

Gene	Genotype	Phenotype
ANKK1/DRD2	DRD2:Taq1A A/G	Altered DRD2 function
Apolipoprotein E	ε3/ε3	No Increased Risk of Hyperlipidemia/Atherosclerotic Vascular Disease
COMT	Val158Met A/A	Low COMT Activity
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility
CYP2B6	*1/*6	Intermediate Metabolizer
CYP2C19	*1/*1	Normal Metabolizer
CYP2C9	*1/*1	Normal Metabolizer
CYP2D6	*1/*1 XN	Ultra-Rapid Metabolizer
CYP3A4	*1/*1	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
Factor II	20210G>A GG	Normal Thrombosis Risk
Factor V Leiden	1691G>A GG	Normal Thrombosis Risk
MTHFR	1298A>C AC	Reduced MTHFR Activity
MTHFR	677C>T CT	Reduced MTHFR Activity
OPRM1	A118G A/A	Normal OPRM1 Function
SLCO1B1	521T>C T/T	Normal Function
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity

Risk Management



Antipsychotic-Induced Tardive Dyskinesia

Moderate Risk of Antipsychotic-Induced Tardive Dyskinesia

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

The genotype results predict that the patient may have reduced dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has moderate risk for tardive dyskinesia when treated with antipsychotics.

Monitor the patient for any signs of tardive dyskinesia.



Antipsychotic-Induced Hyperprolactinemia

Moderate Risk of Antipsychotic-induced Hyperprolactinemia

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

The genotype results predict that the patient may have reduced dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has moderate risk of hyperprolactinemia when treated with antipsychotics.

Monitor patient closely for signs of hyperprolactinemia. An evaluation of the risk-benefit profile of the antipsychotic medication may be required.



Antipsychotic-Induced Weight Gain

Moderate Risk of Antipsychotic-Induced Weight Gain

The patient carries one copy of the Taq1A variant (heterozygous for the A1 allele).

The genotype results predict that the patient may have reduced dopamine receptor DRD2 density and hypodopaminergic functioning. The patient has moderate risk for weight gain when treated with antipsychotics.

Monitor patient closely for signs of weight gain.



Hyperlipidemia/Atherosclerotic Cardiovascular Disease

No increased risk of hyperlipidemia/atherosclerotic vascular disease

The patient is negative for the APOE 388 T>C (Arg112Cys) and 526 C>T (Cys158Arg) mutations. The patient's genotype is wild-type, which is the most common genotype in the general population (frequency: >60%).

A patient with wild-type genotype does not have a defect in the apolipoprotein E (APOE), which is an integral structure of lipoprotein particles that have critical roles in blood lipid metabolism and transport. Defects in APOE can increase a person's risk for developing atherosclerosis and cardiovascular disease.

No action is needed when a patient is normolipidemic.



Hyperhomocysteinemia - Depression

No Increased Risk of Hyperhomocysteinemia

The patient carries one MTHFR C677T mutation (heterozygous). MTHFR enzyme activity is reduced (60% of normal activity).

Patients diagnosed with depression often have low folate levels and homocysteine is a highly sensitive marker of folate status. Functional folate deficiency is indicated by elevated homocysteine. The patient's small reduction in MTHFR activity is not a risk factor for hyperhomocysteinemia.

Patients diagnosed with depression: as lower folate levels are associated with poorer antidepressant response, and baseline levels of folate within the normal range predict antidepressant response, testing for homocysteine levels and serum folate levels may be informative for this patient before prescribing methylfolate as an antidepressant-augmenting agent.



Thrombophilia

No Increased Risk of Thrombosis

The patient does not carry the Factor V Leiden G1691A mutation or Factor II G20210A mutation (wild-type).

The patient's risk of thrombosis is not increased (average risk of clotting is about 1 in 1000 for anyone in a year). However, because this test cannot find all of the inherited reasons for abnormal clotting, other factors may affect this risk assessment.

Unless other genetic and/or circumstantial risk factors are present (e.g., smoking or obesity...), estrogen-containing contraceptive and hormone replacement therapy can be used by the patient.



Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient carries one MTHFR C677T mutation and one A1298C mutation (compound heterozygous). MTHFR enzyme activity is reduced.

The patient's reduced MTHFR activity is not a risk factor for hyperhomocysteinemia. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).

Testing total plasma homocysteine level may be beneficial. Hyperhomocysteinemia can be treated with nutritional supplementation.

Guidance Levels

-  Based upon the patient's genotype, a medication has potentially reduced efficacy or increased toxicity or the patient has an increased risk for the indicated condition.
-  Based upon the patient's genotype, guidelines exist for adjusting dosage or increased vigilance or the patient has a moderate risk for the indicated condition.
-  Based on this patient's genotype, the medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.

Evidence Levels

Actionable - Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA, EMEA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as new knowledge arises.

Informative - There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

Potentially Impacted Medications			
Category	Standard Precautions	Use With Caution	Consider Alternatives
5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia	Dutasteride (Avodart) Finasteride (Proscar)		
Alpha-Blockers for Benign Prostatic Hyperplasia	Alfuzosin (UroXtral) Doxazosin (Cardura) Silodosin (Rapaflo) Tamsulosin (Flomax) Terazosin (Hytrin)		
Angiotensin II Receptor Antagonists	Azilsartan (Edarbi, Edarbyclor) Candesartan (Atacand) Eprosartan (Teveten) Irbesartan (Avapro) Losartan (Cozaar, Hyzaar) Olmesartan (Benicar) Telmisartan (Micardis) Valsartan (Diovan, Entresto)		
Antiaddictives		Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave) Naltrexone (Vivitrol, Contrave)	
Anti-ADHD Agents	Guanfacine (Intuniv)	Amphetamine (Adderall) Clonidine (Kapvay) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine) Lisdexamfetamine (Vyvanse) Methylphenidate (Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER)	Atomoxetine (Strattera)
Antianginal Agents	Ranolazine (Ranexa)		
Antiarrhythmics		Mexiletine (Mexitil) Propafenone (Rythmol)	Flecainide (Tambocor)
Anticoagulants	Apixaban (Eliquis) Dabigatran Etexilate (Pradaxa) Edoxaban (Savaysa) Fondaparinux (Arixtra) Rivaroxaban (Xarelto)	Warfarin (Coumadin)	

Potentially Impacted Medications

Category	Standard Precautions	Use With Caution	Consider Alternatives
Anticonvulsants	Brivaracetam (Briviact) Carbamazepine (Tegretol, Carbatrol, Eptol) Eslicarbazepine (Aptiom) Ethosuximide (Zarontin) Ezogabine (Potiga) Felbamate (Felbatol) Fosphenytoin (Cerebyx) Gabapentin (Neurontin) Lacosamide (Vimpat) Lamotrigine (Lamictal) Levetiracetam (Keppra) Oxcarbazepine (Trileptal, Oxtellar XR) Perampanel (Fycompa) Phenobarbital (Luminal) Phenytoin (Dilantin) Pregabalin (Lyrica) Primidone (Mysoline) Rufinamide (Banzel) Tiagabine (Gabitril) Topiramate (Topamax) Valproic Acid (Depakote, Depakene) Vigabatrin (Sabril) Zonisamide (Zonegran)		
Antidementia Agents	Galantamine (Razadyne) Memantine (Namenda)	Donepezil (Aricept)	
Antidepressants	Citalopram (Celexa) Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Escitalopram (Lexapro) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Nefazodone (Serzone) Sertraline (Zoloft) Trazodone (Oleptro) Vilazodone (Viibryd) Vortioxetine (Trintellix)	Amoxapine (Amoxapine) Fluvoxamine (Luvox) Maprotiline (Ludiomil)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Imipramine (Tofranil) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Protriptyline (Vivactil) Trimipramine (Surmontil) Venlafaxine (Effexor)
Antiemetics	Aprepitant (Emend-oral) Dronabinol (Marinol) Fosaprepitant (Emend-i.v) Granisetron (Sancuso, Sustol) Metoclopramide (Reglan) Rolapitant (Varubi)	Dolasetron (Anzemet) Netupitant-Palonosetron (Akynzeo) Palonosetron (Aloxi)	Ondansetron (Zofran, Zuplenz)
Antifolates		Methotrexate (Trexall)	

Potentially Impacted Medications

Category	Standard Precautions	Use With Caution	Consider Alternatives
Antifungals	Amphotericin B (AmBisome, Abelcet) Anidulafungin (Eraxis) Caspofungin (Cancidas) Fluconazole (Diflucan) Isavuconazonium (Cresemba) Itraconazole (Sporanox) Micafungin (Mycamine) Posaconazole (Noxafil) Voriconazole (Vfend)		
Anti-HIV Agents	Dolutegravir (Tivicay, Triumeq) Raltegravir (Isentress, Dutrebis)		
Anti-Hyperuricemics and Anti-Gout Agents	Colchicine (Mitigare) Febuxostat (Uloric) Lesinurad (Zurampic)		
Antimalarials	Proguanil (Malarone)		
Antiplatelets	Clopidogrel (Plavix) Prasugrel (Effient) Ticagrelor (Brilinta) Vorapaxar (Zontivity)		
Antipsychotics	Aripiprazole (Abilify, Aristada) Asenapine (Saphris) Brexipiprazole (Rexulti) Cariprazine (Vraylar) Iloperidone (Fanapt) Loxapine (Loxitane, Adasuve) Lurasidone (Latuda) Paliperidone (Invega) Pimavanserin (Nuplazid) Quetiapine (Seroquel) Thioridazine (Mellaril) Thiothixene (Navane) Trifluoperazine (Stelazine) Ziprasidone (Geodon)	Chlorpromazine (Thorazine) Clozapine (Clozaril) Fluphenazine (Prolixin) Olanzapine (Zyprexa) Perphenazine (Trilafon) Pimozide (Orap) Tetrabenazine (Xenazine)	Haloperidol (Haldol) Risperidone (Risperdal)
Antispasmodics for Overactive Bladder	Darifenacin (Enablex) Fesoterodine (Toviaz) Mirabegron (Myrbetriq) Oxybutynin (Ditropan) Solifenacin (Vesicare) Tolterodine (Detrol) Trospium (Sanctura)		
Benzodiazepines	Alprazolam (Xanax) Clobazam (Onfi) Clonazepam (Klonopin) Diazepam (Valium)		

Potentially Impacted Medications

Category	Standard Precautions	Use With Caution	Consider Alternatives
Beta Blockers	Atenolol (Tenormin) Bisoprolol (Zebeta) Carvedilol (Coreg) Labetalol (Normodyne, Trandate) Nebivolol (Bystolic) Propranolol (Inderal) Timolol (Timoptic)		Metoprolol (Lopressor)
Diuretics	Torsemide (Demadex)		
Fibromyalgia Agents	Milnacipran (Savella)		
Immunomodulators	Apremilast (Otezla) Leflunomide (Arava) Tofacitinib (Xeljanz)		
Immunosuppressants	Tacrolimus (Prograf)		
Meglitinides	Nateglinide (Starlix) Repaglinide (Prandin, Prandimet)		
Muscle Relaxants	Carisoprodol (Soma) Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin) Methocarbamol (Robaxin)	Tizanidine (Zanaflex)	
NSAIDs	Celecoxib (Celebrex) Diclofenac (Voltaren) Flurbiprofen (Ansaid) Ibuprofen (Advil, Motrin) Indomethacin (Indocin) Ketoprofen (Orudis) Ketorolac (Toradol) Meloxicam (Mobic) Nabumetone (Relafen) Naproxen (Aleve) Piroxicam (Feldene) Sulindac (Clinoril)		
Opioids	Alfentanil (Alfenta) Buprenorphine (Butrans, Buprenex) Fentanyl (Actiq) Hydromorphone (Dilaudid, Exalgo) Levorphanol (Levo Dromoran) Meperidine (Demerol) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Dihydrocodeine (Synalgos-DC) Hydrocodone (Vicodin) Methadone (Dolophine) Morphine (MS Contin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)
Other Neurological Agents	Dextromethorphan / Quinidine (Nuedexta) Flibanserin (Addyi)		

Potentially Impacted Medications

Category	Standard Precautions	Use With Caution	Consider Alternatives
Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil (Stendra) Sildenafil (Viagra) Tadalafil (Cialis) Vardenafil (Levitra)		
Proton Pump Inhibitors	Dexlansoprazole (Dexilant, Kapidex) Esomeprazole (Nexium) Lansoprazole (Prevacid) Omeprazole (Prilosec) Pantoprazole (Protonix) Rabeprazole (Aciphex)		
Statins	Atorvastatin (Lipitor) Fluvastatin (Lescol) Lovastatin (Mevacor, Altoprev, Advicor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor) Simvastatin (Zocor)		
Sulfonylureas	Chlorpropamide (Diabinese) Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase) Tolbutamide (Orinase)		

Dosing Guidance

-  **Amitriptyline (Elavil)**
Non-Response to Amitriptyline (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
Consider an alternative drug, or prescribe amitriptyline at an increased dose and monitor the plasma concentration of amitriptyline and metabolites.
-  **Amoxapine (Amoxapine)**
Possible Non-Response to Amoxapine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**
Like other tricyclic and tetracyclic antidepressants, amoxapine is metabolized by CYP2D6. However, the overall contribution of this enzyme in the metabolism of this drug is not well documented. Patients with increased CYP2D6 function may metabolize amoxapine more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations. There are no established dosing adjustments for patients with increased CYP2D6 function; therapy must be initiated cautiously and adjusted according to the patient's response.
-  **Amphetamine (Adderall)**
Poor Response to Amphetamine salts (COMT Val158Met A/A Low COMT Activity) Evidence Level: **Informative**
The patient's genotype result predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, amphetamines should be administered at the lowest effective dose, and dosage should be individually adjusted.
-  **Atomoxetine (Strattera)**
Non-Response to Atomoxetine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**
The patient may fail to achieve adequate plasma levels of atomoxetine if the drug is prescribed at standard recommended doses. Consider prescribing atomoxetine with careful titration and monitoring for reduced efficacy. There is insufficient data to calculate dose adjustment. Or consider an alternative medication.
-  **Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)**
Decreased Response to Bupropion for Smoking Cessation (ANKK1 DRD2:Taq1A A/G Altered DRD2 function) Evidence Level: **Informative**
Smoking Cessation: The patient's genotype result is associated with a positive response to nicotine replacement therapy and a lesser response to bupropion treatment.
-  **Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)**
Possibly Decreased Response to Bupropion (CYP2B6 *1/*6 Intermediate Metabolizer) Evidence Level: **Informative**
Bupropion is metabolized to its active metabolite hydroxybupropion by CYP2B6. This metabolite contributes to the therapeutic effects of bupropion when used as a smoking cessation agent or as an antidepressant. Individuals who are CYP2B6 intermediate metabolizers may or may not have lower blood levels of hydroxybupropion which may or may not result in a reduced response to bupropion treatment. Bupropion can be prescribed at standard label-recommended dosage with careful monitoring of the patient's response. Therapeutic monitoring of hydroxybupropion levels may be considered to guide dosing adjustment.
-  **Chlorpromazine (Thorazine)**
Possible Non-Response to Chlorpromazine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**
Chlorpromazine is metabolized by CYP2D6, CYP3A4 and flavin-containing monooxygenases. Subjects with increased CYP2D6 function will metabolize chlorpromazine more rapidly which can result in sub-therapeutic drug concentrations. Consider a standard dose and adjust dosage according to the patient's tolerability and response. Higher doses may be necessary to achieve efficacy.
-  **Clomipramine (Anafranil)**
Non-Response to Clomipramine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
Consider an alternative drug, or prescribe clomipramine at an increased dose and monitor the plasma concentration of clomipramine and desmethylclomipramine.

-  **Clonidine (Kapvay)**
Possible Altered Response to Clonidine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**
Treatment with clonidine can cause dose related decreases in blood pressure and heart rate. Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Titrate Clonidine slowly in patients with a history of hypotension, and those with underlying conditions that may be worsened by hypotension and bradycardia.
-  **Clozapine (Clozaril)**
Non-Response to Clozapine (CYP1A2 *1A/*1F Normal Metabolizer - Higher Inducibility) Evidence Level: **Informative**
Smokers have a high risk for non-response at standard doses and may require higher doses. There is an association between high clozapine doses and the risk of seizures, and therefore careful monitoring is recommended during dosing adjustment. Smoking cessation will increase plasma drug levels, leading to adverse events. Therefore, therapeutic drug monitoring accompanied by dose reduction is recommended in patients who have quit smoking.
-  **Codeine (Codeine; Fioricet with Codeine)**
Increased Response to Codeine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
Codeine is converted into its active metabolite morphine by CYP2D6. Since this patient is an ultra-rapid metabolizer, greatly increased morphine levels are expected, and the patient is at high risk of toxicity when taking codeine. Avoid prescribing codeine, and consider an alternative opioid or a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: fentanyl, morphine, hydromorphone, oxycodone, and tapentadol.
-  **Desipramine (Norpramin)**
Non-Response to Desipramine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
Consider an alternative drug, or prescribe desipramine at increased dosage and observe the patient for decreased efficacy. Adjust dosage in response to desipramine and metabolites plasma concentrations and clinical response.
-  **Dexmethylphenidate (Focalin)**
Poor Response to Dexmethylphenidate (COMT Val158Met A/A Low COMT Activity) Evidence Level: **Informative**
The patient's genotype result predicts a reduced therapeutic response to dexmethylphenidate. Dosage should be individualized according to the needs and response of the patient. Therapy should be initiated in small doses, with gradual weekly increments.
-  **Dextroamphetamine (Dexedrine)**
Poor Response to Dextroamphetamine (COMT Val158Met A/A Low COMT Activity) Evidence Level: **Informative**
The patient's genotype result predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, dextroamphetamine should be administered at the lowest effective dose, and dosage should be individually adjusted.
-  **Dihydrocodeine (Synalgos-DC)**
Possible Altered Response to Dihydrocodeine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
Increased conversion of dihydrocodeine to the more active metabolite dihydromorphone is expected in CYP2D6 ultra-rapid metabolizers. This may result in an exaggerated response. Adequate pain relief can be achieved by decreasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 (i.e., morphine, oxycodone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if signs of overdose (excessive sleepiness, confusion, or shallow breathing) are reported.
-  **Dolasetron (Anzemet)**
Possible Altered Response to Dolasetron (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**
The reduction of dolasetron to its active metabolite hydrodolasetron is mediated by a carbonyl reductase. Hydrodolasetron is further eliminated by multiple routes, including renal excretion and by glucuronidation or hydroxylation by CYP2D6. Compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower hydroxydolasetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Dolasetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.



Donepezil (Aricept)

Possible Altered Response to Donepezil (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**

When compared to a normal metabolizer, a ultra-rapid metabolizers has a 24% increase in donepezil clearance. The clinical significance of this increase is not well documented. Consider using a standard dosing regimen and adjust dosage in response to clinical response and tolerability.



Doxepin (Silenor)

Non-Response to Doxepin (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug or increase doxepin dose by 100%. Adjust maintenance dose according to nordoxepin plasma concentrations.



Flecainide (Tambocor)

Altered Response to Flecainide (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

Titrate carefully and consider adjusting the dose in response to plasma concentration and ECG monitoring, OR consider an alternative drug. Examples of alternatives drugs not affected by CYP2D6 include: sotalol, disopyramide, quinidine, and amiodarone.



Fluphenazine (Prolixin)

Possible Non-response to Fluphenazine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**

Fluphenazine is metabolized by CYP2D6, CYP1A2 and other enzymes. **Patients with increased CYP2D6 function will metabolize fluphenazine more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations.** There are no established dosing adjustments for patients with increased CYP2D6 function therefore, therapy must be initiated cautiously with oral or parenteral fluphenazine hydrochloride. When the pharmacological effects and an appropriate dosage are apparent, an equivalent dose of fluphenazine decanoate (IM or SC) may be administered and subsequent dosage adjustments may be necessary.



Fluvoxamine (Luvox)

Possible Reduced Response to Fluvoxamine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**

There is a risk for decreased efficacy at standard dosage. If a standard dose is prescribed to a CYP2D6 ultra-rapid metabolizer, suboptimal plasma concentrations of the drug are likely. There is insufficient data to calculate dose adjustments and careful titration is recommended until a favorable response is achieved. An alternative medication not metabolized by CYP2D6 can also be considered.



Haloperidol (Haldol)

Non-Response to Haloperidol (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, or prescribe haloperidol at the standard dose and adjust dosage to achieve a favorable clinical response. Be alert to decreased haloperidol plasma concentrations.



Hydrocodone (Vicodin)

Possible Altered Response to Hydrocodone (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**

Increased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 ultra-rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower hydrocodone doses. Other opioids not metabolized by CYP2D6 (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if excessive side effects are reported.



Imipramine (Tofranil)

Non-Response to Imipramine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug or consider prescribing imipramine at an increased dose, then adjust dosage in response to imipramine and desipramine plasma concentrations.



Lisdexamfetamine (Vyvanse)

Poor Response to Lisdexamfetamine (COMT Val158Met A/A Low COMT Activity) Evidence Level: **Informative**

The patient's genotype result predicts a reduced therapeutic response to amphetamine stimulants. If prescribed, lisdexamfetamine should be administered at the lowest effective dose, and dosage should be individually adjusted.

**Maprotiline (Ludiomil)**

Possible Non-response to Maprotiline (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer)

Evidence Level: **Informative**

Like other tricyclic and tetracyclic antidepressants, maprotiline is metabolized by CYP2D6 as well as CYP1A2. Patients with increased CYP2D6 function may metabolize maprotiline more rapidly which can result in sub-therapeutic drug concentrations; these patients may require higher doses to achieve adequate plasma concentrations. **There are no established dosing adjustments for patients with increased CYP2D6 function. Seizures have been associated with the use of maprotiline especially at high doses. Therefore, therapy must be initiated at a standard dose and gradually increased in small increments according to the patient's response.**

**Methadone (Dolophine)**

Possible Sensitivity to Methadone (CYP2B6 *1/*6 Intermediate Metabolizer)

Evidence Level: **Informative**

Based on currently available evidence, S-methadone plasma concentrations may increase, resulting in higher risk of cardiac arrhythmias and QTc prolongation. Consider lower starting doses of methadone, and adjust dosing based on the clinical response.

**Methotrexate (Trexall)**

Increased risk for methotrexate toxicity (MTHFR 677C>T CT Reduced MTHFR Activity)

Evidence Level: **Informative**

The patient carries the MTHFR 677 T allele resulting in a reduced MTHFR activity. **Malignancy:** Leukemia or lymphoma patients who are treated with methotrexate standard regimens might have an increased likelihood of treatment interruptions due to methotrexate toxicity. Consider at least a 25% reduction in methotrexate starting dose, followed by titration based on toxicity. Other genetic and clinical factors may also influence the patient's risk for toxicity and response to methotrexate treatment. **Nonmalignant conditions:** a limited number of studies found an association between the MTHFR 677 T allele and methotrexate-induced toxicity in rheumatoid arthritis patients. However, there is insufficient data to calculate dose adjustment. Monitor patient closely for increased side effects and adjust the dose accordingly. Other genetic and clinical factors may also influence the patient's risk for toxicity and response to methotrexate treatment.

**Methylphenidate (Ritalin, Aptensio XR, Concerta, Metadate ER, Quillivant ER)**

Poor Response to Methylphenidate (COMT Val158Met A/A Low COMT Activity)

Evidence Level: **Informative**

The patient's genotype result predicts a reduced therapeutic response to methylphenidate. Dosage should be individualized according to the needs and response of the patient. Therapy should be initiated in small doses, with gradual weekly increments.

**Metoprolol (Lopressor)**

Possible Non-Responder to Metoprolol (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer)

Evidence Level: **Actionable**

The patient may experience a decrease in the pharmacological effect when taking metoprolol at standard dosage. Heart Failure: Consider alternative beta-blockers such as bisoprolol or carvedilol, or prescribe metoprolol at a higher dose. Other indications: Consider alternative beta-blockers such as bisoprolol or atenolol, or prescribe metoprolol at a higher dose. If metoprolol is prescribed, titrate the dose to a maximum of 250% of the normal dose in response to efficacy and adverse events.

**Mexiletine (Mexitil)**

Altered Response to Mexiletine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer)

Evidence Level: **Informative**

Because mexiletine plasma concentrations may be decreased, consider adjusting dose in response to mexiletine plasma concentration and ECG monitoring, until a favorable response is achieved.

**Morphine (MS Contin)**

Altered Response to Morphine (COMT Val158Met A/A Low COMT Activity)

Evidence Level: **Informative**

The patient carries two COMT Val158Met mutations, which translates to a reduced COMT function. The patient may require lower doses of morphine for adequate pain control. The dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.

**Naltrexone (Vivitrol, Contrave)**

Altered Response to Naltrexone (OPRM1 A118G A/A Normal OPRM1 Function)

Evidence Level: **Informative**

Treatment of alcohol dependence: the patient has the wild-type genotype for OPRM1 that is associated with a poorer outcome with naltrexone therapy. Naltrexone-treated patients not carrying the 118A> G mutation are less likely to respond to this drug, and may have higher relapse rates than those who are carriers of this mutation.



Netupitant-Palonosetron (Akynzeo)

Possible Altered Response to Netupitant-Palonosetron (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**

Netupitant: Netupitant is extensively metabolized to three major metabolites (desmethyl, N-oxide and a hydroxy-methyl derivatives). Metabolism is mediated primarily by CYP3A4 and to a lesser extent by CYP2C9 and CYP2D6. No genetically guided drug selection or dosing recommendations are available for this drug. Netupitant can be prescribed at standard label-recommended dosage and administration.

Palonosetron: Palonosetron is eliminated by multiple routes including metabolism. While CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in its metabolism to two inactive metabolites. Compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower palonosetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Palonosetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.



Nortriptyline (Pamelor)

Non-Response to Nortriptyline (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

Consider an alternative drug, or prescribe nortriptyline at an increased dose and monitor the plasma concentration of amitriptyline and hydroxynortriptyline.



Olanzapine (Zyprexa)

Non-Response to Olanzapine (CYP1A2 *1A/*1F Normal Metabolizer - Higher Inducibility) Evidence Level: **Informative**

There is little evidence regarding the impact of CYP1A2 genetic variants on olanzapine response. Smokers may be at risk for non-response at standard doses. Careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to adverse events. Therefore, therapeutic drug monitoring accompanied by dose reduction may be needed in patients who have quit smoking.



Ondansetron (Zofran, Zuplenz)

Non-Response to Ondansetron (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

A substantially decreased antiemetic effect has been reported in CYP2D6 ultra-rapid metabolizers when taking standard doses of this medication. Consider prescribing an alternative drug not metabolized by CYP2D6 such as granisetron.



Oxycodone (Percocet, Oxycontin)

Possible Altered Response to Oxycodone (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

Increased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 ultra-rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower oxycodone doses. Other opioids not metabolized by CYP2D6 (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone) may also be considered if excessive side effects are reported.



Palonosetron (Aloxi)

Possible Altered Response to Palonosetron (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**

Palonosetron is eliminated by multiple routes including metabolism. While CYP2D6 and to a lesser extent, CYP3A4 and CYP1A2 are involved in its metabolism to two inactive metabolites. Compared to CYP2D6 normal metabolizers, CYP2D6 ultra-rapid metabolizers may have lower palonosetron plasma concentrations at standard dosing. However, the clinical significance of this change remains unclear. Palonosetron can be prescribed at standard label-recommended dosage and administration. Monitor the patient for possible decreased efficacy.



Paroxetine (Paxil, Brisdelle)

Reduced Response to Paroxetine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

There is a risk for decreased efficacy at standard dosage. If a standard dose is prescribed to a CYP2D6 ultra-rapid metabolizer, suboptimal plasma concentrations of the drug are likely. Consider an alternative medication.



Perphenazine (Trilafon)

Possible Non-Response to Perphenazine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

Subjects with increased CYP2D6 function will metabolize perphenazine more rapidly, which can result in sub-therapeutic drug concentrations. Consider a dose increase with close monitoring until a favorable response is achieved.

-  **Pimozide (Orap)**
Possible Non-Response to Pimozide (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
There is insufficient data to calculate dose adjustment, and if pimozide is prescribed at standard dosing, monitor response and be alert to reduced efficacy. Standard starting dose: 1 to 2 mg/day (adult) or 0.05 mg/kg/day (children). Doses may be increased to a maximum of 10 mg/day or 0.2 mg/kg/day.
-  **Propafenone (Rythmol)**
Altered Response to Propafenone (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
There is insufficient data to allow calculation of dose adjustment. Titrate carefully and adjust the dose in response to plasma concentration and ECG monitoring. OR consider alternative drug such as sotalol, disopyramide, quinidine, or amiodarone.
-  **Protriptyline (Vivactil)**
Non-Response to Protriptyline (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Informative**
Consider alternative drugs or prescribe protriptyline at increased dosage and observe the patient for decreased efficacy. Adjust dosage in response to protriptyline and metabolites plasma concentrations and clinical response.
-  **Risperidone (Risperdal)**
Non-Response to Risperidone (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
Consider an alternative drug, OR prescribe risperidone, be extra alert to insufficient response, and adjust dosage in response to clinical response and adverse events.
-  **Tetrabenazine (Xenazine)**
Unknown Sensitivity to Tetrabenazine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
There is insufficient data to calculate dose adjustment, and if tetrabenazine is prescribed, individualization of dose with careful weekly titration is required. The first week's starting dose is 12.5 mg daily; second week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose. **The maximum daily dose in CYP2D6 ultra-rapid metabolizers is not defined. The maximum daily dose in normal metabolizers is 100 mg with a maximum single dose of 37.5 mg.** If serious adverse events occur, titration should be stopped and the dose of tetrabenazine should be reduced. If the adverse event(s) do not resolve, consider withdrawal of tetrabenazine.
-  **Tizanidine (Zanaflex)**
Possible Non-Response to Tizanidine (CYP1A2 *1A/*1F Normal Metabolizer - Higher Inducibility) Evidence Level: **Informative**
There is little evidence regarding the impact of CYP1A2 genetic variants on tizanidine response. Smokers may be at risk for non-response and may require higher doses. There is an association between high tizanidine plasma concentrations and the risk of hypotension and excessive sedation. Therefore, careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels, leading to excessive hypotension and sedation. Careful monitoring accompanied by dose reduction may be needed in patients who have quit smoking.
-  **Tramadol (Ultram)**
Increased Response to Tramadol (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
The patient is at high risk of toxicity when taking tramadol at standard dosing. Consider reducing tramadol dose by 30%. Careful monitoring for side effects and weekly titration are recommended. If toxicity, consider alternative opioids other than codeine, or a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: fentanyl, morphine, hydromorphone, oxycodone, and tapentadol.
-  **Trimipramine (Surmontil)**
Non-Response to Trimipramine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
Consider an alternative drug, or consider prescribing trimipramine at an increased dose, then adjust dosage in response to trimipramine plasma concentrations.
-  **Venlafaxine (Effexor)**
Non-Response to Venlafaxine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**
The patient is unlikely to achieve adequate serum levels of venlafaxine and O-desmethylvenlafaxine when taking standard doses of venlafaxine. Consider an alternative drug, or increase the venlafaxine dose to a maximum of 150% of the normal dose and monitor venlafaxine and O-desmethylvenlafaxine plasma concentrations.



Warfarin (Coumadin)

Normal Sensitivity to Warfarin (CYP2C9 *1/*1 VKORC1 -1639G>A G/A)

Evidence Level: **Actionable**

Initiation Therapy: consider using the following standard warfarin dose range as provided in the FDA-approved label: **5-7 mg/day**. OR consider using a personalized dose calculated by a pharmacogenetic algorithm. The estimated time to reach steady state is 4-5 days.

Test Details			
Gene	Genotype	Phenotype	Alleles Tested
ANKK1/DRD2	DRD2:Taq1A A/G	Altered DRD2 function	DRD2:Taq1A
Apolipoprotein E	ε3/ε3	No Increased Risk of Hyperlipidemia/Atherosclerotic Vascular Disease	ε2, ε4
COMT	Val158Met A/A	Low COMT Activity	Val158Met
CYP1A2	*1A/*1F	Normal Metabolizer - Higher Inducibility	*1F, *1K
CYP2B6	*1/*6	Intermediate Metabolizer	*6, *9, *11, *18
CYP2C19	*1/*1	Normal Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *17
CYP2C9	*1/*1	Normal Metabolizer	*2, *3, *5, *6, *8, *11, *27
CYP2D6	*1/*1 XN	Ultra-Rapid Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1/*1	Normal Metabolizer	*1B, *3, *12, *22
CYP3A5	*3/*3	Poor Metabolizer	*3, *3C, *6, *7
Factor II	20210G>A GG	Normal Thrombosis Risk	20210G>A
Factor V Leiden	1691G>A GG	Normal Thrombosis Risk	1691G>A
MTHFR	1298A>C AC	Reduced MTHFR Activity	1298A>C
MTHFR	677C>T CT	Reduced MTHFR Activity	677C>T
OPRM1	A118G A/A	Normal OPRM1 Function	A118G
SLCO1B1	521T>C T/T	Normal Function	521T>C
VKORC1	-1639G>A G/A	Intermediate Warfarin Sensitivity	-1639G>A

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All clinical decisions relative to test results should be directed by the patient's healthcare provider. MyGENETX makes no representations or recommendations in regards to results. Please consult your physician for all medical advice

Methodology: All SNP genotyping tests performed at MyGENETX. use the Applied Biosystems (ABI) TaqMan technology and the LifeTechnology Quant Studio 12K Flex platform. All PCR based methods are subject to rare interference such as inhibitors or quality or quantity of DNA. If present, the interference typically yields a no result requiring a repeat rather than an inaccurate one.

Lab CLIA #: 44D-2031868

Lab Director: Dr. Jack Pearson

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ANKK1/DRD2 Monograph

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.

References

1: Young et al. Prolactin levels in antipsychotic treatment of patients with schizophrenia carrying the DRD2*A1 allele. *Br J Psychiatry*. 2004 Aug;185:147-51. 2 : Zai et al. Meta-analysis of two dopamine D2 receptor gene polymorphisms with tardive dyskinesia in schizophrenia patients. *Mol Psychiatry*. 2007 Sep;12(9):794-5. 3 : Bakker et al. Antipsychotic-induced tardive dyskinesia and polymorphic variations in COMT, DRD2, CYP1A2 and MnSOD genes: a meta-analysis of pharmacogenetic interactions. *Mol Psychiatry*. 2008 May;13(5):544-56. 4 : Johnstone et al. Pharmacogenetics. 2004 Feb;14(2):83-90. Genetic variation in dopaminergic pathways and short-term effectiveness of the nicotine patch. 5 : David et al. Bupropion efficacy for smoking cessation is influenced by the DRD2 Taq1A polymorphism: analysis of pooled data from two clinical trials. *Nicotine Tob Res*. 2007 Dec;9(12):1251-7.

APOE Monograph

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 $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, 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 $\epsilon 2$, 74-78% for $\epsilon 3$, and 14-15% for $\epsilon 4$.

The reference ranges for both mutations of APOE are 388TT and 526CC. This is consistent with a $\epsilon 3/\epsilon 3$ genotype and a normal APOE function.

Clinical Implications

- The APOE $\epsilon 3/\epsilon 3$ 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 $\epsilon 2$ 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 $\epsilon 2/\epsilon 2$ 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 $\epsilon 2/\epsilon 2$ 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 $\epsilon 2$ allele is associated with lower serum cholesterol concentrations, and may confer a protection against hypercholesterolemia.
- The APOE $\epsilon 2/\epsilon 4$ genotype is associated with type III hyperlipoproteinemia in patients who are also heterozygous for familial hypercholesterolemia.
- The APOE $\epsilon 4$ allele has been linked to pure elevations of low-density lipoproteins (LDL), and the $\epsilon 4/\epsilon 4$ and $\epsilon 3/\epsilon 4$ genotypes are associated with increased serum cholesterol levels and increased risk of CVD.

References

- 1: Eichner et al. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol.* 2002 Mar 15;155(6):487-95.
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- 3: Hanis et al. Effects of the apolipoprotein E polymorphism on levels of lipids, lipoproteins, and apolipoproteins among Mexican-Americans in Starr County, Texas. *Arterioscler Thromb.* 1991 Mar-Apr;11(2):362-70.
- 4 : Klos et al. Linkage analysis of plasma ApoE in three ethnic groups: multiple genes with context-dependent effects. *Ann Hum Genet.* 2005 Mar;69(Pt 2):157-67.
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COMT Monograph

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.

References

1: De Gregori et al. Genetic variability at COMT but not at OPRM1 and UGT2B7 loci modulates morphine analgesic response in acute postoperative pain. *Eur J Clin Pharmacol.* 2013 May 19. 2 : Hamidovic et al. Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine. *Psychiatr Genet.* 2010 Jun;20(3):85-92. 3 : Blasi et al. Effect of catechol-O-methyltransferase val158met genotype on attentional control. *J Neurosci.* 2005 May 18;25(20):5038-45. 4 : Mattay et al. Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proc Natl Acad Sci U S A.* 2003 May 13;100(10):6186-91.

CYP1A2 Monograph

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.

Inhibitors

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

Some known **moderate to weak** CYP1A2 inhibitors include: obeticholic acid (Ocaliva), 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.

References

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CYP2B6 Monograph

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 CYP2B6 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.

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 Monograph

Clinical Utility

The cytochrome P450 2C19 (CYP2C19) is involved in the metabolism of 10% of clinically important medications. This enzyme is highly polymorphic and more than 30 different alleles have been identified in various ethnicities. The CYP2C19 assay identifies common and rare variants that are associated with variability in CYP2C19 enzyme, 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 exhibit normal function, reduction function, no function or increased function. The CYP2C19*1 allele is considered wild-type/reference allele and encodes a functionally active enzyme (normal function allele). The alleles *2, *3, *4, *5, *6, and *8 encode an inactive enzyme and are referred to as no function alleles while the *9 and *10 alleles are classified as reduced function alleles. The CYP2C19*17 is an increased function allele.

The CYP2C19 genotype-phenotype relationship is established based on the allele's function. An individual with two normal function alleles is considered a normal metabolizer while an individual carrying two no function alleles is considered a poor metabolizer. An individual carrying one normal function allele with one no function allele or one no function allele with one increased function allele is classified as an intermediate metabolizer. Individuals with two increased function alleles are considered ultra-rapid metabolizers and carriers of one increased function allele with one normal function allele are referred to as rapid metabolizers. Because of limited evidence, individuals carrying two decreased function alleles OR those carrying one normal or increased function allele with one decreased function allele are provisionally categorized as intermediate metabolizers.

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 (Briviact) is primarily metabolized by hydrolysis and by hydroxylation. The hydrolysis reaction is mediated by amidase and the hydroxylation is mediated by CYP2C19. Brivaracetam exposure is increased by 22% and 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.

CYP2C19 is significantly involved in the metabolism of voriconazole (Vfend) and the disposition of this antifungal is affected by CYP2C19 genetic polymorphisms. The CPIC dosing guideline for voriconazole recommends selecting an alternative agent that is not dependent on CYP2C19 metabolism in adults who are CYP2C19 ultrarapid metabolizers, rapid metabolizers or poor metabolizers. In pediatric patients, an alternative agent should be used in patients who are ultrarapid metabolizers or poor metabolizers.

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 (Intence), 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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CYP2C9 Monograph

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 (Ocufer), 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.

Inhibitors

Some known CYP2C9 inhibitors include: amiodarone (Cordarone), 5-fluorouracil (Aduvicol), 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), sulfapyrazone (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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CYP2D6 Monograph

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.

Morphine, oxycodone (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), rolapitant (Varubi), 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.

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CYP3A4 Monograph

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 variant results in an enzyme with no activity, and is the most common variant in the general population. This variant is found on all the CYP3A5*3 alleles. The CYP3A5 *6 and *7 are also no function alleles. The functional effects of the CYP3A5 alleles *2, *4, *5 *8, and *9 are not well established. The CYP3A5 *1 functional allele produces an active enzyme, and is found in 5% of Caucasians, 20% of Asians, and 15-50% of Africans. Individuals with two CYP3A5 no function alleles are classified as poor metabolizers while those carrying one copy of a functional CYP3A5*1 allele are considered intermediate metabolizers. A subject carrying two copies of the functional CYP3A5*1 allele is considered a normal metabolizer. **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.

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), nifedipine (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), lesinurad (Zurampic), oxcarbazepine (Trileptal), methylprednisolone (Medrol), and rufinamide (Banzel).

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CYP3A5 Monograph

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 variant results in an enzyme with no activity, and is the most common variant in the general population. This variant is found on all the CYP3A5*3 alleles. The CYP3A5 *6 and *7 are also no function alleles. The functional effects of the CYP3A5 alleles *2, *4, *5 *8, and *9 are not well established. The CYP3A5 *1 functional allele produces an active enzyme, and is found in 5% of Caucasians, 20% of Asians, and 15-50% of Africans. Individuals with two CYP3A5 no function alleles are classified as poor metabolizers while those carrying one copy of a functional CYP3A5*1 allele are considered intermediate metabolizers. A subject carrying two copies of the functional CYP3A5*1 allele is considered a normal metabolizer. **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.

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), nifedipine (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), lesinurad (Zurampic), oxcarbazepine (Trileptal), methylprednisolone (Medrol), and rufinamide (Banzel).

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Factor II Monograph

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.

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Factor V Leiden Monograph

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.

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MTHFR Monograph

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.

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OPRM1 Monograph

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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SLCO1B1 Monograph

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 potentially 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.

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 Monograph

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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