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Genetic determinants of response to cardiovascular drugs

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Abstract

Purpose of review—To survey genetic variation contributing to variable responsiveness and toxicity to important cardiovascular drugs and highlight recent developments in the field of cardiovascular pharmacogenomics and personalized medicine.

Recent findings—Previously recognized pharmacogenomic associations with drug efficacy have been further validated (e.g. with clopidogrel and warfarin) and shown to influence clinically important outcomes. The clinical significance of variants modulating toxicity (e.g. *SLCO1B1* with simvastatin) has also been confirmed. The genetic contribution to variable efficacy and toxicity of other important classes of cardiovascular drugs, such as beta-blockers, is becoming increasingly recognized. Prospective trials testing whether the use of genomic information improves clinical care are underway. Guidance based on the most well-established pharmacogenomic findings has appeared in prescribing labeling and is in the early stages of being implemented into routine clinical care.

Summary—Clinically validated gene variants that modulate responsiveness to cardiovascular drugs continue to be discovered and validated. Early steps are underway to translate these discoveries into clinical care.

Keywords

personalized medicine; pharmacogenomics; variable drug response

Introduction

Pharmacogenomics seeks to determine the contribution of genetic variants to drug efficacy and toxicity. Cardiac pharmacogenomics is a rapidly growing field, offering the potential for improved treatment outcomes and prevention of adverse drug events. Variants common in the population have been shown to modify drug metabolism, drug transport, and drug targets, and could be utilized to predict an individual's treatment response. We discuss recent findings in cardiac pharmacogenetics and their translation into clinical practice for those variants that have been comprehensively studied. Examples of genetic variants influencing response to cardiovascular drugs and the strength of evidence supporting their translation into clinical practice are listed in Table 1.

There are several types of common genetic variation relevant to pharmacogenomics. The most common form, termed a single-nucleotide polymorphism (SNP), is the change of a

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single nucleotide within the genome. SNPs may occur in regions that do not encode proteins (noncoding variants). However, SNPs also occur in protein-coding regions of the genome (coding variants), in which they do not necessarily cause an alteration in protein (synonymous variant), but may also lead to the incorporation of a different amino acid (nonsynonymous variant). Additionally, a SNP may introduce a premature stop codon into the DNA sequence and thereby cause production of a truncated protein product (nonsense variant). Other common types of variation include the addition or removal of nucleotides, termed insertions and deletions, respectively. Similarly, a genomic region may be copied multiple times, referred to as duplication.

In general, identification of genomic variation can proceed by focused studies of genes or genomic regions suspected of being related to the disease or phenotype of interest or through unbiased, genome-wide approaches that seek association between genomic variation and selected traits or conditions. The candidate gene approach builds on known or predicted biologic functions, but findings have frequently been difficult to validate [1]. Genome-wide association studies (GWAS) are not limited by biological models and have the potential to discover associations outside current understanding. The GWAS paradigm frequently results in identification of common variants of relatively small effect size; however, a recurrent finding is that pharmacogenetic effect sizes are often significantly higher than those seen in complex diseases [2].

It is interesting to note that trials demonstrating differential treatment outcomes by genotype have generally included a placebo arm, as is seen in the case of β-blockers [3]. One interpretation is that carriers of low-risk alleles receive less benefit from active therapy and treatment of all patients has the effects of making the treated high-risk genotypes more similar to the low-risk genotype (regardless of treatment) and therefore ‘equalizing’ the outcomes. Future pharmacogenomics studies will need to take this observation into account.

Clopidogrel

The thienopyridine antiplatelet agent, clopidogrel, primarily used for the prevention of adverse cardiac events including stent thrombosis, has become one of the most widely prescribed medications [4]. A two-step oxidative process catalyzed by enzymes in the cytochrome P450 system converts clopidogrel to the active thiol metabolite [5]. Response to clopidogrel is variable and this response is in part dependent on an individual's genotype for *CYP2C19*, a cytochrome P450 enzyme central to clopidogrel bioactivation. Carriers of *CYP2C19*2* and *CYP2C19*3* have reduced CYP2C19 enzyme activity and are called poor metabolizers, whereas carriers of CYP2C19*17 have increased CYP2C19 enzyme activity and are called ultra-rapid metabolizers. Recent findings have found the *CYP2C19*2* polymorphism, which is present in approximately 15% of Caucasians and Africans and approximately 30% of Asians, to be associated with reduced clopidogrel efficacy [5–12]. This has prompted a Food and Drug Administration (FDA) black box warning for cautious use among carriers of the reduced function alleles [13,14].

Among patients treated with clopidogrel for acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI), studies have consistently found carriers of at least one loss-of-function allele to have a significantly increased risk of adverse cardiac events, particularly stent thrombosis [11, 12, 15–18, 19•–21•]. The few studies that did not find an associated risk among carriers of reduced function allele had lower rates of stent placement, suggesting the greatest risk for adverse events occurs among those undergoing stent placement [22,23]. A meta-analysis including nine studies and 9685 patients reported a hazard ratio of 1.57 [95% confidence interval (CI) 1.13–2.16, $P = 0.006$] for the composite endpoint of cardiovascular death, myocardial infarction, and ischemic stroke among

carsriers of either one or two copies of the reduced function allele [19•]. Additionally, a gene dose effect was observed, with carriers of two reduced function alleles having an even greater risk (hazard ratio 1.76, 95% CI 1.24–2.50, $P = 0.002$) and the risk of stent thrombosis was further increased in carriers of the reduced function allele (hazard ratio 2.81, 95% CI 1.81–4.37). Apart from *CYP2C19*2*, the polymorphisms *3 and *17 have had limited study, with *3 being associated with reduced clopidogrel response and *17 being associated with increased bleeding and possibly improved efficacy while on clopidogrel therapy [9,17,24,25]. Notably, *3 is almost exclusively found in people of Asian descent.

Genome-wide association studies of platelet response to clopidogrel exposure has shown that approximately 12% variability in the trait is attributable to *CYP2C19*2* carrier status [11]. The common C3435T polymorphism in *ABCB1*, encoding p-glycoprotein, a drug efflux transporter, has also been associated with reduced clopidogrel efficacy and increased adverse cardiac events while on clopidogrel therapy, but this has not been a consistent finding [22,25–27]. Other candidate genes for clopidogrel efficacy have included *CYP1A2*, *CYP3A4*, *CYP3A5*, *CYP2B6*, *PON1*, and *P2YR12*, all with inconclusive or negative results [27–30, 31•, 32–39].

The Clinical Pharmacogenetics Implementation Consortium has presented a treatment algorithm for antiplatelet agents incorporating genetic information [40••]. For those undergoing PCI or with an ACS, these guidelines recommend placing those who are carriers of one or two copies of the variant allele to be treated with an alternative antiplatelet agent, including prasugrel or the recently approved agent ticagrelor [41, 42, 43•, 44–46]. Neither agent requires extensive bioactivation by the CYP2C19 enzyme and therefore both can be given to CYP2C19-poor metabolizers without reduced efficacy. It is unclear whether increasing the dose of clopidogrel can over-ride resistance, with a recent study finding that heterozygotes can have an adequate platelet response with clopidogrel 225–300 mg daily measured *in vitro*; however, whether this strategy will reduce clinical events is unknown [47–49]. Ongoing trials to test these treatment options include the Genotyping Infarct patients to Adjust and Normalize Thienopyridine treatment study with physicianguided therapy after CYP2C19 genotyping among patients post-PCI for ST-segment elevation myocardial infarction (STEMI), and the RAPID STEMI study evaluating treatment with prasugrel or high-dose clopidogrel for carriers of *CYP2C19*2* and *ABCB1* 3435 TT.

Beta-Blockers

Beta-adrenergic receptor antagonists (β-blockers) are an important class of cardiovascular drugs used for a range of conditions including cardiac arrhythmias, ACS, stable angina, hypertension, and heart failure. Beta-blockers antagonize endogenous catecholamines at beta-adrenergic receptors, of which two subtypes, β_1 and β_2, are most important for cardiovascular pharmacology [50]. Important autoregulatory mechanisms include G-protein-coupled receptor kinases (GRKs), enzymes that moderate signaling through phosphorylation of activated b-receptors, and presynaptic α_{2C}-adrenergic receptors (ADRA2C), which regulate norepinephrine release via a negative feedback pathway [51].

Two commonly used β-blockers, metoprolol and carvedilol, are metabolized through the CYP2D6 metabolic pathway and carry FDA labeling that polymorphisms in *CYP2D6* alter plasma drug concentrations [52]. *CYP2D6* variants with a range of enzymatic activity have been described, and the expected pharmacokinetic effects have been demonstrated repeatedly. For example, *CYP2D6* genotype has been shown to correlate with a several-fold difference in metoprolol plasma concentrations during both short-term and long-term therapy [53,54]. Clinical implications of *CYP2D6* have been shown for a wide range of noncardiovascular classes of drugs [55–57]. However, in regard to cardiovascular agents,

there are few studies examining differences in response, adverse events, or survival. Some studies have suggested differences by *CYP2D6* genotype; however, the data have not been consistent [3,58–61].

There are two common nonsynonymous SNPs in the β_1 receptor gene, *ADRB1*, resulting in Ser49Gly and Arg389Gly [62,63]. The Arg389 form, more common in those of European descent, demonstrates enhanced G-protein-coupled signaling [64], and provides the theoretical rationale for increased β-blocker responsiveness in individuals possessing this polymorphism. Indeed, among individuals homozygous for this variant (∼50% of Caucasians), there has been greater b-blocker-related improvements in ventricular function have been seen in patients with heart failure [65–67], though this observation has not been universal [66,68]. Clinical outcome studies in patients with heart failure have also been mixed [3,69–73].

Polymorphisms in the β_2 adrenergic receptor (*ADRB2*) have also been shown to have functional significance. Two nonsynonymous SNPs, Arg16Gly and Gln27Glu, appear to associate with augmented agonist-mediated down-regulation [74]. However, studies investigating variants in *ADRB2* have generally showed no association with improvements in left ventricular ejection fraction in response to β-blockers [67,68].

Functional polymorphisms in the α_{2C}-adrenergic receptor, ADRA2C, can theoretically modulate response to β-blockers. The common deletion polymorphism, ADRA2C Del322–325, resulting in the loss of four amino acids, shows decreased activity in transfected cells, suggesting the potential for enhanced norepinephrine release, and therefore β-blocker responsiveness [75]. Further, patients with heart failure who carry the ADRA2C Del322–325 genotype have been found to have worse disease-related outcomes [76]. One study indicates that individuals carrying the *ADRA2C* Del322–325 genotype had a greater improvement in left-ventricular function when given metoprolol. On the contrary, no effect was seen with bucindolol in the Beta-Blocker Evaluation of Survival Trial [77,78].

A gain-of-function Gln41Leu variant has been described in *GRK5*. This polymorphism is seen much more frequently in those of African descent and was found to protect against catecholamine-induced cardiomyopathy in a transgenic mouse model [51,79]. African Americans with the *GRK5* Gln41Gln genotype receiving β-blocker therapy have shown a significant benefit and, interestingly, have a survival similar to untreated Leu41 carriers; suggesting that Leu carriers may not benefit from β-blocker therapy [79]. Enrichment of the US population, relative to European populations, with genotypes unfavorable to β-blocker responsiveness has been proposed as a cause for apparent differences in outcome for US patients in heart failure trials [80•].

Warfarin

Vitamin K antagonists (warfarin in the US) are anticoagulants commonly used for the treatment and prevention of arterial and venous thromboembolism. Although effective, use is complicated by wide inter-individual variation in drug response and a narrow therapeutic index. Response to warfarin is affected by several patient factors, such as age, weight, and diet; as well, a large portion of the variation is related to known common variants in pharmacokinetic and pharmacodynamic genes, *CYP2C9* and *VKORC1*, respectively.

CYP2C9 metabolizes S-warfarin, the more active enantiomer of warfarin, to an inactive form. Two loss-of-function alleles, *CYP2C9*2* and *CYP2C9*3*, have been associated with decreased warfarin dose requirements and increased risk of hemorrhagic complications [81–84]. These findings have been confirmed in a large meta-analysis in which, for example, maintenance doses in the *2 and *3 homozygotes were reduced by 36 and 78.1%,

respectively [85]. There is a considerable impact of race, with these variants being significantly less common in those of African descent, and having a correspondingly smaller effect at a population level [86].

Vitamin K epoxide reductase, coded by *VKORC1*, is critical to normal vitamin K metabolism (and hence synthesis of vitamin K-dependent clotting factors) and represents the pharmacologic target of warfarin. Multiple polymorphisms in the promoter region of *VKORC1* associate with variable gene expression and warfarin dose requirements in people of European and African descent [82,87]. GWAS have identified *VKORC1* and *CYP2C9* as the primary contributors to differential warfarin responsiveness, together accounting for approximately 40% of variation, with other genes contributing only small effects [88,89].

The epoxide form of vitamin K may also be metabolized to an inactive form by the enzyme vitamin K_1 oxidase (CYP4F2). Polymorphisms in *CYP4F2* have been associated with variable warfarin dose requirements [90,91]; however, findings have been inconsistent [92]. Additional genes have been identified that affect warfarin responsiveness, including *APOE*, glutamyl carboxylase (*GGCX*), calumenin (*CALU*), *CYP4F2*, epoxide hydrolase 1 (*EPHX1*), and factor VII (F7) [63]; however, their collective contribution to warfarin dosing variability is less than that of *CYP2C9* and *VKORC1*. When clinical information such as age, sex, and concomitant drug therapy are combined with *VKORC1* and *CYP2C9* polymorphisms, 50–60% of variation in warfarin dose can be explained [93]. Given these compelling data, the FDA has included the range of expected therapeutic warfarin doses based on *CYP2C9* and *VKORC1* genotypes in the warfarin labeling [94]. Prospective trials are underway to determine whether a genotype-guided dosing strategy improves patient care [95••, 96, 97].

Two novel oral anticoagulants have recently received FDA approval. Dabigatran, a reversible direct thrombin inhibitor, was approved in 2010 for the indication stroke prevention in atrial fibrillation, and rivaroxaban, a factor Xa inhibitor, was approved for deep venous thrombosis prophylaxis after orthopedic surgery in 2011. Dabigatran is administered as a pro-drug that is rapidly biotrans-formed after absorption. Both dabigatran and rivaroxaban are substrates for the drug efflux pump P-glycoprotein, coded by the *ABCB1* gene, and dabigatran (but not rivaroxaban) undergoes metabolism by CYP450 enzymes, predominantly CYP3A4 and CYP2J2 [98–100]. To date, no data regarding pharmacogenomic studies of these agents have been published and it is currently unknown whether genetic variants modulate their effectiveness.

Statins

3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) catalyzes the rate-limiting step of cholesterol biosynthesis. HMGCR inhibitors, or statins, lower serum cholesterol by blocking endogenous cholesterol synthesis, with subsequent up-regulation of the low-density lipoprotein receptor (LDLR). Statins are very effective for the treatment and prevention of cardiovascular disease. However, they are also associated with muscle toxicity that is commonly mild, but can rarely present as rhabdomyolysis.

Genetic variants have also been shown to modulate statin dosing and efficacy. Atorvastatin, simvastatin, and lovastatin are inactivated via CYP3A4 and common polymorphisms in this gene are believed to affect dosing requirements through pharmacokinetic effects [101]. Also, certain haplotypes, combinations of alleles (or SNPs) at adjacent locations on the chromosome used to identify other polymorphic sites in the region, have been associated with statin responsiveness. The H7 haplotype of *HMGCR*, defined by the presence of three intronic SNPs, rs17244841, rs3846662, and rs17238540, leads to an 11–19% reduction in statin sensitivity, and is thought to involve variable production of an *HMGCR* isoform

through alternate splicing [102– 106]. In individuals of African descent, the L5 hap-lotype of *LDLR*, defined by six SNPs within the LDLR 3′ untranslated region, is associated with reduced statin responsiveness, possibly related to attenuated induction of LDLR surface expression [101,107]. Statin efficacy for those who carry both the H7 *HMGCR* haplotype and L5 *LDLR* haplotypeis further reduced. Other associations between genetic variants and statin efficacy are less clear. *CLMN*, encoding calmin, a protein of unknown function, has been identified through combined GWA analysis from three clinical trials [108], but the finding requires further study. Additionally, some studies have found an association between the Trp719Arg variant in kinesin-like protein 6 (KIF6) and coronary artery disease (CAD) as well as an increased protective effect from events by statins [109,110]. However, the association with CAD was not seen in a recent large replication study [111], casting uncertainty on the relationship.

Important genetic associations have also been made with statin myotoxicity. A GWAS including only 85 individuals with myotoxicity while taking high-dose simvastatin was nevertheless successful in identifying the V174A variant in the drug uptake transporter encoded by *SLCO1B1* as a risk allele. Strikingly, this variant carried an odds ratio (OR) of 16.9 (95% CI 4.7–61.1) for myopathy in homozy-gotes and 4.5 (95% CI 2.6–7.7) in heterozygotes and accounted for approximately 60% of the risk in this population [112]. The *SLCO1B1* variant has been independently validated [113,114]. *SLCO1B1* genotype information may be integrated into clinical care to inform providers regarding patient risk of myotoxicity and help guide therapeutic decisions [115].

Angiotensin-Converting Enzyme Inhibitors

Most data regarding genomic modulators of angiotensin-converting enzyme (ACE) inhibitor response refer to a common insertion/deletion (I/D) polymorphism in the *ACE* gene that is strongly correlated with plasma enzyme levels [116,117]. In an observational study, carriers of the DD genotype were found to have significantly higher mortality than those with the I/I genotype, with the risk for heterozygotes being intermediate [118]. However, prospective trials have failed to validate these findings [119,120] and, at present, there is no strong evidence that this variant influences response to ACE inhibitors. A number of other candidates in the renin–angiotensin–aldosterone pathway have been analyzed, including angiotensinogen (*AGT*) and angiotensin II receptor types I and II (*AGTR1* and *AGTR2*). Signals for higher risk of adverse cardiovascular outcomes while taking ACE inhibitors have emerged with variants in *AGT*[63]; however, the data are not conclusive.

Recently the Perindopril Genetic Association study (PERGENE) [121•] evaluated 12 genes from the pharmacodynamic pathway of ACE inhibitors in 8907 patients with stable CAD treated with perindopril or placebo. Two polymorphisms in AGTR1 and a third in the bradykinin type I receptor were significantly associated with the combined primary outcome of cardiovascular mortality, nonfatal myocardial infarction, and resuscitated cardiac arrest during 4.2 years of follow-up. A pharmacogenetic score combining these SNPs demonstrated a stepwise decrease in treatment benefit of perindopril with an increasing score and identified a subgroup of 26.5% of the population that did not benefit from therapy [121•]. This finding requires independent replication, but represents a potential advance toward understanding variable response to ACE inhibitors.

Arrhythmia-Related Drugs

Cardiac arrhythmias are a heterogeneous and complex collection of clinical entities associated with substantial morbidity and mortality. Atrial fibrillation, for example, is the commonest sustained arrhythmia encountered in clinical practice and affects more than 2

million Americans [122]. Treatment of atrial fibrillation may be directed at maintenance of normal sinus rhythm or focus on control of ventricular rate. In either case, management is characterized by variable drug response and high recurrence rates. Functional variants influencing drug response in atrial fibrillation have recently been described. The ADRB1 Arg389Gly polymorphism has been associated with improved rate control in patients with atrial fibrillation [123]. A SNP (rs10033464) at the 4q25 locus near the *PITX2* gene, which has been associated with increased risk of atrial fibrillation, appears to modulate response to antiarrhythmic drugs and predicts successful rhythm control [124].

Life-threatening arrhythmias, such as Torsade de Pointes (TdP), may also arise as a complication of drug treatment. This adverse event occurs in association with an exaggerated prolongation of the QT interval, most commonly, though not exclusively, due to certain antiarrhythmic agents [125– 127]. Small cohort studies in which known long-QT disease genes were genotyped identified variants in these ion channel genes in up to 15% of affected patients [128,129]. Using a candidate approach in which nearly 1500 SNPs in 18 key genes related to cardiac electrical properties were genotyped, the nonsynonymous SNP *KCNE1*-D85N (rs1805128) was significantly associated with increased risk of TdP with an OR of 9.0 [130••]. This SNP, which codes a potassium channel known to modulate an important cardiac current, had also been identified in prior candidate gene studies and is relatively common in the population: minor allele frequency 1–2% [128,131].

Conclusion

Despite improvements in the efficacy and safety of pharmacologic therapies for cardiovascular disease, patients vary considerably in their benefit from therapy and propensity for adverse drug events. There is an increasing appreciation that genetic variation is an important contributor to this variability, and understanding these pharmacogenomic relationships has provided key insights into mechanisms of disease and drug response. The field is in an exciting stage of rapid discovery, and the most robust findings are undergoing translation into clinical practice. Understanding the genomic basis of variable drug response is a key step in making personalized medicine a reality.

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• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 322).

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Key Points

- Genetic variation within individuals and populations contributes to the variable efficacy and toxicity of many important cardiovascular drugs.
- A number of pharmacogenomic associations have shown clinical relevance and are included in FDA labels.
- Prospective trials evaluating genomic data care are underway.
- Translation of pharmacogenomic findings into routine clinical care will be challenging, but early efforts have begun.

Table 1

Examples of genetic variants influencing response to cardiovascular drugs

Gene	SNP	Chr	Position	Reported effect on function	Possible implication for clinical practice
Tier 1 – Strong level of evidence for clinical translation					
*CYP2C19**2	rs4244285	10	96531606	Reduced enzyme function→ Resistance to clopidogrel	For carriers of 1 or 2 copies of *2 allele, consider alternate antiplatelet agent when undergoing PCI or after ACS. Consider higher maintenance dose in heterozygotes
VKORC1	rs9923231	16	31107689	Increased sensitivity to warfarin	For carriers of 1 or 2 copies of the A allele, consider a lower initial dose of warfarin compared with carriers of the G allele (use in conjunction with *CYP2C9* genotype information)
*CYP2C9*2*	rs1799853	10	96702047	Increased sensitivity to warfarin	For carriers of 1 or 2 copies of the *2 allele, consider a lower initial dose of warfarin (use in conjunction with *CYP2C9* genotype information)
*CYP2C9*3*	rs1057910	10	96741053	Increased sensitivity to warfarin	For carriers of 1 or 2 copies of the *3 allele, consider a lower initial dose of warfarin (use in conjunction with *VKORC1* genotype information)
SLCO1B1	rs4149056	12	21331549	Increased likelihood of simvastatin-related myotoxicity	For carriers of this variant consider an alternate lipid lowering therapy
Tier 2 – Weaker evidence, clinical implementation premature					
ABCB1-C3435T	rs1045642	7	86976581	Resistance to clopidogrel	If genotype known, may consider alternate antiplatelet agent
*CYP2C19*17*	rs12248560	10	96511647	Increased clopidogrel efficacy	Concern for bleeding with clopidogrel, monitor patients closely if genotype known
*CYP2C19*3*	rs4986893	10	96540410	Resistance to clopidogrel	If genotype known, may consider alternate antiplatelet agent
ADRB1-R389G	rs1801253	10	115805056	Increased response to beta-blockers	May consider alternate therapeutic class (e.g. maximize ACEi over beta-blocker in heart failure or calcium channel antagonist for rate control in atrial fibrillation)
ADRB1-R389G	rs1801253	10	115805056	Associated with successful rate control strategy for AF	May assist in selection of atrial fibrillation treatment strategy (i.e. rate versus rhythm control)
4q25 (intergenic near *PITX2*)	rs10033464	4	136232206	Associated with successful rhythm control strategy for AF	May assist in selection of atrial fibrillation treatment strategy (i.e. rate versus rhythm control)
KCNE1-D85N	rs1805128	21	35821680	Increased risk of drug-induced TdP	Assist in assessment of risk for drug-related TdP

ACEi, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; SNP, single-nucleotide polymorphism; TdP, torsades de pointes