antithrombotic agents, and a considerable number of treated patients will continue to experience a new thrombotic event. Such lack of clinical benefit may be related to a wide variability of responses to antithrombotic treatment among individuals (i.e., interindividual heterogeneity). Several factors have been identified in this interindividual heterogeneity in response to antithrombotic treatment. Pharmacogenetics has emerged as a field that identifies specific gene variants able to explain the variability in patient response to a given drug. Polymorphisms affecting the disposition, metabolism, transporters, or targets of a drug can all be implicated in the modification of an individual’s antithrombotic drug response and therefore the safety and efficacy of the aforementioned drug. The present paper reviews the modulating role of different polymorphisms on individuals’ responses to antithrombotic drugs commonly used in clinical practice. (J Am Coll Cardiol 2009;54:1041–57) © 2009 by the American College of Cardiology Foundation

There is increasing interest in the role of genetic polymorphisms in the pathophysiology of cardiovascular disease (1). Cardiovascular disease is complex and multifactorial; therefore, multiple genes, including many that are as-yet unidentified, are likely to be involved in thrombotic risk (2). The well-demonstrated relevance of common polymorphisms in deep venous thrombosis encouraged the search for polymorphisms involved in arterial thrombosis (3). However, the influence of only 1 polymorphism of a candidate gene is likely to be weak in itself, and certainly much weaker than that of clinical risk factors such as age or classic cardiovascular risk factors (4). The authors of several large-scale studies (4–6) have demonstrated only a minor role of many different polymorphisms in development and prognosis of myocardial infarction (MI). It is possible that complex polymorphism profiles could play a stronger role in thromboembolic disorders. Although some preliminary studies are supportive of the latter hypothesis, this effect has yet to be validated (7,8). In contrast, a single polymorphism could be relevant in other aspects of the cardiovascular disease, such as pharmacogenetics.

Pharmacogenetics has emerged as a field that tries to identify specific gene variants that are able to explain the variability in patient response to a given drug. This variability may explain the efficacy of a specific drug in a given patient as well as its adverse side effects (9). Polymorphisms affecting genes that encode disposition, metabolism, transporters, or targets of the drug can all potentially modify an individual’s response to one therapy and thus explain its efficacy and safety profiles (10). Because such interindividual heterogeneity in antithrombotic drug response is less complex than the risk of developing cardiovascular diseases, the role of a single functional polymorphism affecting any step modulating the pharmacokinetics or pharmacodynamics of a drug could potentially be more relevant.

Thrombosis is the most important underlying mechanism of coronary artery disease and embolic stroke. Hence, numerous agents with antithrombotic properties, including platelet inhibitors, antithrombins, oral anticoagulants, and fibrinolytics, are commonly used in the treatment of cardiovascular disease (11–13). Clinical outcomes associated with antithrombotic drug usage are not homogeneous, and an important proportion of treated patients will continue to experience a new thrombotic event. Several factors (age,
Pharmacogenetics: A Brief Overview

Pharmacogenetics is the study of how genetic differences influence the variability in patients’ responses to drugs (14). Most genetic changes involved in pharmacogenetics are common polymorphisms. Certainly, genetic polymorphism could also explain the individual risk of developing an adverse drug reaction or drug inefficacy (9,15).

Candidate genes encode proteins involved in different pathways of a given treatment (16). Therefore, polymorphisms can influence drug metabolism by modifying the function of drug-metabolizing enzymes (17). In this case, candidate polymorphisms shall determine the extent of the metabolism and, as a consequence, the same administered dose may reach therapeutic levels in some individuals but not in others. In the latter case, this may either be responsible for supratherapeutic levels of a given drug (thus exceeding safety margins and increasing the risk of adverse effects or toxicity) or infratherapeutic levels (thus patients continue to be exposed to the risks related to the disease process for which a given drug was prescribed). However, polymorphisms also could modify the pharmacokinetics of a given drug by affecting its binding capacity to target proteins as carriers or receptors (18).

Absorption, distribution, excretion, and targetting to the site of action also can be influenced, thus modulating the ultimate pharmacological response to the drug (19). Finally, polymorphisms that affect the level or function of the target of the treatment might also influence the effectiveness of such therapy. The study of pharmacogenetics encompasses the search for answers to the hereditary basis for interindividual differences in drug response with the ultimate goal of personalized therapy selection to reduce the incidence of adverse drugs reactions and improve treatment efficacy (10,20).

Antiplatelet Agents

The pivotal role of the platelets in the pathogenesis of atherothrombosis emphasizes the importance of early and sustained antiplatelet therapy. Unfortunately, there are limitations to currently approved antiplatelet agents, and a considerable number of treated patients will experience a new thrombotic event despite being on recommended treatment regimens, giving rise to the concept of antiplatelet drug resistance (21). The definition of antiplatelet drug resistance is controversial; thus, the reported prevalence varies widely, depending on laboratory methods used and/or the population studied (22). Several clinical (age, other underlying comorbidities such as diabetes, lifestyle variables such as smoking, and importantly compliance) and cellular (increased platelet turnover, up-regulation of platelet-signaling pathways, drug–drug interactions) factors have been involved in this interindividual response heterogeneity. Genetic factors also have been implicated as having an important role in patient response to antiplatelet drugs (23,24). Importantly, the majority of candidate genes in antiplatelet drug resistance are also implicated in the pre-existent variability in platelet function (25). Although it has been proposed that antiplatelet resistance confers a worse prognosis, perhaps it may indicate pre-existing greater risk (26).

The most relevant proteins involved in platelet function and platelet hyper-reactivity are those expressed on the platelet surface. These proteins play a key role in the steps of platelet adhesion, activation, and aggregation. The glycoprotein (GP) IIb/IIIa receptor is among the most important platelet complexes, as demonstrated by the severe bleeding associated with deficiency of these proteins (27). The platelet GP IIb/IIIa receptor plays a pivotal role in platelet activation and aggregation by binding fibrinogen and von Willebrand factor. Many antiplatelet therapies have this complex directly or indirectly as their main target. The GP IIb/IIIa complex is highly polymorphic. The most studied polymorphism affecting this complex is the $P^H$ polymorphism of the GP IIIa subunit, which is responsible for the Pro333Leu amino acid change. It has been suggested that this polymorphism modulates platelet function and, in particu-
lar, the $P^g_{32}$ allele is associated with increased platelet reactivity (28).

A second complex in the platelet surface that plays a key role in platelet adhesion is the high-affinity receptor for collagen, the GP Ia/IIa complex. Some polymorphisms have been identified that affect the structure and density of this complex on the platelet surface. The most relevant is $C807T$ (Phe 224), which, albeit being a silent polymorphism affecting the Ia subunit, is associated with variations in expression of the whole receptor on the platelet surface (29). Thus, the $807T$ allele, which is associated with up to 10 times more expression of this receptor, might affect platelet function and could modify the effect of antiplatelet drugs. Finally, other antiplatelet therapies target platelet receptors such as the adenosine diphosphate (ADP) receptor or the generation of compounds relevant for secondary activation pathways. Table 1 summarizes pharmacogenetic studies on antiplatelet agents.

### Table 1: Pharmacogenetic Studies on Antiplatelet Agents

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Ref. #s</th>
<th>Patients Studied</th>
<th>Functional Effects</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIIa $P^a$ (Pro33Leu)</td>
<td>28,52–56,58–63</td>
<td>&gt;5,000</td>
<td>$P^g_{32}$ allele would require a greater dose of aspirin to reach the same antiaggregant effect as wild-type homozygotes</td>
<td>Increased risk of thrombosis and worse clinical outcomes after angioplasty and stent implantation</td>
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<tr>
<td>GP Ia $C807T$</td>
<td>29,45,53,64–67</td>
<td>1,170</td>
<td>Associated with collagen receptor density on the platelet membrane surface and greater platelet reactivity</td>
<td>Conflicting data</td>
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<tr>
<td>COX-1 $C50T$</td>
<td>45,69,71,72</td>
<td>563</td>
<td>Associated with higher levels of TxB2</td>
<td>No clinical data</td>
</tr>
<tr>
<td>COX-2 $G-765C$</td>
<td>45</td>
<td>24</td>
<td>Associated with a higher reduction of TxB2 levels after aspirin treatment</td>
<td>No clinical data</td>
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<tr>
<td>ADP subtype receptor $P2Y_{12}$</td>
<td>64,72,74,75</td>
<td>980</td>
<td>Associated with reduced platelet aggregation after aspirin intake</td>
<td>No clinical data</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytochrome P450 $CYP3A4$ (IVS10 +12G→A)</td>
<td>106,107</td>
<td>1,501</td>
<td>Conflicting data</td>
<td>No clinical data</td>
</tr>
<tr>
<td>Cytochrome P450 $CYP2C19$ (681G→A)</td>
<td>91,93–98,100–104</td>
<td>8,444</td>
<td>Less reduction of platelet aggregation with clopidogrel and lower plasmatic levels of clopidogrel’s active metabolite</td>
<td>Poor clinical outcome after myocardial infarction and coronary stent implantation</td>
</tr>
<tr>
<td>MDR1 $C3435T$ and $C1236T$</td>
<td>102,108,109</td>
<td>2,330</td>
<td>Diminished clopidogrel absorption and active metabolite formation</td>
<td>Poor clinical outcome after myocardial infarction</td>
</tr>
<tr>
<td>GP IIIa $P^a$ (Pro33Leu)</td>
<td>54,110,111</td>
<td>124</td>
<td>Reduced platelet aggregation with clopidogrel in the acute phase of treatment</td>
<td>No clinical data</td>
</tr>
<tr>
<td>GP Ia $C807T$</td>
<td>65–67,112,113</td>
<td>1,175</td>
<td>$T$ allele shows increased platelet reactivity, probably related to enhanced reactivity to fibrillar collagens</td>
<td>Increased thrombotic risk in $T$-allele carriers</td>
</tr>
<tr>
<td>Protease-activated receptor-1 $–14 A&gt;T$</td>
<td>115</td>
<td>54</td>
<td>Greater platelet reactivity</td>
<td>No clinical data</td>
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<tr>
<td>ADP subtype receptor $P2Y_{12}$</td>
<td>65,87,102,107,116–121</td>
<td>7,143</td>
<td>No consistent functional changes</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP IIIa $P^a$ (Pro33Leu)</td>
<td>60,61</td>
<td>1,318</td>
<td>Conflicting data</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors (Parenteral) GP IIIa $P^a$ (Pro33Leu)</td>
<td>28,61,124–129</td>
<td>1,000</td>
<td>Conflicting data</td>
<td>Conflicting data</td>
</tr>
<tr>
<td>(Oral) GP IIIa $P^a$ (Pro33Leu)</td>
<td>132</td>
<td>1,014</td>
<td>Adverse interaction</td>
<td>Poor outcomes</td>
</tr>
</tbody>
</table>

ADP = adenosine diphosphate; COX = cyclooxygenase; GP = glycoprotein; MDR = multidrug resistance-associated protein; TxB2 = thromboxane $B_2$. 
tplatelet effects of aspirin are related to its ability to irreversibly acetylate the cyclooxygenase (COX)-1 enzyme, leading to the suppression of thromboxane A₂ and related metabolites (34). However, a high percentage of patients with symptomatic atherosclerosis can still experience a serious vascular event despite taking aspirin, which gives rise to the concept of aspirin resistance (35,36).

Unfortunately, the definition of aspirin resistance remains controversial (37), and the reported range of aspirin resistance varies broadly, from 5% to 40%, depending on the assay used for identification and the population studied (38,39). However, strictly speaking the term "resistance" refers to the inability of an antiplatelet agent to block its target. Thus, aspirin resistance should be defined as the failure of aspirin to block arachidonic acid-induced platelet aggregation, inhibiting platelet thromboxane A₂ production mediated by COX-1 (40).

Several laboratory assays are available to test for aspirin effects: light transmittance aggregometry, Platelet Function Analyzer (PFA)-100 (Dade Behring, Deerfield, Illinois), VerifyNow-ASA assay (Accumetrics, San Diego, California), thromboelastography, or the determinations of serum thromboxane B₂ levels or its urinary metabolite 11-dehydro-thromboxane B₂ (22,41). Controversial data have been recently published regarding the real prevalence of aspirin resistance when it is assessed by methods that directly indicate the degree of platelet COX-1 inhibition (42). In fact, studies (43–45) in which the authors used COX-1–specific assays have shown that the prevalence of aspirin resistance is extremely low (<5%).

Importantly, poor compliance of the patient to treatment has been identified as a primary cause of resistance (42). Nevertheless, the authors of several studies (36,46–48) have shown a relationship between markers of residual platelet activation determined by assays that are not highly COX-1–specific and the risk of new ischemic events or cardiovascular death. Aspirin in fact has been suggested to have COX-1–independent effects, which may be subject to more interindividual variability and may explain the adverse outcomes among patients with high platelet reactivity (22,44).

Many mechanisms could be related to aspirin resistance (49). Clinical factors, including poor patient compliance, drug-absorption abnormalities, or drug–drug interactions, play a role (50). Importantly, ibuprofen blocks the inhibition of serum thromboxane B₂ formation and platelet aggregation by aspirin (51). Other conditions and entities associated with enhanced platelet reactivity can modify responsiveness (i.e., acute coronary syndrome, congestive heart failure, dyslipidemia, or exercise) (23). Different cellular factors have been proposed to influence aspirin efficacy, such as inadequate suppression of platelet COX-1 due to increased platelet turnover, overexpression of COX-2 mRNA, erythrocyte–platelet interaction, catecholamine levels, or the generation of 8-iso-PGF₂ (23).

Genetic background also could play a role in interindividual response to antiplatelet drugs, which raises the putative number of candidate polymorphisms that could be involved in the aspirin resistance phenomenon. Several of these have been investigated, as summarized in Table 1. The authors of different studies (28,52–56) support that the PlA⁻¹ polymorphism may account for differences in aspirin-induced effects. Apparently, carriers of the PlA⁻¹ allele would require a greater dose of aspirin to experience the same antiaggregant effect as do subjects with a PlA⁻² homozygous genotype and have an increased risk of cardiovascular thrombosis (49,52,56–58). It is also interesting to point out that some reports found a significant association between the PlA⁻² allele and aspirin resistance in complications after coronary angioplasty (59,60) or after coronary stent implantation (61–63).

The authors of one study (29) investigated the relevance of the GP Ia C807T polymorphism, which is associated with the expression of this collagen receptor on the platelet surface. However, in most studies (45,53,64,65) performed either in patients or healthy control subjects, the authors did not find an association with aspirin resistance. However, it has been observed that the C807T polymorphism and another polymorphism of GP Ia, G873A, could be independently related with greater platelet reactivity in patients under dual antiplatelet therapy (66,67).

Understanding the role of polymorphisms affecting the target of aspirin, the COX-1 enzyme, is also of importance. Interestingly, some polymorphisms of the COX-1 gene could modify the activity of the enzyme, having an influence on aspirin dose requirements (68,69). Hence, our group has found that the COX-1 C50T polymorphism is associated with thromboxane B₂ levels before and after aspirin treatment in healthy subjects (44). Importantly, high levels of this metabolite have shown to be a good marker of thrombotic risk in patients treated with aspirin (70). The potential influence of polymorphisms of the COX-2 enzyme on aspirin response was evaluated. A recent Japanese study (71) did not find any influence of COX-1 or -2 polymorphisms on platelet responsiveness, but the authors did not find any patients with the C50T polymorphism. This polymorphism also was not found in a Chinese population (72).

These findings underscore the importance of defining ethnicity in pharmacogenetic analyses. Moreover, a functional polymorphism of the COX-2 (G–765C) enzyme also might be relevant in aspirin resistance (73). We found a significant association between the COX-2 G–765C polymorphism and the efficiency of reduction of thromboxane B₂ after aspirin treatment (45). Additional studies should be performed to confirm such associations and to evaluate the role of these polymorphisms in thromboembolic disease of patients treated with aspirin.

Other polymorphisms investigated include a C893T polymorphism in the ADP subtype P2Y₁ receptor, but without a clear mechanism involved (74). More recently, the presence of the P2Y₁ 893CC genotype appears to confer an attenuated antiplatelet effect during aspirin treatment in
healthy Chinese volunteers (72). However, these findings have not been confirmed in other studies (64,75).

Ultimately, it is important to note that factors extrinsic to the platelet, such as hemostatic factors, may affect platelet function. Therefore, aspirin also may have different degrees of efficacy according to hemostatic polymorphisms. The Val34Leu polymorphism is a functional genetic change affecting the activation of factor XIII (FXIII), its transglutaminase activity, and the structure of the clot. It has been shown that inhibition of FXIII activation by aspirin is enhanced in the Leu34 carriers, suggesting that these subjects might benefit more than the Leu34-negative subjects from the reduction in risk for MI with low-dose aspirin (76).

In conclusion, several genetic polymorphisms have been proposed to influence aspirin response and contribute to poor prognosis. Of these, the P2Y12 receptor on the platelet surface (77,78). Although ticlopidine has been prescribed in different cardiovascular disease manifestations, it has been mainly assessed in combination with aspirin in patients undergoing percutaneous coronary intervention (PCI) (79). However, the more favorable safety profile of clopidogrel (80) has made it the thienopyridine derivative that irreversibly inhibits the ADP P2Y12 receptor on the platelet surface (77,78). Although ticlopidine has been prescribed in different cardiovascular disease manifestations, it has been mainly assessed in combination with aspirin in patients undergoing percutaneous coronary intervention (PCI) (79). However, the more favorable safety profile of clopidogrel (80) has made it the thienopyridine derivative that irreversibly inhibits the ADP P2Y12 receptor on the platelet surface (77,78).

**Thienopyridine derivatives.** Ticlopidine and clopidogrel are thienopyridine derivatives that irreversibly inhibit the ADP P2Y12 receptor on the platelet surface (77,78). Although ticlopidine has been prescribed in different cardiovascular disease manifestations, it has been mainly assessed in combination with aspirin in patients undergoing percutaneous coronary intervention (PCI) (79). However, the more favorable safety profile of clopidogrel (80) has made it the thienopyridine derivative that irreversibly inhibits the ADP P2Y12 receptor on the platelet surface (77,78).

More recently, 4 large-scale studies (101–104) have confirmed these findings in a healthy volunteer population but failed to find any influence of this polymorphism on clopidogrel response when studied in patients with coronary artery disease (94). However, the latter was performed in a relatively small cohort of patients, and numerous cohort studies (95–100) confirmed the modulating effect of the CYP2C19*2 loss-of-function allele on clopidogrel response as assessed by various pharmacodynamic measurements.

The greater prevalence of the CYP2C19*2 loss-of-function allele among Asian subjects may explain why the prevalence of suboptimal clopidogrel responders is greater in Japanese patients than in Caucasian ones (96). Geisler et al. (97) showed that prediction of responsiveness after clopidogrel loading dose may substantially be improved by adding CYP2C19*2 genotype to nongenetic risk factors. In addition to pharmacodynamic studies, pharmacokinetic analyses (98) have confirmed the role of the CYP2C19 gene on clopidogrel response and have shown it to be associated with variations in the plasmatic levels of clopidogrel’s active metabolite. The latter study failed to show an impact of this polymorphism on the plasmatic levels of prasugrel, a third-generation thienopyridine with more efficient pharmacokinetic, and consequently pharmacodynamic, profiles (98,99).

In a recent study, Trenk et al. (100) showed that patients carrying at least one CYP2C19*2 allele are more prone to high-on clopidogrel platelet reactivity, which was associated with poor clinical outcome after coronary stent placement.

More recently, 4 large-scale studies (101–104) have confirmed the prognostic implications of the CYP2C19 polymorphism in clopidogrel-treated patients. In a pre-defined subgroup analysis of the TRITON–TIMI 38 (Trial
to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction (38) trial (101,105), which showed significantly improved clinical outcomes in patients (n = 13,608) with moderate- to high-risk ACS undergoing PCI who were administered prasugrel compared with clopidogrel, a subgroup underwent genetic testing (n = 1,477) (101). Carriers of the CYP2C19 reduced function allele, which is present in 30% of the study population, had a 53% relative increased risk of the composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke (12.1% vs. 8.0%; hazard ratio [HR]: 1.53, 95% confidence interval: 1.07 to 2.19; p = 0.014). These patients also had a 3-fold risk of stent thrombosis.

These outcomes are attributed to the markedly diminished pharmacokinetic and pharmacodynamic responses to clopidogrel associated with CYP2C19 polymorphisms (101). Pharmacokinetic and pharmacodynamic responses to prasugrel as well as clinical outcomes were not affected by CYP2C19 polymorphisms associated with reduced clopidogrel metabolism (101). Authors examining a French registry of MI (102) showed an increased event rate (adjusted HR: 1.98) that was more pronounced in the subgroup that underwent PCI (adjusted HR: 3.58). In another study (103), the influence of CYP2C19 polymorphisms was assessed in a selected population of young patients who survived a first MI; results showed an independent association with cardiovascular events. Finally, another recent study (104) demonstrated an association between CYP2C19 and stent thrombosis.

CYP3A4 plays a pivotal role in CYP system; therefore, the role of genetic variants of this enzyme on clopidogrel response was the first to evaluated (106). In particular, 5 CYP3A4 polymorphisms were studied in patients with coronary artery disease before and after a 300-mg loading dose as well as in the chronic phase of clopidogrel therapy. Of the 5 polymorphisms, only 1 (IVS10 +12G>A) was associated with variable degrees of clopidogrel response, as assessed by measures of platelet activation but not aggregation (106). However, a lack of modulation effects of the IVS10 +12G>A polymorphism on platelet aggregation was observed by others (107). The possible influence of CYP3A5 on prognosis has been assessed, without showing any significant influence (102).

The absorption of clopidogrel and thereby active metabolite formation have shown to be diminished by P-GP–mediated efflux and to be influenced by the multidrug resistance-associated protein (MDR)-1 C3435T genotype (108). Interestingly, this polymorphism has been associated with a greater rate of cardiovascular events at 1 year (102). Pharmacodynamic differences have shown to be associated with the MDR1 C1236T (rs1128503) genotype after a high (600-mg) but not standard (300-mg) clopidogrel loading dose regimen, suggesting that the capacity to absorb greater amounts of clopidogrel is reduced in some patients.
concentrations of clopidogrel varies among individuals and may be genetically determined (109).

However, changes in genes encoding platelet glycoprotein also have been explored. Indeed, the first study to evaluate the presence of a pharmacogenetic modulation of clopidogrel response was performed by Angiolillo et al. (110), in which the PlA1 polymorphism was considered as the genetic target. Platelet activation before and after a 300-mg loading dose of clopidogrel was assessed in aspirin-treated patients undergoing PCI. The study confirmed the modulating effects of this polymorphism on aspirin-induced effects and showed that platelet activation was significantly attenuated (35% less inhibition) in PlA1 carriers compared with the PlA2/A1 genotype (110). At 24 h, GP IIb/IIIa activation persisted significantly greater in PlA1/A2 patients (110). However, the modulating effects of the PlA1 polymorphism on clopidogrel response are limited to the acute phase of treatment, as no differences were observed in patients on maintenance therapy (111). The latter finding was also confirmed by Cooke et al. (54).

The effect of polymorphisms of other platelet membrane receptors on clopidogrel response has also been evaluated. The role of the GP Ia C807T polymorphism on modulating platelet function in patients undergoing coronary stenting receiving a 300-mg clopidogrel loading dose was also analyzed by our group (112). The T allele of the GP Ia gene was shown to modulate platelet aggregation and clopidogrel antiplatelet effects. These findings were confirmed in a larger cohort of stable patients in the chronic maintenance phase of clopidogrel therapy (66) as well as those presenting with an ACS (67). Overall, these findings suggest an enhanced reactivity to fibrillar collagens, typically exposed during coronary stenting, in T-allele carriers and might contribute to the increased thrombotic risk observed in these patients (113,114). However, the modulating effects of the GP Ia C807T polymorphism on clopidogrel response were not confirmed by Cuisset et al. (65). Another potential target modulating the effects of clopidogrel is the protease-activated receptor-1, the receptor for thrombin on the platelet surface. Smith et al. (115) showed the intervening sequence-14 A>T dimorphism of protease-activated receptor-1 to be associated with greater platelet reactivity before and after clopidogrel administration.

Because the ADP P2Y12 receptor is the target for the active metabolite of clopidogrel, the authors of several studies have investigated the potential role of gene sequence variations of this receptor on clopidogrel responsivity. Fontana et al. (116) identified 5 frequent polymorphisms, of which 4 were in total linkage disequilibrium leading to 2 haplotypes (H1 and H2). The H2 haplotype was associated with enhanced ADP-induced platelet aggregation in a cohort of nonmedicated, healthy volunteers. In case-control studies in which platelet aggregation was not assessed, this haplotype was associated with the presence of coronary artery disease (117) and peripheral arterial disease (118). Numerous other investigations (87,102,107,119–121) have therefore evaluated the functional implications of gene sequence variations of the P2Y12 receptor in patients with coronary artery disease treated with clopidogrel in both the acute (i.e., after a loading dose) and chronic (i.e., during maintenance therapy) phases of treatment. However, none of these studies showed any functional impact of genetic variations of the P2Y12 receptor on clopidogrel response or impact on clinical outcomes.

In conclusion, there are consistent data that relate clopidogrel variability response to hepatic CYP polymorphisms, mainly, the CYP2C19 loss-of-function polymorphism. Importantly, in addition to modulation of pharmacodynamic and pharmacokinetic profiles, this polymorphism has also been associated with greater ischemic event rates, including stent thrombosis. These findings have led many to suggest genetic testing for this polymorphism as a screening measure for clopidogrel response. Point-of-care assays are currently under development to allow rapid genetic testing for this polymorphism.

The GP IIb/IIIa receptor inhibitors. The relevance of the GP IIb/IIIa complex in platelet activation and aggregation supports the development of intravenous GP IIb/IIIa receptor inhibitors as potent antiplatelet drugs (122). These drugs have consistently demonstrated their utility in high-risk patients with ACS, especially those who undergo early PCI (123). The role of polymorphisms, specifically affecting the target of these agents, has been investigated in this setting (Table 1). Most studies have evaluated the role of the PlA1 polymorphism on the antiplatelet effects of GP IIb/IIIa agents and have obtained controversial results. Some reports (28,124) suggest that GP IIb/IIIa antagonists have lower platelet-inhibiting effects in carriers of the PlA1 allele. These findings are in line with the worse clinical outcomes and the greatest rates of in-stent restenosis observed in PlA1 carrier patients treated with these agents (62). In contrast, other studies (125–128) found no significant effect of PlA1 genotype in platelet inhibition or in myocardial reperfusion (129).

Oral GP IIb/IIIa inhibitors have not demonstrated any beneficial effect in ACS (130,131). A significant interaction with the PlA1 polymorphism has been suggested to be one of the causes leading to failure of these drugs (132,133). An adverse interaction was observed between PlA1 allele and orbofiban therapy (133). In particular, this finding suggests that slight differences in receptor structure, a change of a proline in place of a leucine at position 33 of GP IIIa, may influence the response to specific GP IIb/IIIa inhibitors, not only attenuating any beneficial effect but also contributing to the increase of deleterious responses.

Anticoagulants

Unfractionated heparin and low molecular weight heparin (LMWH). Most pharmacogenetic analyses on heparin (134) have been related to heparin-induced thrombocytopenia (HIT) and its thromboembolic complications (Table 2).
Recently, it has been proposed that the $P^T$ polymorphism of the $GP IIIa$ gene may modulate the pro-thrombotic effects of HIT (135). However, data on this association are not consistent (136). There are also controversial data regarding the association between platelet $FcgammaRIIA$ $H131R$ and platelet factor 4 polymorphisms with HIT (137–140), whereas the association of hemostatic polymorphisms with thromboembolic complications is certainly weak (136).

To the best of our knowledge, there are no published studies demonstrating a pharmacogenetic effect in LMWHs. However, it has been suggested that interleukin-1 receptor antagonist polymorphisms may be a useful marker to identify patients that benefit from LMWH in non–ST-segment elevation ACS (141). In particular, carriers of this polymorphism showed a better control of von Willebrand factor increase in a small cohort of ACS patients (141).

### Oral anticoagulants

Unfractional heparin

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Ref. #s</th>
<th>Patients Studied</th>
<th>Functional Effects</th>
<th>Clinical Effects</th>
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<tbody>
<tr>
<td>$GP IIIa$</td>
<td>$P^T$ (Pro33Leu)</td>
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<td>205</td>
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<tr>
<td>$Fc gamma$</td>
<td>$Rila$-R$H131$</td>
<td>137–139</td>
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<tr>
<td>Platelet factor 4</td>
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Oral anticoagulants

Cytochrome P450

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<tr>
<td>$CYP2C9$</td>
<td>150–157,159,165,178</td>
<td>&gt;8,000</td>
<td>Reduced enzymatic activity</td>
<td>Increased response to VKA and association with bleeding complications</td>
</tr>
</tbody>
</table>

$VKOR$

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Ref. #s</th>
<th>Patients Studied</th>
<th>Functional Effects</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$VKORC1$ haplotypes</td>
<td>158–165,178</td>
<td>&gt;6,400</td>
<td>Changes at the transcriptional level modifies warfarin dose response</td>
<td>Initial variability in the INR response</td>
</tr>
</tbody>
</table>

Fibrinolytic drugs

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Ref. #s</th>
<th>Patients Studied</th>
<th>Functional Effects</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$GP IIIa$</td>
<td>$P^T$ (Pro33Leu)</td>
<td>127,129</td>
<td>469</td>
<td>No effect</td>
</tr>
<tr>
<td>MMP-9</td>
<td>C-1562T</td>
<td>191</td>
<td>61</td>
<td>No effect</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor-1</td>
<td>4G/5G</td>
<td>192,193</td>
<td>432</td>
<td>Not assessed</td>
</tr>
<tr>
<td>TAFI</td>
<td>Thr325Ile</td>
<td>193</td>
<td>139</td>
<td>Not assessed</td>
</tr>
</tbody>
</table>

Factor XII

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Ref. #s</th>
<th>Patients Studied</th>
<th>Functional Effects</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Val34Leu$</td>
<td>196,197,202–204</td>
<td>565</td>
<td>Related to differences in clot resistance</td>
<td>Fibrinolysis less efficient</td>
</tr>
</tbody>
</table>

Angiotensin-converting enzyme

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Ref. #s</th>
<th>Patients Studied</th>
<th>Functional Effects</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/D</td>
<td>205</td>
<td>96</td>
<td>Not assessed</td>
<td>DD homozygosis associated with recanalization after fibrinolysis</td>
</tr>
</tbody>
</table>

Methylenetetrahydrofolate reductase

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Ref. #s</th>
<th>Patients Studied</th>
<th>Functional Effects</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>C677T</td>
<td>206</td>
<td>101</td>
<td>Not assessed</td>
<td>677T homozygosis independently associated with persistently occluded infarct-related artery</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; MMP = matrix metalloproteinase; TAFI = thrombin-activable fibrinolysis inhibitor; VKA = vitamin K antagonist; VKOR = vitamin K epoxide reductase; other abbreviations as in Table 1.
vitamin K epoxide reductase (VKOR). The identification of the VKOR gene remained elusive until 2004, when 2 laboratories using different approaches (147,148) cloned it. Thus, they found that mutations in VKOR occurred in 2 families with defective vitamin K-dependent clotting factors, in 4 families with hereditary warfarin resistance, and in several rat strains with resistance to warfarin-like poisons. These studies discovered VKOR to be the target of VKAs.

Metabolism of VKAs: role of CYP2C9 in interpatient variability. The pharmacological effect of either warfarin or acenocoumarol depends on hepatic metabolism, catalyzed largely by CYP2C9, a member of the CYP system, which converts therapeutic concentrations of these drugs into inactive metabolites excreted in the urine (149). Then, it was soon expected that variations in the CYP2C9 gene might contribute to interindividual variability in VKA response (Table 2). Semisystematic polymorphism discovery was conducted in a variety of ethnic populations, and 30 CYP2C9 alleles were described. CYP2C9*1 represents the reference sequence and wild-type allele. The CYP2C9*2 and CYP2C9*3 alleles encode the Arg144Cys and Ile359Leu variants and are present at allele frequencies of 12% and 8%, respectively, in Caucasian patients (150). Other polymorphisms also identified in Japanese (CYP2C9*4; Arg144/Thr359) or CYP2C9*5 (Asp360Glu) in African-American patients are less common. The clinical impact of these variants has been extensively studied.

It is well established that the in vivo elimination of VKAs is largely influenced by the CYP2C9 genotype. Of note, the decreased clearance caused by CYP2C9*2 and *3 alleles also has a significant clinical impact (151), so that these 2 polymorphisms have been associated with increased responsiveness to warfarin. Aithal et al. (152) compared control patients requiring a typical dose of warfarin with those who take /H11349 10.5 mg weekly. This second group showed a high risk of reaching a supratherapeutic international normalized ratio (INR) during the induction phase and a 4-fold risk of bleeding. Also, the presence of *2 and *3 variants in these patients was 6-fold more frequent. Similarly, the relationship of CYP2C9 genotype with bleeding complications, with the time to achieve the maintenance dose, and with overanticoagulation also has been established (153–155). Therefore, it has been shown that patients with at least 1 variant allele had not only an increased risk of a supratherapeutic INR during the warfarin initial treatment period but not during long-term therapy (156). Similar results have been obtained concerning other coumarin derivatives (157).
Target of VKAs: vitamin K epoxide reductase subunit 1 (VKORC1) genotype and interpatient variability. Understanding why patients with the same CYP2C9 genotype have such a great standard deviation to the mean maintenance dose was critical. This was partly elucidated with the posterior discovery of the VKOR gene. It is now well established that common polymorphisms in regulatory regions of the VKOR gene correlate strongly with VKA response (Table 2). Rieder et al. (158) resequenced the VKOR gene in almost 200 European-American warfarin patients and identified 5 haplotypes in the VKOR subunit 1 (VKORC1) associated with warfarin dose requirements (Table 2). Among possible variations, a single allelic site, C1173T in intron 1, assigns European-American subjects to a high- or low-dose group 95% of the time. The molecular mechanism of this warfarin dose-response appears to be regulated at the transcriptional level.

Rieder et al. (158) found that VKORC1 mRNA levels varied according to the haplotype. This highly useful single polymorphism has been repeatedly shown to be associated with optimal coumarin anticoagulant dose in both European and Asian patients (159–162). There are 2 types of patients exhibiting a clinical phenotype that is compatible with partial-to-complete warfarin (or other coumarins) resistance; the most frequent corresponds to patients carrying the combination of VKORC1 haplotypes for high dose and CYP2C9*11/*1 genotype, whose incidence has been calculated as 20% for Caucasian patients (163). Other less-frequent polymorphisms in VKOR, such as R98W, also can reduce VKORC1 activity (164). The second type of warfarin resistance is caused by single amino acid mutations like R58G, V29L, V45A, and L128R (164). These cases range from a very high dose of therapeutic warfarin (>40 mg/day) to complete failure to respond to therapy (147).

Toward personalized oral anticoagulation. In a study including 297 patients with stable anticoagulation genotyped for both CYP2C9 and VKORC1 polymorphisms, a multivariate regression model including age and height produced a model for estimating warfarin dose of R² 55% (165). The performance of commercial platforms for rapid genotyping of polymorphisms affecting warfarin dose and modeling stable dose requirements based on clinical, physiologic, environmental, and genetic factors represents a promising strategic approach to predict individualized stable warfarin dose requirements (166,167). The initiation of VKA is associated with one of the highest adverse event rates for any single drug, and physicians often are reluctant to initiate therapy in elderly patients or patients at risk of bleeding (168). Up to one-half of patients with atrial fibrillation and no contraindication to warfarin therapy who are at high risk of stroke (annual risk >4%) are currently not receiving anticoagulant therapy because of the risk perceived to be associated with such therapy by both patients and health care providers (169).

The first month of anticoagulant therapy is especially problematic because the therapeutic dose is empirically assessed, and further adjustment is made on the basis of a trial-and-error strategy. This adjustment leads to the risk of overanticoagulation with potential bleeding complications or undertreatment with potential thrombotic events. In a study of approximately 300 patients starting warfarin therapy, the authors assessed the relationship between CYP2C9 genotypes and VKORC1 haplotypes to the INR responses that are used to adjust doses. Conversely to previous published data, the authors showed that VKORC1 haplotypes modulate the early response to warfarin and not CYP2C9 genotypes. VKORC1 haplotypes predict the time to reach a first therapeutic INR and the time to an INR >4. CYP2C9 genotypes only predict the time to a supratherapeutic INR (>4) (170).

As previously described, in extensively studied Caucasian populations, the CYP2C9 genotype predicts ~10% of the interpatient variability in warfarin dose. Similarly, in Caucasian and Asian populations, the VKORC1 genotype predicts 25% of such variability. The importance of these strong genetic effects was recognized by recent relabeling of warfarin by the Food and Drug Administration to increase awareness in the clinical community (171). However, it is important to note that patient demographics, clinical factors, and established genetic variants combined only explain 45% to 55% of the total dose variation (Table 3) (171). Recently published studies in which the authors use a genome-wide scan strategy for common genetic variants potentially modulating warfarin response concluded that none of the other candidate genes (besides VKORC1 and CYP2C9) substantially influence such response (172,173).

The genome-wide analysis of 181 Caucasian individuals administered warfarin showed that the most significant independent effect of variation in warfarin maintenance dose was conferred by polymorphisms in the VKORC1 gene, with lesser associations with the CYP2C9 variants. The study did not find any significant associations with

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**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect on Warfarin Dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>−13</td>
</tr>
<tr>
<td>BSA (per SD)</td>
<td>+15</td>
</tr>
<tr>
<td>Caucasian vs. African American</td>
<td>−15</td>
</tr>
<tr>
<td>Female vs. male</td>
<td>−12</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Target INR (per 0.5 increase)</td>
<td>+17</td>
</tr>
<tr>
<td>Creatinine clearance (per SD)</td>
<td>+10</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>−24</td>
</tr>
<tr>
<td>Drugs that increase INR (per drug)</td>
<td>−5</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>−12</td>
</tr>
<tr>
<td>Genetic</td>
<td></td>
</tr>
<tr>
<td>CYP2C9*2/*3 genotype</td>
<td>−10</td>
</tr>
<tr>
<td>VKORC1 C1173T</td>
<td>−25</td>
</tr>
</tbody>
</table>

Adapted from Gage et al. (171).

BSA = body surface area; other abbreviations as in Table 2.
other polymorphisms; therefore, it is concluded that theVKORC1 and CYP2C9 genes are the primary genetic
determinants of stabilized warfarin dose and that common
SNPs with large effects on warfarin dose are unlikely to be
discovered outside of these genes (172). However, these
data do not discount that other genetic mutations could be
implied in intermediate phenotypes, which may have a
minor role in the variability in interindividual response
profiles. Indeed, minor contributions from other genes, such
as gamma-glutamyl carboxylase, microsomal epoxide hydro-
lase, apolipoprotein E, MDR1 (174), cytochrome 4F2
(175), or calumenin (176), have been described.

The controversy about the relationship between these
new genetic factors and the pharmacogenetics of VKA
deserves further evaluation. New models will be forthcom-
ing and will continue to evolve with data from large genome
association studies and with the inclusion of acquired or
environmental factors not considered to date. Importantly,
it must be kept in mind that important pharmacogenetic
differences also exist among VKAs (177). A recent study
shows how clinical and genetic data from 4,043 patients
were used to create a dose algorithm where genetic data
were added to clinical variables (178). This pharmaco-
genetic approach produces recommendations that are signifi-
cantly closer to the required therapeutic dose than if only
clinical data or a fixed-dose were used, although the greatest
benefits were observed in the approximately 50% of the
population that required a greater or lesser warfarin dose
than the mean. In any case, randomized, controlled trials are
necessary to determine whether pharmacogenetic testing is
worthwhile or which patients would better benefit by this
strategy (178). In conclusion, pharmacogenetic studies can
explain the heterogeneity to VKA response and may be
potentially useful, particularly in patients at the 2 extremes
of dose requirements.

**Fibrinolytic Drugs**

Fibrinolytic therapy is used to achieve pharmacological
reperfusion and restoration of flow of an acute coronary
occlusion in patients with an acute ST-segment elevation
MI (179), acute ischemic stroke (180), and pulmonary
embolism (181). Indeed, fibrinolytic therapy leads to better
survival, recovery of left ventricular function, and remodel-
ing after acute MI (182–184). Thrombolytic therapy within
3 h of the onset of symptoms of ischemic stroke significantly
reduced the number of patients experiencing the combined
end point of death or dependency (185), and there is good
evidence that thrombolytic therapy accelerates resolution of
pulmonary embolism and results in more rapid hemody-
namic improvement. The evidence that thrombolytic ther-
apy improves clinical outcome is less evident (181).

Unfortunately, up to 40% of treated patients do not
achieve optimal tissue perfusion (186), and the potential
benefits are limited by early (thrombotic) reocclusion of the
infarct-related artery (187). However, a few factors have
been identified to be involved in this interindividual heter-
ogeneity. They include age, delay between symptom onset
and fibrinolytic therapy, smoking habits, and infarct size or
site (188,189). During the last few years, interest has
increased regarding initiatives that could improve the effi-
cacy of fibrinolytic therapy, including pre-hospital fibrino-
lysis programs, the administration of new drugs (e.g.,
tenecteplase), or new pharmacological reperfusion strategies
(e.g., half-dose fibrinolytic plus GP IIb/IIIa receptor block-
ade or adjunctive clopidogrel therapy) (190).

Only a few studies have analyzed the influence of genetic
factors on the efficacy of fibrinolytic therapy (Table 2). One
study (191) analyzed the role of the C-1562T polymorphism
affecting the promoter region of the matrix metalloproteinase-9
gene in the hemorrhagic transformation of stroke after
fibrinolytic therapy in 61 patients; the authors found no
significant effect. Similarly, negative results were found
when authors analyzed the relationship between PT gene
polymorphism and myocardial salvage after fibrinolysis
(127,129). Again, negative findings were found when au-
thors analyzed plasminogen activating inhibitor-1 4G/5G
polymorphism (192,193).

The FXIII Val34Leu polymorphism is among the most
relevant functional polymorphisms identified in the hemo-
static system; thus, it plays a key role in the stability and
structure of the fibrin clot. Therefore, polymorphisms of
this gene have been evaluated in understanding variations in
individual response to fibrinolytic therapy. Activated FXIII
catalyses the formation of covalent gamma-glutamyl-
gamma-lysine bonds between fibrin monomers, increasing
the resistance of fibrin to degradation by plasmin (194,195).
The Val34Leu polymorphism affects the function of FXIII
by increasing the rate of FXIII activation by thrombin,
which results in an increased and faster rate of fibrin
stabilization (196,197). Moreover, interesting reports clearly
demonstrated a different fibrin structure associated with the
FXIII Val34Leu genotype (198). However, the thrombotic
role of this polymorphism is controversial and might be
population specific (198–201). The faster activation rate of
the Leu34 variant and the different structure and resistance
of the fibrin-bound clot observed in subjects carrying this
allele encouraged the study of this polymorphism on fi-
britinolytic therapy (197).

In a small and retrospective cohort of patients after a
premature MI, our group (202) observed that Leu34 allele
carriers could show more “resistance” to fibrinolytic therapy.
Afterward, we prospectively studied a cohort of patients
from 2 different European populations undergoing fibrino-
lytic treatment. Evaluation of the efficacy of fibrinolytic
therapy was assessed noninvasively (203). In a multivariate
analysis, fibrinolysis in patients who carried the Leu34 allele
was significantly less efficient. Re-evaluation at 24 h re-
vealed that the FXIII Val34Leu polymorphism was the only
factor displaying a significant role.

Additionally, we showed that the simultaneous combina-
tion of Leu34 allele and nonsmokers significantly increases
the risk of poorer efficacy of fibrinolysis and had the worst 24-h outcome. Accordingly, our study supports that the combination of genetic and environmental factors may explain the heterogeneity in the efficacy of fibrinolytic therapy. Overall, these findings may have implications in clinical practice, as demonstrated by a study from our group evaluating the role in the efficacy and side-adverse effects of thrombolytic therapy in stroke in which patients with the FXIII V/V genotype and low fibrinogen (<3.6 g/l) displayed the best clinical outcome (204). In contrast, carriers of the L34 variant and high fibrinogen levels showed almost no clinical response. The FXIII V34L polymorphism was also associated with mortality (204).

During the past few years, it has been shown that several polymorphisms can influence the efficacy of fibrinolytic therapy. Therefore, thrombin-activatable fibrinolysis inhibitor, TAFI, Tbr:1251le (193), and the ACE gene I/D polymorphism (205) were associated with recanalization resistance by the end of tissue plasminogen activator infusion in acute ischemic stroke, assessed by transcranial Doppler, whereas no association was found between PAI-1 4 G/5 G polymorphism and recanalization rate (193). Methyleneetrahydrofolate reductase C677T polymorphism was independently associated with the presence of persistently occluded infarct-related artery after thrombolysis (206). Newer studies are warranted to better elucidate the role of genetic modulation on the efficacy of pharmacological recanalization therapy with fibrinolytic agents. In conclusion, promising results suggest that an underlying genetic background could explain the heterogeneity in response to fibrinolytic drugs.

Conclusions

Despite being a relatively young field in medicine, pharmacogenetics has emerged as a relevant discipline that will help find the most appropriate treatment for each patient, increasing the efficacy (improving outcomes) and safety (reducing the side effects) of a given drug. Here, we have reviewed the most important polymorphisms that have been associated with antithrombotic therapies used in cardiovascular diseases. The present review emphasizes the importance of identifying individuals in whom their potential clinical benefits may be limited as the result of an inadequate response based on a specific genetic profile. Titrating antithrombotic drug regimens according to antithrombotic function may overcome this phenomenon. In clinical practice, all patients are different, and the identification of the genetic basis of such heterogeneity will help replace general protocols with specific and individualized treatment regimens. Pharmacogenetics will help the development of such personalized medicine.

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REFERENCES


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