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ANKK1/DRD2

Clinical Utility

Dopamine, a key neurotransmitter that controls cognition, emotion, locomotor activity, and other endocrine functions, exerts its action by binding to five different receptors, including the dopamine D2 receptor (DRD2). Dysregulation of dopaminergic signal transmission is found in many pathological conditions such as Parkinson's disease and schizophrenia, and compounds that act as DRD2 agonists or antagonists are used to treat these conditions. Therapeutic and adverse events of several antipsychotics both result from their high affinity to antagonize DRD2.

Assay Interpretation

Within the several genetic variants of DRD2 that are relevant to disease susceptibility and therapeutic response, the Taq1A (32806C>T; rs1800497) is one of the most studied. This variant is located downstream of the DRD2 gene within the ankyrin repeat of the ANKK1 gene. The presence of the Taq1A T variant defines the A1 allele that is associated with a reduced DRD2 gene expression and function. The A2 allele defines the reference allele. The frequency of the minor Taq1A T allele differs among ethnic populations. It occurs in 22% of Caucasians, and 42% of Asians and Africans.
The reference range for the Taq1A variant is 32806C>T CC (A2/A2) and is associated with a normal DRD2 expression.

Clinical Implications

The presence of the Taq1A A1 allele (32806C>T) seems to be associated with nicotine dependence and the efficacy of bupropion and nicotine replacement therapy. Smokers carrying the normal DRD2 phenotype (A2/A2 genotype) using bupropion for smoking cessation are three times more likely to be abstinent at the end of treatment than non-carriers of this genotype. Smokers with the Taq1A T variant allele (A1) seem to derive greater benefits from nicotine replacement therapies. Antipsychotic agents have been associated with hyperprolactinemia and tardive dyskinesia (TD). TD-positive patients taking antipsychotics have a higher A2 allele frequency, while A1 allele is overrepresented among those experiencing hyperprolactinemia.

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Patients Choice Laboratories

Apolipoprotein E

Clinical Utility

Apolipoproteins (APO) are structural constituents of lipoprotein particles that have critical roles in blood lipid metabolism and transport. Apolipoprotein E (APOE) is a major constituent of triglyceride-rich chylomicrons, very low-density lipoproteins (VLDL), and some subclasses of high-density lipoproteins (HDL). The primary function of APOE is to transport cholesterol from the cells in the blood vessel wall to the liver for excretion. Defects in apolipoprotein E (APOE) can result in dyslipidemia, which is an important risk factor in the genesis of atherosclerosis and subsequent development of cardiovascular disease (CVD).

Assay Interpretation

There are three common APOE alleles designated ε2, ε3, and ε4, resulting from combinations of the two genetic polymorphisms 388T>C and 526 C>T. These alleles result in E2, E3, and E4 protein isoforms, respectively. The approximate allele frequencies for most populations are 8-12% for ε2, 74-78% for ε3, and 14-15% for ε4.

The reference ranges for both mutations of APOE are 388TT and 526CC. This is consistent with a ε3/ε3 genotype and a normal APOE function.

Clinical Implications

- The APOE ε3/ε3 genotype is considered the normal genotype and is associated with normal lipid metabolism. It is not associated with an increased risk of atherosclerotic CVD.
- The APOE ε2 allele is strongly associated with type III hyperlipoproteinemia. This may increase the risk for premature CVD.
- Patients with symptoms (xanthomas) and with a lipid profile consistent with type III hyperlipidemia are candidates for APOE genotype analysis. Over 90% of individuals presenting the type III hyperlipoproteinemia have the rare ε2/ε2 genotype. However, only 1-5% of individuals with this genotype develop type III hyperlipoproteinemia, suggesting that other genetic, hormonal, or environmental factors must contribute to this disease.
- Although individuals with the APOE ε2/ε2 genotype are at higher risk of premature vascular disease, they may never develop the disease because this genotype is only one of the risk factors.
- In normolipidemic patients, the ε2 allele is associated with lower serum cholesterol concentrations, and may confer a protection against hypercholesterolemia.
- The APOE ε2/ε4 genotype is associated with type III hyperlipoproteinemia in patients who are also heterozygous for familial hypercholesterolemia.
- The APOE ε4 allele has been linked to pure elevations of low-density lipoproteins (LDL), and the ε4/ε4 and ε3/ε4 genotypes are associated with increased serum cholesterol levels and increased risk of CVD.

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Apolipoprotein E (continued)

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COMT

Clinical Utility

Catechol-O-Methyltransferase (COMT) is an enzyme responsible for the metabolism of catecholamines and catechol-estrogens in the central nervous system and other organs. Dopamine is cleared mainly by COMT in the frontal cortex, and a reduced activity of this enzyme results in higher synaptic levels of dopamine, which affects prefrontal cortex cognitive response to certain drugs. A single nucleotide polymorphism of the COMT gene produces an amino acid change from valine to methionine (Val158Met) and reduces the enzyme activity by 3- to 4-fold.

Assay Interpretation

The most well studied COMT genetic variant (rs4680; 472G>A) is the one resulting in a valine to methionine change at codon 158. The variant allele called the Met allele is found in 30-47% of Caucasians, 23% of Africans, and 27-32% of Asians. The phenotype is defined by the presence of the reduced activity Met allele (A variant). The wild-type genotype (Val/Val; GG) predicts a high/normal COMT activity, the heterozygous genotype (Val/Met; GA) predicts an intermediate COMT activity, and the homozygous (Met/Met; AA) results in a low COMT activity.
The reference range for COMT metabolic status is COMT Val158Met GG (Val/Val) (wild-type), which is consistent with a high/normal COMT activity.

Clinical Implications

Several complex associations with the Val158Met variant as a risk factor for numerous diseases have been found, but seem to have limited predictive value. The response to some psychotropic medications seems to be dependent to some extent upon the COMT status. In general, the wild-type genotype result predicts a good response to methylphenidate and amphetamines in the treatment of attention deficit hyperactivity disorder. In the treatment of pain, patients who are homozygous for the Met allele require lower doses of morphine to achieve analgesia.

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CYP1A2

Clinical Utility

The cytochrome P450 1A2 (CYP1A2) accounts for 13% of total CYP in the human liver, and is responsible for metabolizing 8-10% of commonly used drugs as well as natural compounds such as caffeine. A large inter-individual variability in the elimination of drugs that are metabolized by CYP1A2 has been observed, which has been ascribed to genetic variations and environmental factors. CYP1A2 activity is highly inducible (increased) by environmental factors including smoking (tobacco), some drugs, and several dietary compounds (cruciferous vegetables).

Assay Interpretation

More than 20 different alleles have been characterized for the CYP1A2 gene, and some have been shown to affect enzyme activity and its sensitivity towards inducers (inducibility). The CYP1A2*1F is the most studied allele and results in a rapid metabolizer phenotype in the presence of inducers, while CYP1A2*1K and *1C alleles result in enzymes that are less active and less sensitive to induction. The CYP1A2*1F allele is found in 25-50% of Caucasians, 30% of Asians, and 50% of Ethiopians. The genotype-phenotype relationship for CYP1A2 is not well established, and can be expressed in terms of metabolic capacity as well as sensitivity towards induction (inducibility). Individuals are predicted to have CYP1A2 normal, intermediate, or poor metabolic capacity, with high, possible, or low inducibility depending on their genotype.

The reference range for CYP1A2 metabolic status is CYP1A2 *1A/ *1A, which is consistent with a normal metabolizer that is possibly inducible.

Clinical Implications

CYP1A2 genotype can help identify patients with high or low sensitivity to inducing agents, especially those released during smoking. **The clinical relevance of this sensitivity becomes important in patients who are smokers or who quit smoking.** Patients with the highly inducible genotype CYP1A2*1F/*1F can experience loss of response to drug substrates while they are exposed to dietary or environmental inducers, and therefore may require higher doses.

The following drugs used in the management of pain and various psychiatric conditions are metabolized extensively by CYP1A2 and are sensitive to its function: clozapine (Clozaril), duloxetine (Cymbalta), olanzapine (Zyprexa), and tizanidine (Zanaflex). CYP1A2 also metabolizes other important drugs such as melatonin, ondansetron (Zofran), pomalidomide (Pomalyst), ramelteon (Rozerem), ropivacaine (Naropin), and tasimelteon (Hetlioz).

CYP1A2 metabolism is highly sensitive to inhibition and induction, and the occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, response, and safety profiles of many CYP1A2 drug substrates.

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CYP1A2 (continued)

Inhibitors
Some known **strong** CYP1A2 inhibitors include: ciprofloxacin (Cipro), enoxacin (Penetrex), fluvoxamine (Luvox), and zafirlukast (Accolate).

Some known **moderate to weak** CYP1A2 inhibitors include: oral contraceptives, mexiletine (Mexitil), allopurinol (Zyloprim), peginterferon alfa-2a (Pegasys), norfloxacin (Norflox), ticlopidine (Ticlid), vemurafenib (Zelboraf), and zileuton (Zyflo).

Inducers
Known CYP1A2 inducers include: carbamazepine (Tegretol), montelukast (Singulair), rifampin (Rifadin), phenytoin (Dilantin), moricizine
(Ethmozine), omeprazole (Prilosec), phenobarbital, and primidone (Mysoline).
Some dietary and environmental compounds found in cigarette smoke, cruciferous vegetables, and charcoal-grilled food can also increase CYP1A2 activity.

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CYP2B6

Clinical Utility

The cytochrome P450 2B6 (CYP2B6) is involved in the metabolism of 4% of clinically important medications. This enzyme is highly polymorphic: to date, 37 different variants have been identified. The CYP2B6 assay identifies some common variants that are associated with variability in enzyme activity.

Assay Interpretation

CYP2B6 enzyme activity defines a normal or an abnormal (intermediate or poor) metabolizer status for a given individual. Several variant alleles have been identified and result in different CYP2B6 isoforms that functionally are fully active, partially active, inactive, or have increased activity. The CYP2B6*1 allele is considered wild-type and encodes a functionally active enzyme (normal). The alleles *6, *7, *9, *11, *16, *18, and *36 encode a decreased activity enzyme. The *22 alleles represents a gain-of-function allele. The functional impact of variants that define the CYP2B6 *4 and *5 alleles is drug dependent.

The most common functionally deficient allele is CYP2B6*6. It is found in 7-18%, 10-17%, 23%, and 33% of Caucasians, Asians, Mexican-Americans, and African-Americans, respectively. CYP2B6 *18 is found only in individuals of African descent, with a frequency of 4-7%.

The genotype-phenotype relationship is not well established, and there is a lack of consistency regarding the clinical impact of certain allelic variants. The following provisional genotype-to-phenotype assignment can be used: individuals with two fully active alleles are considered normal (extensive) metabolizers. Individuals with one fully active allele with either a partially active or an inactive allele are considered intermediate metabolizers. Individuals with two partially active alleles or two inactive alleles are considered poor metabolizers. Individuals carrying two increased function alleles or one active allele with a gain-of-function allele are classified as normal/rapid metabolizers.

The reference range for CYP2B6 metabolic status is CYP2B6 *1/ *1, which is consistent with a normal metabolizer.

Clinical Implications

CYP2B6 plays a role in the metabolism of the following drugs: artemisinin, bupropion (Wellbutrin), cyclophosphamide (Cytoxan), efavirenz
(Sustiva), ketamine (Ketalar), meperidine (Demerol), methadone (Dolophine), nevirapine (Viramune), propofol (Diprivan), and selegiline
(Eldepryl).

The impact of CYP2B*6 polymorphism on the pharmacokinetics and the clinical response have been studied in patients taking methadone, bupropion, and efavirenz. Limited evidence exists regarding the clinical impact of other polymorphisms.

Inhibitors or inducers of the CYP2B6 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2B6 inhibitors or inducers.

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CYP2B6 (continued)

Inhibitors

Some known CYP2B6 inhibitors include: clopidogrel, darunavir, prasugrel, ticlopidine, voriconazole, ritonavir, and thiotepa.

Inducers

Some CYP2B6 inducers include: artemether, carbamazepine, dabrafenib, efavirenz, metamizole, nevirapine, phenobarbital, phenytoin, rifampin, ritonavir, and St. John's wort.

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CYP2C19

Clinical Utility

The cytochrome P450 2C19 (CYP2C19) is involved in the metabolism of 10% of clinically important medications. This enzyme is highly polymorphic: more than 30 different variant alleles have been identified. The CYP2C19 assay identifies some common variants that are associated with variability in CYP2C19 enzyme activity, which has important pharmacological and toxicological implications for antidepressants, benzodiazepines, antiplatelets, and proton-pump inhibitors.

Assay Interpretation

CYP2C19 enzyme activity defines a normal or abnormal (intermediate, poor, rapid or ultra-rapid) metabolizer status for a given individual. Several variant alleles have been identified and result in different isoforms of the CYP2C19 enzyme that functionally are fully active, partially active, inactive, or with increased activity. The CYP2C19*1 allele is considered wild-type and encodes a functionally active enzyme (normal). The alleles *2, *3 *4, *5, *6, and *8 encode an inactive enzyme and are referred to as loss-of-function alleles. Individuals with a *17 allele have an increased CYP2C19 activity.

The genotype-phenotype relationship is established based on the allele's activity. Individuals with two fully functional alleles are considered normal (extensive) metabolizers. Individuals with one or two loss-of-function alleles are considered intermediate or poor metabolizers, respectively. Individuals with one or two increased function alleles are considered rapid or ultra-rapid metabolizers, respectively. Because of limited evidence, an individual with one increased function allele and one loss-of-function allele is provisionally classified as an intermediate metabolizer.

The reference range for CYP2C19 metabolic status is CYP2C19 *1/*1, which is consistent with a normal metabolizer.

Clinical Implications

There is substantial evidence linking the CYP2C19 polymorphisms to variability in the pharmacological and safety profiles of the following therapies used in psychiatric conditions and pain management: amitriptyline (Elavil), sertraline (Zoloft), clobazam (Onfi), citalopram (Celexa), escitalopram (Lexapro), diazepam (Valium), imipramine (Tofranil), and carisoprodol (Soma). CYP2C19 plays a minor role in the elimination of methadone (Dolophine).

Cardiovascular medications that are metabolized by CYP2C19 include the prodrug clopidogrel (Plavix), propranolol (Inderal), and cilostazol
(Pletal). Proton-pump inhibitors such as omeprazole (Prilosec), esomeprazole (Nexium), lansoprazole (Prevacid), dexlansoprazole (Dexilant), and pantoprazole (Protonix) are major substrates of CYP2C19.

Brivaracetam is primarily metabolized by hydrolysis and by hydroxylation The hydrolysis reaction is mediated by amidase and the hydroxylation pathway is mediated by CYP2C19. In patients carrying genetic variations in CYP2C19 the blood level of brivaracetam is increased by 22% or 42%, in CYP2C19 intermediate and poor metabolizers, respectively. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may therefore require dose reduction to avoid concentration-dependent toxicity.

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CYP2C19 (continued)

Inhibitors or inducers of CYP2C19 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2C19 inhibitors or inducers.

Inhibitors

Some known CYP2C19 inhibitors include: fluconazole (Diflucan), fluvoxamine (Luvox), fluoxetine (Prozac), felbamate (Felbatol), ticlopidine
(Ticlid), omeprazole (Prilosec), esomeprazole (Nexium), voriconazole (Vfend), armodafinil (Nuvigil), delavirdine (Rescriptor), modafinil
(Provigil), oxcarbazepine (Trileptal), etravirine (Intelence), topiramate (Topamax), and moclobemide (Manerix).
Inducers
Some known CYP2C19 inducers include: artemether (Coartem), carbamazepine (Tegretol), efavirenz (Sustiva), enzalutamide (Xtandi), fosphenytoin (cerebyx), primidone (Mysoline), phenobarbital, phenytoin (Dilantin), rifampin (Rifadin), and St. John's wort.

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Patients Choice Laboratories

CYP2C9

Clinical Utility

The cytochrome P450 2C9 (CYP2C9) is involved in the metabolism of 15% of clinically important medications. This enzyme is highly polymorphic: to date, 30 variants have been identified. The CYP2C9 assay identifies some common variants that are associated with variability in CYP2C9 enzyme activity, which has important pharmacological and toxicological implications for anticonvulsants, anticoagulants, and certain antidiabetics.

Assay Interpretation

CYP2C9 enzyme activity defines a normal or abnormal (intermediate and poor) metabolizer status for a given individual. Several variant alleles have been identified and result in different CYP2C9 isoforms that functionally are fully active, partially active, or inactive. The CYP2C9*1 allele is considered wild-type and encodes a functionally active enzyme (normal). The alleles *2, *3, *4, *5, and *11 encode a partially active enzyme. The allele *6 is a null allele encoding for an inactive enzyme.

The genotype-phenotype relationship is established based on the allele's activity. Individuals with two fully active alleles are considered normal (extensive) metabolizers. Individuals with one fully active allele with either a partially active or an inactive allele are considered intermediate metabolizers. Individuals with two partially active alleles or with two inactive alleles are considered poor metabolizers.

The reference range for CYP2C9 metabolic status is CYP2C9 *1/*1, which is consistent with a normal metabolizer.

Clinical Implications

Abnormal CYP2C9 activity affects the therapeutic outcome of a variety of drugs used to treat cardiovascular and other conditions. Following the administration of drug substrates, the clinical manifestation in a poor or an intermediate metabolizer depends on the characteristics of the drug (i.e., the amount of drug/metabolites that is cleared by the enzyme), and the safety and pharmacological profiles of the drug and its metabolites. Within the medications used to treat cardiovascular conditions, there is compelling evidence that the response to certain angiotensin II inhibitors, statins, and anticoagulants is altered in individuals exhibiting abnormal CYP2C9 activity.

CYP2C9 plays a role in the metabolism of the following psychotropic drugs: fluoxetine (Prozac), phenytoin (Dilantin), and primidone (Mysoline). Several NSAIDs and Cox-2 inhibitors are substrates of CYP2C9, and patients with reduced CYP2C9 activity may have higher plasma levels of celecoxib (Celebrex), flurbiprofen (Ocufen), piroxicam (Feldene), or meloxicam (Mobic). CYP2C9 plays a minor role in the elimination of diclofenac (Voltaren), sulindac (Clinoril), and naproxen (Aleve).

Cardiovascular medications that are metabolized by CYP2C9 include warfarin (Coumadin), fluvastatin (Lescol), losartan (Cozaar), and irbesartan (Avapro).

Other important drugs metabolized by CYP2C9 include antidiabetics such as tolbutamide, glibenclamide (Micronase), glipizide (Glucotrol), and nateglinide (Starlix).

Inhibitors or inducers of the CYP2C9 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2C9 inhibitors or inducers.

Patients Choice Laboratories

CYP2C9 (continued)

Inhibitors

Some known CYP2C9 inhibitors include: amiodarone (Cordarone), 5-fluorouracil (Adrucil), chloramphenicol, cimetidine (Tagamet), danazol (Danocrine), disulfiram (Antabuse), fluconazole (Diflucan), fluoxetine (Prozac), fluvoxamine (Luvox), miconazole (Oravig), oxandrolone (Oxandrin), capecitabine (Xeloda), co-trimoxazole (Septra), delavirdine (Rescriptor), etravirine (Intelence), fluvastatin (Lescol), efavirenz (Sustiva), gemfibrozil (Lopid), lomitapide (Juxtapid), metronidazole (Flagyl), phenytoin (Dilantin), sulfamethoxazole (Bactrim), sulfinpyrazone (Anturane), tamoxifen (Nolvadex), toremifene (Fareston), tigecycline (Tygacil), voriconazole (Vfend), and zafirlukast (Accolate).

Inducers

Some known CYP2C9 inducers include: carbamazepine (Tegretol), rifampin (Rifadin, Rimactane), rifapentine (Priftin), St. John's wort, enzalutamide (Xtandi), aprepitant (Emend), bosentan (Tracleer), dabrafenib (Tafinlar), phenobarbital, primidone (Mysoline), phenytoin (Dilantin), and ritonavir (Norvir).

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Patients Choice Laboratories

CYP2D6

Clinical Utility
The cytochrome P450 2D6 (CYP2D6) is involved in the metabolism of 25% of clinically important medications. This enzyme is highly polymorphic: more than 100 different variants have been identified. The CYP2D6 assay identifies common variants that are associated with variability in CYP2D6 enzyme activity, which has important pharmacological and toxicological implications for antidepressants, antipsychotics, opioids, beta-blockers, and antiarrhythmics.

Assay Interpretation
CYP2D6 enzyme activity defines a normal or abnormal (intermediate, poor, or ultra-rapid) metabolizer status for a given individual. Commonly tested CYP2D6 variant alleles are classified into functional groups: Full or normal function (e.g., CYP2D6 *1, *2 and *35), reduced function (e.g., CYP2D6*9, *10, *14B, *17, *29, and *41) and no function (e.g., CYP2D6 *3, *4, *5, *6, *7, *8, *11, *12, *14A, *15, *36 and *56). Increased CYP2D6 activity is found in individuals carrying multiple copies of functional alleles. CYP2D6 is subject to gene duplications, and these are denoted “XN”, where N represents the number of CYP2D6 gene copies when available.
The genotype-phenotype relationship is established using a scoring system that assigns an activity value to every CYP2D6 allele, in order to assign a predicted phenotype. For a given genotype, the activity values of the constituent alleles are added together to calculate the CYP2D6 activity score. This activity score (AS) is then used to assign a predicted phenotype as follows: AS of 0 predicts a poor metabolizer, AS ranging between 1 and 2 predicts a normal (extensive) metabolizer, AS=0.5 predicts an intermediate metabolizer, and AS greater than 2 predicts an ultra-rapid metabolizer. Fully functional alleles are assigned an activity value of 1, reduced function alleles have an activity value of 0.5, while non-functional alleles are assigned an activity value of 0.
The reference range for CYP2D6 metabolic status is a CYP2D6 *1/ *1 genotype, which is consistent with a normal metabolizer.

Clinical Implications
There is substantial evidence linking the CYP2D6 polymorphisms to variability in the pharmacological and safety profiles of the following psychotropics: desipramine (Norpramin), imipramine (Tofranil), amitriptyline (Elavil), nortriptyline (Pamelor), haloperidol (Haldol), trimipramine (Surmontil), venlafaxine (Effexor), doxepin (Silenor), aripiprazole (Abilify), atomoxetine (Strattera), duloxetine (Cymbalta), risperidone (Risperdal), clomipramine (Anafranil), and pimozide (Orap).
CYP2D6 polymorphisms have been shown to affect the pharmacological and safety profiles of the following analgesics: codeine, tramadol (Ultram), and hydrocodone (Vicodin). Codeine and tramadol are prodrugs that need to be activated by CYP2D6. Poor metabolizers are at high risk of therapy failure when given codeine or tramadol. On the other hand, ultra-rapid metabolizers may experience increased toxicity when given standard dosage of codeine or tramadol. Because CYP3A4 is also involved in the metabolism of oxycodone, patients with abnormal CYP2D6 activity may still experience adequate analgesia when taking this drug. CYP2D6 polymorphism has been shown to affect dihydrocodeine (Synalgos-DC) pharmacokinetics and can potentially alter the response to this drug.

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CYP2D6 (continued)

Morphine, oxymorphone (Opana), hydromorphone (Dilaudid), butorphanol (Stadol), fentanyl (Duragesic), buprenorphine (Butrans), methadone (Dolophine), morphine (Avinza), and tapentadol (Nucynta) are not substrates of CYP2D6, and the patient's response to these drugs is not expected to be affected by polymorphisms in this enzyme.
Several important cardiovascular medications are metabolized by CYP2D6, and include: metoprolol (Lopressor), carvedilol (Coreg), flecainide (Tambocor), and propafenone (Rythmol).
Eliglustat (Cerdelga) is a glucosylceramide synthase inhibitor used for the long-term treatment of adult patients with Gaucher disease type 1. Both the FDA-approved drug label and the EMA Summary of Product Characteristics for this drug state that CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of eliglustat to achieve a therapeutic effect. Therefore this drug should not be used in these individuals. Patients who are CYP2D6 intermediate and normal metabolizers have a recommended dose of 84 mg twice daily, while poor metabolizers have a recommended dose of 84 mg once daily.
Cevimeline (Evoxac) is a muscarinic agonist indicated for the treatment of symptoms of dry mouth in patients with Sjögrens Syndrome. Both CYP2D6 and CYP3A are responsible for the metabolism of cevimeline, and this drug should be used with caution in individuals who are CYP2D6 poor metabolizers, as they may be at a higher risk of adverse events.
Inhibitors of the CYP2D6 enzyme may modify its activity and change the patient's metabolizer status. This can result in drug-drug interactions when a drug substrate is prescribed with known CYP2D6 inhibitors. Although there are no known clinical inducers of CYP2D6, the pharmacokinetics of a drug substrate can be affected by inducers of other enzymes (such as CYP3A) that are involved in the metabolism of that drug.

Inhibitors
Some known strong and moderate CYP2D6 inhibitors include: abiraterone (Zytiga), bupropion (wellbutrin), cobicistat (Stribild), fluoxetine (Prozac), quinidine (Quinidex), paroxetine (Paxil), cinacalcet (Sensipar), duloxetine (Cymbalta), terbinafine (Lamisil), tipranavir/ritonavir (Aptivus), mirabegron (Myrbetriq), peginterferon alfa-2b (Sylatron) and ecstasy.
Some known weak CYP2D6 inhibitors include: amiodarone (Cordarone), celecoxib (Celebrex), clobazam (Onfi), desvenlafaxine (Pristiq), diltiazem (Cardiazem), diphenhydramine (Benadryl), escitalopram (Lexapro), febuxostat (Uloric), gefitinib (Iressa), hydralazine (Apresoline), hydroxychloroquine (Plaquenil), imatinib (Gleevec), lorcaserin (Belviq), methadone (Dolophine), perphenazine (Trilafon), propafenone (Rythmol), ranitidine (Zantac), ritonavir (Norvir), sertraline (Zoloft), telithromycin (Ketek), verapamil (Isoptin, Covera-HS), venlafaxine (Effexor), and Echinacea.

Patients Choice Laboratories

CYP2D6 (continued)

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Patients Choice Laboratories

CYP3A4 & CYP3A5

Clinical Utility

The cytochrome P450 3A4 and 3A5 (CYP3A4 and CYP3A5) account for 40-80% of total CYP in human liver and intestine, respectively. Most importantly, CYP3A enzymes metabolize 50% of commonly used drugs. CYP3A4 and CYP3A5 enzymes have overlapping substrate specificity, and the contribution of CYP3A5 in the overall metabolism is smaller than the one for CYP3A4. The overall CYP3A metabolism status is expected to affect drugs that have a narrow therapeutic index.

Assay Interpretation

A limited number of variants identified within the CYP3A4 and CYP3A5 genes have been associated with significant alterations in enzyme activity and subsequent variability in therapeutic response. For CYP3A5, individuals with the less prevalent “normal metabolizer phenotype” may metabolize drugs faster than those with the more common “poor metabolizer phenotype”. This may result in increased toxicity or loss of efficacy.

The CYP3A4*1B variant is the most studied, and results in an enzyme with a moderately decreased activity. It occurs in 50% of African-Americans, 3-5% of Caucasians, and <1% of Asians. The CYP3A4*2, *3, *12, and *17 are also considered decreased activity alleles. Recently, the CYP3A4 *22 allele has been characterized as a decreased function allele that can be clinically relevant (associated with a decreased clearance of certain substrates). The genotype-phenotype relationship for CYP3A4 is not well established, and individuals are predicted to have a CYP3A4 normal or intermediate metabolic capacity.

The reference range for CYP3A4 metabolic status is CYP3A4 *1/ *1, which is consistent with a normal metabolizer.

The CYP3A5*3 variant results in an enzyme with no activity, and is the most common variant in the general population. The CYP3A5*3B, *6 and *7 are also null alleles resulting in no enzyme activity. The functional effects of the CYP3A5 alleles *2, *4, *5 *8, and *9 are not well established. The CYP3A5 *1 allele produces an active enzyme, and is found in 5% of Caucasians, 20% of Asians, and 15-50% of Africans. Individuals with two CYP3A5 inactive alleles are classified as poor metabolizers. Individuals carrying at least one copy of a CYP3A5 active allele are normal or intermediate metabolizers. CYP3A5 poor metabolizers represent 50% of Asians and 90% of Caucasians.

The reference range for CYP3A5 metabolic status is CYP3A5 *1/ *1, which is consistent with a normal metabolizer. This genotype is the least prevalent in Caucasians and Asians.

Clinical Implications

CYP3A4 and CYP3A5 genotypes can help identify patients with high or low overall CYP3A activity. Although these two enzymes metabolize many drugs, the response of only a few (such as narrow therapeutic index drugs) is expected to change significantly by genetic polymorphisms. Fentanyl (Duragesic) is a narrow therapeutic drug that is mainly metabolized by CYP3A. There is limited evidence suggesting that the response to this drug is altered in individuals with abnormal CYP3A activity.

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CYP3A4 & CYP3A5 (continued)

The following drugs used in pain management and various psychiatric conditions are metabolized extensively by CYP3A: fentanyl (Duragesic), oxycodone (Oxycontin), buprenorphine (Suboxone), carbamazepine (Tegretol), quetiapine (Seroquel), ziprasidone (Geodon), alprazolam (Xanax), midazolam (Versed), triazolam (Halcion), nefazodone (Serzone), trazodone (Oleptro), vilazodone (Vibryd), zaleplon (Sonata), and zolpidem (Ambien). CYP3A contributes to a small extent in the elimination of methadone (Dolophine).
Within the major therapeutic classes used in cardiovascular conditions, the following drugs are substantially metabolized by CYP3A: atorvastatin (Lipitor), simvastatin (Zocor), lovastatin (Mevacor), nifedipine (Procardia), verapamil (Verelan), nicardipine (Cardene), felodipine (Plendil), nisoldipine (Sular), clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), cilostazol (Pletal), amiodarone (Cordarone), quinidine (Qualaquin), disopyramide (Norpace), losartan (Cozaar), rivaroxaban (Xarelto), and apixaban (Eliquis).
CYP3A metabolism is highly sensitive to inhibition and induction when a patient is taking multiple drugs. In this case, occurrence of drug-drug interactions can have profound effects on the pharmacokinetics, as well as the responses and safety profiles of many CYP3A drug substrates.

Inhibitors
Some known **strong** CYP3A inhibitors include: ketoconazole (Nizoral), itraconazole (Sporanox), posaconazole (Noxafil), voriconazole (Vfend), clarithromycin (Biaxin), telithromycin (Ketek), troleandomycin (TAO), conivaptan (Vaprisol), nefazodone (Serzone), ritonavir (Norvir), saquinavir (Invirase), lopinavir, (Kaletra), nelfinavir (viracept), tipranavir (aptivus), boceprevir (Victrelis), telaprevir (Incivek), grapefruit juice (high dose) and idelalisib (Zydelig).
Some known **moderate** CYP3A inhibitors include: amprenavir (agenerase), aprepitant (Emend), atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Lexiva), erythromycin (Eryc), ciprofloxacin (Cipro), diltiazem (cardizem), verapamil (Isoptin, Covera-HS), fluconazole (Diflucan), imatinib (Gleevec), quinupristin/dalfopristin (Synercid), and grapefruit juice (low dose).
Some known **weak** CYP3A inhibitors include: amiodarone (Cordarone), amlodipine (Norvasc), atorvastatin (Lipitor), bicalutamide (Casodex), cilostazol (Pletal), fluvoxamine (Luvox), fluoxetine (Prozac), sertraline, cimetidine, ranitidine (Zantac), ranolazine (Ranexa), and ticagrelor (Brilinta).

Inducers
Some known **strong** CYP3A inducers include: carbamazepine (Tegretol), enzalutamide (Xtandi), fosphenytoin (Cerebyx), phenytoin (Dilantin), phenobarbital, primidone (Mysoline), rifampin (Rifadin), rifapentine (Priftin), and St. John's wort.
Some known **moderate** CYP3A inducers include: artemether (Coartem), bosentan (Tracleer), dabrafenib (Tafinlar), efavirenz (Sustiva), etravirine (Intelence), modafinil (Provigil), nafcillin (Unipen), rifabutin (Mycobutin), and nevirapine (Viramune).
Some known **weak** CYP3A inducers include: fosamprenavir (Lexiva), aprepitant (Emend), clobazam (Onfi), Echinacea, pioglitazone (Actos), dexamethasone (Decadron), oxcarbazepine (Trileptal), methylprednisolone (Medrol), and rufinamide (Banzel).

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CYP3A4 & CYP3A5 (continued)

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Factor II

Clinical Utility

Clotting Factor II, or prothrombin, is a vitamin K–dependent proenzyme that functions in the blood coagulation cascade. It is a precursor to thrombin, which converts fibrinogen into fibrin, which in turn strengthens a protective clot.

The prothrombin 20210G>A mutation in the Factor II gene results in increased levels of plasma prothrombin and a concurrent increased risk for thrombosis. Prothrombin-related thrombophilia is characterized by venous thromboembolism (VTE). This risk of thrombosis is also increased when mutations exist for other coagulation factors such as Factor V Leiden, or in presence of non-genetic risk factors such as obesity, injury, surgery, smoking, pregnancy, use of estrogen-containing contraceptives, or replacement therapy. The clinical expression of Factor II thrombophilia is variable, and many individuals may never develop thrombosis, while others may experience venous thrombotic events or pregnancy complications.

Assay Interpretation

The Factor II thrombophilia is the second most common inherited risk factor for thrombosis. The Factor II 20210G>A mutation is associated with a hypercoagulable state. In the United States, the prevalence of this mutation is 1.1% in Caucasians and Hispanics and 0.3% in African-Americans. The prevalence of heterozygosity is 2%-5% in whites and 0%-0.3% in African-Americans. The prevalence of homozygosity is approximately one in 10,000.

The reference range for Factor II 20210G>A mutation is Factor II 20210GG.

Clinical Implications

The Factor II 20210G>A mutation is associated with an elevation of plasma prothrombin levels to about 30% above normal in heterozygotes and to 70% above normal in homozygotes. Heterozygotes are at a 2- to 5-fold increased risk of an initial VTE. The risk for VTE in Factor II 20210G>A homozygotes is not well defined, but is presumed to be higher than in 20210G>A heterozygotes. Factor II 20210G>A homozygotes tend to develop thrombosis more frequently and at a younger age. Individuals who are doubly heterozygotes for Factor V Leiden and Factor II 20210G>A have an estimated 20-fold increased risk when compared to individuals without either mutation, suggesting a multiplicative elevation in risk. Certain circumstantial factors can increase the risk of thrombosis, and include: travel, central venous catheter use, pregnancy, oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), organ transplantation, injury, age, and surgery.

Patients Choice Laboratories

Factor II (continued)

Management Guidelines

Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment. The first acute thrombosis should be treated according to standard guidelines. Following a first acute thrombotic event, long-term anticoagulation can be considered in homozygotes or in individuals with multiple thrombophilic disorders. In the absence of a history of thrombosis, anticoagulation is not routinely recommended for asymptomatic individuals who are heterozygotes. In asymptomatic individuals with a history of thrombosis and with one or two Factor II 20210G>A mutation(s), a short course of prophylactic anticoagulation may be considered in high-risk settings such as surgery, pregnancy, or prolonged immobilization. 2- Estrogen-containing contraceptives and replacement therapies: Heterozygote or homozygous women for Factor II 20210G>A mutation and with a history of VTE should avoid estrogen contraception and replacement therapy. Asymptomatic women who are heterozygote for Factor II 20210G>A mutation should be counseled on the risks of estrogen contraception and replacement therapy. Asymptomatic heterozygote women electing to use oral contraceptives should avoid third-generation formulations because of their higher thrombotic risk. Women homozygous for the Factor II 20210G>A mutation with or without prior VTE should avoid estrogen contraception and replacement therapy.

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Patients Choice Laboratories

Factor V Leiden

Clinical Utility

The Factor V gene encodes the coagulation Factor V. In normal conditions, Factor V is inactivated during the clotting process by the activated protein C (APC). In subjects with Factor V Leiden thrombophilia, a mutation in the gene produces a Factor V that cannot be inactivated normally by APC. As a result, the clotting process remains active longer than usual, leading to more thrombin generation. This hypercoagulable state is also increased when other mutations exist in other coagulation factors such as Factor II, or in the presence of non-genetic risk factors such as obesity, injury, surgery, smoking, pregnancy, or use of estrogen-containing contraceptive or estrogen containing replacement therapy. The clinical expression of Factor V Leiden thrombophilia is variable. Many individuals may never develop thrombosis, while others may experience venous thrombotic events or pregnancy complications. Certain circumstantial factors can increase the risk of thrombosis, and include: travel, central venous catheter use, pregnancy, oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), organ transplantation, injury, age, and surgery. These factors are associated with the first thrombotic episode in at least 50% of individuals with a Factor V Leiden mutation.

Assay Interpretation

Factor V Leiden is the most common known inherited risk factor for thrombosis. Factor V Leiden refers to a base change (from G to A at position 1691) in the gene. As a result, Factor V is inactivated to a lesser extent and persists for longer in the circulation, leading to hypercoagulability. In the US, the frequency of the Factor V Leiden mutation varies by ethnicity, with about 5% of Caucasians, 2% of Hispanics, and 1% of African-Americans having one mutation. Only 1 in 5000 individuals have two Factor V Leiden mutations.

The reference range for Factor V Leiden mutation is Factor V 1691 GG.

Clinical Implications

About 1 in 1000 people in the U.S. experience a first venous thromboembolism (VTE) each year. VTE is caused by inherited and environmental factors, and while the Factor V Leiden mutation is present in only 15-20% of individuals with a first VTE, it is found in 50% of individuals with recurrent VTE or estrogen-related thrombosis. The risk for VTE is increased 3- to 8-fold in Factor V Leiden heterozygotes and 9- to 80-fold in homozygotes. This risk is increased further if other genetic or circumstantial factors are present. A heterozygote individual for both the Factor V Leiden and the Factor II (compound heterozygote) has an even greater risk of VTE (20-fold) than an individual with a mutation in only one factor. This illustrates the multiplicative effect of these two factors on overall thrombotic risk.

Patients Choice Laboratories

Factor V Leiden (continued)

Management Guidelines

Decisions regarding prophylactic anticoagulation should be based on a risk/benefit assessment. The first acute thrombosis should be treated according to standard guidelines. Following a first acute thrombotic event, long-term anticoagulation can be considered in individuals homozygous for the Factor V Leiden mutation or with multiple thrombophilic disorders. In the absence of a history of thrombosis, anticoagulation is not routinely recommended for asymptomatic individuals who are heterozygote for the Factor V Leiden allele, because the 1-3%/year risk for major bleeding from anticoagulation is greater than the estimated < 1%/year risk for thrombosis. In heterozygote individuals, a short course of prophylactic anticoagulation during exposure to hemostatic stresses may be considered. These situations include: surgery, pregnancy, and prolonged immobilization.
2- Estrogen-containing contraceptives and replacement therapies: women with one or two Factor V Leiden mutations and a history of VTE should avoid estrogen contraception and replacement therapy. Asymptomatic women who are heterozygote for Factor V Leiden should be counseled on the risks of estrogen contraception and replacement therapy. Asymptomatic women electing to use oral contraceptives should avoid third-generation formulations because of their higher thrombotic risk. Homozygote women with or without prior VTE should avoid estrogen contraception and replacement therapy.

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Patients Choice Laboratories

GRIK4

Clinical Utility

The GRIK4 gene encodes the kainic acid-type glutamate receptor, a protein that belongs to the glutamate-gated ionic channel family. Glutamate functions as the major excitatory neurotransmitter in the central nervous system, and a disturbance in the glutamate system is found during depression. Limited evidence suggests that genetic variations in GRIK4 are associated with certain psychiatric conditions such as bipolar affective disorder and schizophrenia. A genetic variant rs1954787 located in the 3' region of the first intron of the GRIK4 gene has also been found to be predictive of antidepressant response and remission.

Assay Interpretation

Preliminary studies in depressive patients suggest an association between the presence of the rs1954787 (c.83-10039T>C) genetic marker in the GRIK4 gene and the response to citalopram. The C allele of rs1954787 variant was more frequent in depressive patients who responded to citalopram treatment than in non-responders. In a group of "Caucasian" patients, homozygous carriers of the C-allele had a 10% reduction of nonresponse relative to TT homozygote carriers (wild-type). The C allele occurs in 50% of Caucasians.

The reference ranges for the c.83-10039T>C (rs19544787) mutation of GRIK4 is TT.

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Patients Choice Laboratories

MTHFR

Clinical Utility

Methylenetetrahydrofolate reductase (MTHFR) is involved in folate metabolism and is essential for the remethylation of homocysteine. Two common mutations in the MTHFR gene: 677C>T and 1298A> result in an enzyme with decreased activity, which is linked to increased plasma homocysteine levels (i.e., hyperhomocysteinemia). Mild to moderate hyperhomocysteinemia has been identified as a risk factor for venous thromboembolism and other cardiovascular diseases such as coronary heart disease and stroke. Other conditions in which hyperhomocysteinemia is found include recurrent pregnancy loss, placental infarction, and birth defects. However, the causal role of MTHFR mutations in these conditions is not well established.

Assay Interpretation

The approximate minor allele frequencies for most populations are 30-50% for the MTHFR 1298 A variant and 18-30% for the MTHFR 677 T variant. Heterozygotes and homozygotes for the MTHFR 677C>T mutation have 60% and 30% of normal MTHFR activity, respectively. Heterozygotes and homozygotes for the MTHFR 1298A>C mutation have 80% and 60% of normal MTHFR activity, respectively.

The reference ranges for both mutations of MTHFR are 677CC and 1298AA. This is consistent with a normal MTHFR activity.

Clinical Implications

The MTHFR assay provides information about potential causes of elevated homocysteine, and approaches for addressing it.

- Homozygosity for the MTHFR 677C>T mutation (individual with MTHFR 677 TT genotype) predisposes for hyperhomocysteinemia (especially during times of folate insufficiency) and an increase in premature cardiovascular disease. Measurement of total plasma homocysteine is informative in this case.
- Compound heterozygosity (individual with MTHFR 677 CT and MTHFR 1298AC genotypes) is not associated with an increase in plasma homocysteine level. Measurement of total plasma homocysteine is informative in this case.
- Homozygosity or heterozygosity for the MTHFR 1298A>C mutation alone (individual with MTHFR 1298AC or MTHFR 1298CC genotypes) does not increase homocysteine levels. Similarly, heterozygosity for the MTHFR 677C>T mutation alone (individuals with MTHFR 677 CT genotype) does not increase homocysteine levels.
- Hyperhomocysteinemia related to MTHFR genetic mutations has been associated with neural tube defects, stillbirths, and recurrent pregnancy loss. However, because hyperhomocysteinemia is multifactorial, involving a combination of other genetic, physiologic, and environmental factors, the presence of MTHFR mutations in an individual should not be used alone to predict the risk of these conditions.
- MTHFR in depression: Low MTHFR activity may exacerbate folate deficiency in patients with depression and may increase the risk of depressive relapse or delay the response to antidepressants. Testing for homocysteine levels and serum folate levels are recommended in patients with depression. Methylfolate may substantially benefit patients with hyperhomocysteinemia and depression when used as an adjuvant to antidepressant medication.
- The response to methotrexate, a drug used in cancer and autoimmune diseases, is affected by the presence of MTHFR genetic mutations. Methotrexate intolerance is observed in individuals that are heterozygous or homozygous for the MTHFR 677C>T mutation.

Patients Choice Laboratories

MTHFR (continued)

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OPRM1

Clinical Utility

"Mu" opioid receptors are the most important site of action of opioid drugs. Single polymorphisms in the human mu-opioid receptor (OPRM1) have been investigated for their role in human nociception, opiate efficacy, and addiction.

Assay Interpretation

The variant mostly studied is a single substitution at position 118, from an adenine to a guanine (A118G). This variant reduces the OPRM1 receptor signaling efficiency induced by exogenous opioids. Reduced OPRM1 mRNA expression levels were observed in carriers of the G variant. The variant allele (G) is present in 7-15% of Caucasians, 1.5% of African-Americans, and up to 48.5% of Asians. The major interest of this particular SNP is due to its pharmacological and physiological consequences; however the exact mechanism by which the altered receptor influences opioid analgesia is still unresolved. The presence of the G allele seems to reduce the effect of exogenous agonists but increase the effects of exogenous antagonists.

The reference range for the A118G SNP is A118G AA, and is associated with a normal OPRM1 receptor signaling efficiency.

Clinical Implications

The presence of the G allele (A118G) seems to be associated with pain sensitivity as well as opioid dosage requirements. But only weak evidence of these associations is available to date. It is suggested that patients carrying the G allele report higher intensity pain. In terms of drug response, patients with the G allele have a favorable response to the anti-addictive drug naltrexone. Several studies conducted in post-surgical settings or in cancer analgesia showed that G allele carriers require slightly higher doses of morphine or fentanyl. This association still needs to be confirmed in larger studies and does not hold in other situations such as labor pain.

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OPRM1 (continued)

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Patients Choice Laboratories

SLCO1B1

Clinical Utility

The SLCO1B1 gene encodes a liver-specific transporter involved in the removal of endogenous compounds (bile acids, bilirubin) and drugs such as statins from the blood to the liver. Some variants of the SLCO1B1 gene result in a low-functioning protein, which impairs statin clearance, and may lead to an increased risk of muscle pain, tenderness, or weakness, called myopathy.
Certain medications can potently inhibit SLCO1B1, causing clinically significant drug interactions.

Assay Interpretation

The functional SLCO1B1 activity (phenotype) is estimated from the genotype at 521T>C. Non-carriers of the 521T>C variant are predicted to have a SLCO1B1 normal function, those with one copy of the 521T>C variant have a SLCO1B1 decreased function, and those with two copies of the variant have poor SLCO1B1 function.
There are several variants of the SLCO1B1 that define over 15 alleles. One relatively common variant 521T>C (rs4149056) results in SLCO1B1 decreased function, which affects the transport of drug substrates such as statins. This variant is present alone on the *5 allele and in presence with another variant (388A>G; rs2306283) on the *15 allele. Both alleles are low-activity alleles (reduced hepatic uptake), and have a combined frequency of 15-20% in Caucasians, 10-15% in Asians, and 2% in sub-Saharan Africans and African-Americans.
The reference range for the 521T>C mutation of SLCO1B1 is 521 TT. This is consistent with normal SLCO1B1 function.

Clinical Implications

All statins are substrates of SLCO1B1, but the effects of SLCO1B1 genetic polymorphism differ between individual statins. The effect is the largest on simvastatin, and individuals with the 521T>C variant have increased levels of the active simvastatin form. The variant is strongly associated with simvastatin-induced myopathy (with or without CK elevation), especially with high-dose simvastatin therapy. More than 60% of the myopathy cases could be attributed to its presence. The clinical spectrum of statin-induced myopathy ranges from a mild and common myalgia to a life-threatening and rare rhabdomyolysis. Other known risk factors for statin-induced myopathy include a high-statin dose, interacting drugs that raise statin levels, age, hypothyroidism, and certain inherited muscle disorders. At therapeutic doses, the apparent sensitivity levels of the five statins to the presence of the 521T>C variant are simvastatin>pitavastatin>atorvastatin>pravastatin>rosuvastatin. Carriers of the 521 T>C variant should avoid high-dose simvastatin therapy. These patients can take other statins, such as atorvastatin, pitavastatin, rosuvastatin, or pravastatin, but at reduced doses. Fluvastatin is not affected by the 521 T>C variant and could therefore be considered a suitable alternative.
Other drugs that are substrates of SLCO1B1 transporter include enalapril, olmesartan, valsartan, atrasentan, repaglinide, nateglinide, methotrexate, and bosentan. However, there is insufficient evidence documenting the impact of the 521 T>C variant on the systemic exposure and safety profile of these drugs.

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SLCO1B1 (continued)

Inhibitors

Inhibitors of SLCO1B1 transporter may alter its activity and result in increased levels of drug substrates. These include gemfibrozil, cyclosporine, clarithromycin, protease inhibitors, simeprevir, teriflunomide, boceprevir, telaprevir, and eltrombopag.

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VKORC1

Clinical Utility

The Vitamin K epoxide reductase complex, subunit 1 (VKORC1) is the target of anticoagulants. This enzyme is the rate-limiting step in the vitamin K cycle. Mutations in the VKORC1 gene results in variable expression levels of the VKORC1 enzyme and altered sensitivities towards anticoagulants. VKORC1 genotype defines three levels of clinical phenotype: high, moderate, and low sensitivity phenotypes towards warfarin (a widely used anticoagulant). Therefore, VKORC1 variant testing is usually used in conjunction with CYP2C9 variant testing to optimize warfarin dosing and minimize the risks of bleeding or thrombotic complications.

Assay Interpretation

The clinically relevant variants in the VKORC1 gene are in strong linkage disequilibrium, meaning that some allele combinations occur more frequently than others. These combinations are referred to as haplotypes. The eight variants analyzed by the VKORC1 assay are used to define three haplotypes that are associated with different warfarin sensitivities, as shown in the following table.

Clinical Implications

The -1639G>A is the common variant seen in the Caucasian populations, and is believed to be the causative agent for the low-dose warfarin requirement phenotype. The G>A mutation results in a decreased expression of VKORC1. The 358C>T (found in 21% of African-Americans) and 3730G>A variants are associated with high warfarin dose requirements.

When CYP2C9 and VKORC1 genotypes are combined with other demographic (age, weight, height), clinical (disease, co-medications), and environmental (smoking) factors, they account for 50% of warfarin dose variation between individuals.

The FDA changed the warfarin label to help clinicians offer genotype-guided warfarin therapy for their patients.

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