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Hypertension

Report Type: Health Conditions

About: The prevalence of hypertension, also known as high blood pressure, is estimated to be 29% in the U.S.[1] This condition can lead to stroke, heart attack and kidney failure. Risk factors for hypertension include high salt intake, being overweight and high alcohol consumption.[2] Research indicates that genetic factors are also associated with risk for the condition.[3,4,5,6]

Genetics: Over 90% of individuals who develop hypertension are considered to have essential or primary hypertension, meaning that no underlying medical cause can be identified. Hypertension can also be secondary to existing medical problems, such as kidney disease. Some rare forms of hypertension are caused by mutations in single genes. Individuals with these mutations usually have a family history of the disease and hypertension occurs at a younger age. This genetic test focuses on essential hypertension, for which several susceptibility alleles have been identified through large population studies.[3,4,5,6]

Because of the complex interactions of different physiologic pathways regulating blood pressure, it has been difficult to definitively identify risk alleles in candidate genes for hypertension. Contradictory results have been reported for many genes identified in an early study but not replicated in further research. A few large population-based genome-wide scans and candidate gene association studies have identified two genes as risk factors for hypertension: PPARGC1A and BCAT1.[3,4,5,6]

The PPARGC1A gene encodes the protein PPAR-gamma coactivator 1,[7] which regulates the expression of genes involved in several metabolic processes related to blood pressure homeostasis. The Gly482Ser (rs7961152) allele causes an amino acid change in the protein, but the functional consequence of this change is unknown. The Ser allele was associated with decreased risk for essential hypertension in a Danish population.[5] The same allele was also modestly associated with decreased risk for severe essential hypertension in a Chinese population.[6]

The BCAT1 gene encodes branched-chain aminotransferase 1, which catalyzes the first reaction in the catabolism of the essential branched-chain amino acids leucine, isoleucine and valine. The rs7961152 marker is in a non-coding region of the BCAT1 gene, making it difficult to discern the functional impact of a nucleotide change. The variant may be linked to another causative mutation in the same gene or a neighboring gene. The A allele of the rs7961152 marker was associated with an increased risk for essential hypertension in a study of a British Caucasian population.[4] In a Korean population, the same allele was moderately associated with increased blood pressure.[3]

Recommendations: The U.S. Preventive Services Task Force recommends screening for high blood pressure in adults aged 18 and older.[8]

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
BCAT1	rs7961152	A	1.29	Asian	16.9%	Preliminary	19424278
BCAT1	rs7961152	A	1.16	Caucasian	46.5%	Preliminary	17554300
PPARGC1A	rs8192678	A	0.60	Asian	40.5%	Preliminary	17971240
PPARGC1A	rs8192678	A	0.70	Caucasian	35.0%	Preliminary	15738346

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
401.1 Benign essential hypertension	N/A

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Beta-blockers, LVEF response

(DC:TB-0208.002 07MAY2013)

Report Type: Pharmacogenetics

About: Beta-blockers (carvedilol, metoprolol, etc.) are used as a standard therapy for heart failure.[1] This class of drugs antagonizes beta-adrenergic receptors and down-regulates the effects of catecholamine hormones (epinephrine and norepinephrine). Genetic variants that affect beta-adrenergic signaling may influence outcomes in heart failure patients treated with beta-blockers.

Genetics: In heart failure patients, the benefits of treatment with beta-blockers for left ventricular ejection fraction (LVEF) are associated with variants in the ADRB1 gene, which encodes the beta(1)-adrenergic receptor.[2] A meta-analysis of three pharmacogenetic studies in heart failure patients found that individuals who are homozygous for the Arg389 allele have a greater increase in LVEF in response to beta-blockers (carvedilol, metoprolol or bisoprolol) compared to individuals who carry the Gly389 allele.[2] This genetic effect was also reported in a study involving patients who underwent 1.5 years of carvedilol treatment.[3]

In a number of small studies, the Arg389 allele has been studied in relation to other phenotypes, including exercise heart rate, response to rate-control therapy in atrial fibrillation, changes in heart rate and blood pressure in patients with essential hypertension and LV hypertrophy, and transplant-free survival in heart failure patients.[4,5,6,7] However, it is still controversial whether Arg389 modifies the outcomes of beta-blocker therapy. Some studies showed no association, while others reported significant associations but do not always agree on the direction of the genetic effect.

Recommendations: NA

Possible Outcomes: Enhanced Benefit, Beneficial

Markers or Alleles Tested: ADRB1 [rs1801253]

Ethnic Distribution of Tested Alleles:

Ethnicity	Arg389 allele (C allele) frequency[8]
Caucasian	~70%
East Asians	75-85%
Africans	~60%

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test,

nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

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Myocardial infarction

Report Type: Health Conditions

About: Myocardial infarction (MI) kills approximately half a million people in the U.S. each year.[1] Symptoms of this condition include chest pain, shortness of breath and other symptoms.[1,2] Risk factors include a family history of MI, diabetes, hypertension and hypercholesteremia.[2] Research indicates that genetic factors are also associated with MI.[2,3]

Genetics: Genetic susceptibility factors contribute to the risk of MI. Their importance is highlighted by the fact that about 15% to 20% of individuals who have an MI lack conventional risk factors.[4] Studies suggest that many genetic variations associated with the disease are in genes involved in processes involving endothelial cell function, inflammation, lipid metabolism, thrombosis and fibrinolysis.[2,3]

Many SNPs associated with heart disease are in genes involved in inflammation. A marker in the CXCL12 gene, which encodes a chemokine molecule important for attracting lymphocytes,[5] was shown to be also associated with the risk for MI in a large study of Caucasians.[6] Additionally, in a large genome-wide association study identifying markers affecting eosinophil counts, a marker at 12q24 (rs3184504) in the SH2B3 gene, which encodes a protein important for cytokine pathway inhibition, was associated with risk for MI in six different populations.[7]

A number of high-impact studies have identified 9p21.3 as an important genetic region associated with risk for MI or coronary artery disease.[8] This region contains no annotated genes but lies close to the CDKN2A and CDKN2B genes, which regulate important cell cycle pathways. An allele of the rs10757278 marker in the 9p21.3 region is associated with MI in Icelandic, U.S. Caucasian, and Italian populations.[9,10,11] When the Italian patient group was subdivided into those with and without a family history of MI, only the individuals with a family history of MI still showed a significant association with the allele.[11] This research suggests that in cases with a family history of heart disease and heart attack, the relative risk for an individual carrying a risk allele can be significantly higher.

Another large study carried out by the Myocardial Infarction Genetics Consortium replicated the region of 9p21, as well as identified or replicated other markers in MIA3 (rs17465637), 1p13 (rs646776), 10q11 in CXCL12 (rs1746048), 21q22 (rs9982601), 6p24 in PHACTR1 (rs12526453), and 2q33 in WDR12 (rs6725887).[6]

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers Tested

Gene/Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
PSMA6	rs1048990	G	1.21	Asian	37.8%	Validated	16845397
Intergenic_9p21	rs10757278	G	1.28	Caucasian	50.0%	Validated	17478679
PCSK9	rs11206510	T	1.15	Caucasian	83.6%	Validated	19198609
PHACTR1	rs12526453	C	1.12	Caucasian	63.3%	Validated	19198609
CXCL12	rs1746048	C	1.17	Caucasian	85.4%	Validated	19198609
MIA3	rs17465637	C	1.14	Caucasian	26.8%	Validated	19198609
SH2B3	rs3184504	T	1.13	Caucasian	44.5%	Validated	19198610
Intergenic_1p13	rs646776	T[i]	1.19	Caucasian	74.6%	Validated	19198609
WDR12	rs6725887	C	1.17	Caucasian	15.9%	Validated	19198609
LGALS2	rs7291467	C[j]	1.23	Asian	73.3%	Validated	15129282
Intergenic_21q22	rs9982601	T	1.20	Caucasian	20.6%	Validated	19198609
LTA	rs1041981	A	1.78	Asian	43.5%	Preliminary	12426569
OR13G1	rs1151640	G	1.31	Caucasian	46.0%	Preliminary	16175505
PRR4	rs1376251	C	1.23	Caucasian	65.3%	Preliminary	16175505
MIAT	rs2331291	T	1.38	Asian	13.1%	Preliminary	17066261

[a]Gene or locus containing the tested marker.

[b]Marker tested.

[c]Allele associated with disease risk.

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele.

[e]Ethnicity of the population in the corresponding study.

[f]Percentage of people who have the associated allele in the population studied.

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; the PubMed ID (PMID) number identifies the referenced study.

[i]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either an A or a T in the patient report.

[j]This marker can be assayed on either strand of DNA. Therefore, the associated allele could be reported as either a C or a G in the patient report.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
410.9 Acute myocardial infarction of unspecified site Applies to: • Acute myocardial infarction NOS • Coronary occlusion NOS • Myocardial infarction NOS	V81.2 Screening for other and unspecified cardiovascular conditions

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Perindopril

(DC:TB-0236.001 06DEC2012)

Report Type: Pharmacogenetics

About: Perindopril is an angiotensin-converting enzyme (ACE) inhibitor that is used to manage or treat hypertension, stable coronary artery disease, myocardial infarction and heart failure.[1,2] ACE is a zinc metallopeptidase that plays a role in the production of angiotensin II, the primary blood pressure effector in the renin-angiotensin-aldosterone system.[3] It also acts in the degradation of bradykinin, a strong vasodilator of the Kinin-Kallikrein cascade.[4] By preventing the production of angiotensin II and blocking the degradation of bradykinin, ACE inhibitors prevent arteriolar vasoconstriction and promote vasodilation.[5]

Genetics: Two markers located in the angiotensin II receptor type I (AGTR1) gene and one in the bradykinin type I receptor (BDKRB1) gene are associated with perindopril's treatment benefit. The benefit of perindopril in stable coronary artery disease patients is calculated using these three markers to generate a pharmacogenetic score.[6]

In a study that examined the effect of perindopril (8 mg/day) in predominantly Caucasian male patients with stable coronary artery disease, markers in AGTR1 (rs275651 and rs5182) and BDKRB1 (rs12050217) were associated with the treatment benefits of perindopril. Combining these three markers in a pharmacogenetic score demonstrated a stepwise decrease in treatment benefit of perindopril. A pronounced treatment benefit was observed in a subgroup of 73.5% of patients, whereas no benefit was apparent in the remaining 26.5%, with a trend towards a harmful effect.[6] Prospective studies are yet to be completed to test whether patients with a "non-responder" genetic profile should avoid treatment with ACE inhibitors.[7]

Recommendations: NA

Possible Outcomes: Likely Non-Responder, Likely Responder

Markers or Alleles Tested: AGTR1 [rs275651, rs5182]; BDKRB1 [rs12050217]

Limitations and Warnings: This test can inform perindopril treatment optimization for stable coronary artery disease patients only. The results of this test do not apply to patients that are being treated with perindopril for other indications.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

References

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Peripheral arterial disease

Report Type: Health Conditions

About: Peripheral arterial disease (PAD) affects 20% of individuals in the U.S. over the age of 55 and is strongly associated with a risk for myocardial infarction and stroke.[1] This progressive disease is characterized by the accumulation of plaque in the arterial system, especially the abdominal aorta and arteries in the legs.[1,2] Risk factors for PAD include age, sex, smoking, diabetes, hypertension and hyperlipidemia.[1] Research indicates that genetic factors are also associated with PAD.[3]

Genetics: Peripheral arterial disease (PAD) is caused by atherosclerosis, a complex disorder involving both genetic risk factors as well as traditional risk factors, such as cigarette smoking, cholesterol levels, hypertension and stress. Within various populations, genetic differences are thought to account for greater than 50% of the risk for atherosclerosis.[3] It is estimated that the genetic risk of atherosclerosis involves variants in hundreds of genes with a variety of functions in regulating blood pressure, lipid and cholesterol metabolism, pro-inflammatory processes, cell adhesion and migration.[3]

The CHRNA3 gene encodes a subunit of the nicotinic acetylcholine receptor, which binds to nicotine.[4] A large study of PAD in Caucasians from Iceland, New Zealand, Austria, Sweden and Italy[5] showed that a variant in CHRNA3 increased the risk for PAD by approximately 20%. No significant differences in risk were shown between males and females. The results from this study suggest that this variant may also partly confer a risk for cardiovascular disease indirectly through its relationship with exposure to nicotine as a function of smoking history.

Recommendations: NA

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Marker Tested

Gene/ Locus[a]	Marker[b]	Associated Allele[c]	Odds Ratio[d]	Ethnicity[e]	Population Frequency[f]	Scientific Strength[g]	PMID[h]
CHRNA3	rs1051730	T	1.19	Caucasian	38.5%	Validated	18385739

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]Allele associated with disease risk

[d]Measure of the likelihood that an individual will get the disease if carrying a specific allele

[e]Ethnicity of the population in the corresponding study

[f]Percentage of people who have the associated allele in the population studied

[g]Validated markers represent the highest quality genetic markers available; preliminary markers represent the latest in

genetic research and have not met our highest standards for validation.

[h]PubMed is a service managed by the National Library of Medicine; thePubMed ID (PMID) number identifies the referenced study.

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
443.9 Peripheral vascular disease, unspecified Applies to: • Intermittent claudication NOS • Peripheral: ◦ angiopathy NOS ◦ vascular disease NOS • Spasm of artery	V81.2 Screening for other and unspecified cardiovascular conditions

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Sickle cell anemia

Report Type: Carrier Status

About: Sickle cell anemia (also known as homozygous sickle cell disease or HbSS) is the most common inherited blood disorder in the U.S., accounting for 60% to 70% of all sickle cell disease in the country. The condition is a chronic, lifelong, inherited disorder that is associated with a decreased lifespan and characterized by the clumping of red blood cells, which can cause painful episodes and permanent damage to the eyes, brain, heart, lungs, kidneys, liver, bones and spleen. Infections and lung disease are the leading causes of death for people with sickle cell anemia.[1,2,3]

Genetics: Sickle cell anemia is caused by a mutation in the HBB gene, which encodes the beta subunit of hemoglobin. Individuals with two copies of the HbS mutation have sickle cell anemia, whereas individuals with one copy of the HbS mutation have sickle cell trait and can pass this mutation to their children.[1,4] Most people with sickle cell trait lead normal lives, but they are at increased risk for exertional rhabdomyolysis, a condition that may lead to exercise-induced sudden cardiac death.[5,6,7]

Sickle cell anemia is a hemoglobinopathy. In some individuals, the sickele cell mutation in HBB will occur along with other mutations in the HBB gene, including hemoglobin (HbC), hemoglobin E (HbE) and beta-thalassemia, complicating and increasing the severity of these hemoglobinopathies..[1]

Sickle cell anemia occurs in 1 in 600 to 700 African American births and in 1 in 19,000 to 46,000 Hispanic American births.[8]

Mode of Inheritance: Autosomal Recessive

Possible Outcomes: Not a Carrier, Carrier, Homozygote

Recommendations: The American College of Obstetricians and Gynecologists (ACOG) recommends offering carrier screening for hemoglobinopathies to people of African, Southeast Asian and Mediterranean ancestry.[9] The American College of Medical Genetics identified sickle cell anemia as one of 29 diseases for which newborn screening should be mandated.[10]

The NCAA requires that all Division I athletes undergo testing for sickle cell trait.[11] Individuals with sickle cell trait can compete and play sports at all levels as long as they are aware of the trait and take proper precautions.[12]

Mutations Tested: The test includes one mutation in the HBB gene.

HBB [hemoglobin S]

Ethnic Prevalence and Frequency of Mutation Tested

Gene	Population	Detection Rate[a]	Pre-Test Carrier Rate[b]	Post-Test Residual Risk[c]
HBB	African American	100%	1 in 15	0
HBB	Native American	100%	1 in 150	0
HBB	Hispanic American	100%	1 in 203	0
HBB	Middle Eastern	100%	1 in 478	0
HBB	Caucasian	100%	1 in 642	0
HBB	Asian Indian	100%	1 in 652	0
HBB	Flilipino	100%	1 in 879	0
HBB	Asian	100%	1 in 1,315	0
HBB	Southeast Asian	100%	1 in 2,365	0

[a]Percentage of affected patients carrying mutations detected by this test.

[b]Carrier risk before testing.[13]

[c]Carrier risk after a “not a carrier” test result.

Limitations and Warnings: Sickle cell anemia carriers may have misleading results in the hemoglobin A1C test (also known as glycated hemoglobin, glycosylated hemoglobin, and HbA1c) that is used to diagnose diabetes and to monitor blood glucose levels in diabetics. False A1C test results can lead to false diagnosis, over-treatment or under-treatment of diabetes in people with hemoglobin variants.[14]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
282.60 Sickle-cell disease, unspecified Applies to: • Sickle-cell anemia NOS	V78.2 Screening for sickle cell disease/trait

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Simvastatin-induced myopathy

(DC:TB-0229.001 06DEC2012)

Report Type: Pharmacogenetics

About: Simvastatin is a member of the statins, a class of cholesterol-lowering drugs whose major adverse effect is skeletal muscle toxicity. Approximately 5% to 10% of patients taking statins experience muscle pain (myalgia).[1] A small portion of patients, (1.5% to 5.0%) may develop more severe symptoms indicating muscle degradation (myopathy).[1] In rare cases (0.1 to 0.2 cases per 1,000 person-years), severe muscle damage leads to acute, potentially lethal kidney failure (rhabdomyolysis).[1,2]

Genetics: Simvastatin-induced myopathy has been shown to be influenced by variation in the SLCO1B1 gene.[3] Approximately 60% of myopathy cases in a simvastatin (80 mg/day) clinical trial were attributed to the C allele of the rs4149056 marker in the SLCO1B1 gene.[3] SLCO1B1 encodes the organic anion-transporting polypeptide 1B1 (OATP1B1, also known as OATP-C or OATP2), which regulates the hepatic uptake of statins and other drugs. The C allele at rs4149056 reduces the activity of the OATP1B1 transporter,[4] leading to increased blood simvastatin levels and the potential for increased toxicity to the muscles. However, available clinical data are insufficient to show whether the SLCO1B1 variant also alters myopathy risk associated with the use of statins other than simvastatin.[5]

The risk of myopathy varies with the type of statin and is dose-related. Some statins are associated with lower risk of myopathy compared with others,[1] and the pharmacokinetic effects of variants of rs4149056 are not uniform for different statins.[6,7] The incidences of myopathy and rhabdomyolysis while taking 80 mg simvastatin daily are disproportionally higher than those with lower doses.[8]

Genetic variation in SLCO1B1 also affects pharmacokinetics of other drugs, such as methotrexate and HIV protease inhibitors.[9]

Recommendations: The NIH Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines for SLCO1B1 genotyping and simvastatin-induced myopathy, recommending reduced dose or alternative statins for patients with the C allele at rs4149056. The CPIC also recommends routine surveillance of serum creatine kinase levels for those patients.[5]

Possible Outcomes: Increased Risk, Typical Risk

Markers and Alleles Tested: SLCO1B1 [rs4149056]

Ethnic Distribution of Tested Allele

Frequency of C allele of the rs4149056 marker in major ethnic groups.[5]

Ethnicity	C allele frequency (rs4149056)
Caucasian	15%
African	3%
Middle Eastern	20%
Asian	13%

Limitations and Warnings: Although the tested SLCO1B1 variant has the most significant genetic effect on the risk of simvastatin-induced myopathy in clinical studies, rarer mutations in SLCO1B1 that may also affect the function of the encoded protein are not screened in this test. Current knowledge is limited on the involvement of other genes in the metabolism and clinical effects of simvastatin. In addition to genetic effects, the risk of simvastatin-induced myopathy varies with the patient's age, gender, body mass index, ethnicity and other clinical factors.[5]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
359.4 Toxic myopathy	N/A

References

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Venous thrombosis

Report Type: Health Condition

About: Venous thrombosis is the formation of a blood clot in the veins that can potentially lead to thromboembolism. The individual risk of venous thromboembolism (VTE) is determined by a complex interaction of genetic, circumstantial and environmental factors. Risk factors include immobility, surgery, trauma, cancer, hormonal therapy, pregnancy, advanced age and family history.[1,2] Genetic factors are also associated with the risk of VTE development.

Genetics: Factor V Leiden, a mutation in the F5 gene, is the most common and most studied genetic prothrombotic defect, with an overall prevalence in Caucasians of approximately 5%. It is found in 20% of all patients with venous thrombosis, and in up to 50% of patients with thrombophilia.[3] The F5 gene encodes coagulation factor V, an important cofactor that accelerates the activation of prothrombin to thrombin in the blood coagulation cascade. The Factor V Leiden mutation impairs down-regulation of coagulation factor V, resulting in increased risk of clotting.

Individuals who are heterozygous for the Factor V Leiden mutation have a 3.5-fold increase in risk of VTE.[1,4,5,6] Homozygous patients are at a higher risk than heterozygous patients.[1,4]

After Factor V Leiden, the most common mutation associated with heritable thrombophilia is prothrombin G20210A,[7] which is located in the 3'-untranslated region of the gene and is associated with increased levels of prothrombin.[3] Increased levels of prothrombin are a risk factor for thrombosis.[8] Individuals with the mutation are at increased risk of VTE,[1,4,5,6] and risk further increases in individuals who have the Factor V Leiden mutation.[9,10] Individuals who are heterozygous for both mutations have a 20-fold increase in risk, whereas individuals who are heterozygous for either mutation only have a four- to five-fold increase in VTE risk.[11]

Among women with history of VTE, the Factor V Leiden and prothrombin G20210A mutations are independently associated with increased risk of VTE during pregnancy and puerperium.[10] Risk of thrombosis increases more than 100-fold in pregnant women who have both mutations compared to women without the mutations.[10,12]

MTHFR is an important enzyme in folate metabolism and DNA synthesis. The homozygous MTHFR C677T genotype has been associated with an increased risk of elevated plasma homocysteine levels[13] and hyperhomocysteinemia, an independent risk factor for VTE.[14,15,16] The homozygous C677T genotype has also been associated with risk of VTE in Chinese and Korean populations.[5,14,17,18] A meta-analysis found that, in studies of non-Americans, the homozygous C677T genotype was associated with a 20% higher risk of VTE compared to the homozygous wild-type genotype.[16] In contrast, the homozygous C677T genotype had no effect on VTE in North America, possibly due to the higher intake rates of folate and riboflavin. In support of this hypothesis, one study found that homocysteine levels in homozygous C677T individuals were significantly higher than in homozygous wild-type individuals only if folate levels were below 15.4 nmol/L.[15,19] Thus, individuals who are homozygous for C677T may require more dietary folate than individuals who are wild-type.

Recommendations: The American College of Medical Genetics, the American College of Obstetricians and Gynecologists and the European International Thrombophilia Guidelines recommend Factor V Leiden and/or G20210A testing in populations that are likely to have a mutation.[7,20,21]

Possible Outcomes: Increased Risk, Above Average Risk, Average Risk

Markers and Alleles Tested: F5 [Factor V Leiden/R506Q]; F2 [G20210A]; MTHFR [C677T]

Ethnic Distribution of Tested Alleles: The Factor V Leiden and prothrombin G20210A mutations are common in Caucasians but extremely rare in Asians and Africans.[22] The allele frequency of Factor V Leiden in the U.S. population is 5% in Caucasians, 2.2% in Hispanics and 1.2% in blacks.[1,23] Prothrombin G20210A has a prevalence of approximately 2% in the US population and occurs primarily in Caucasians.[1] Double heterozygosity for Factor V Leiden and prothrombin G20210A is estimated to affect 1 in 1,000 individuals in the general population.

There is significant ethnic and geographic variation in the frequency of C677T. The prevalence of the homozygous C677T genotype ranges from around 1% in Black populations in the US, sub-Saharan Africa, and South America to more than 20% in US Hispanics, Colombians and Amerindians in Brazil. The homozygous C677T genotype occurs at a frequency of 8-20% in Caucasians in Europe, North America, and Australia and at 12% in Japanese.[24]

Limitations and Warnings: Genetic variants in other proteins, such as protein S, protein C and antithrombin are known to increase the risk of venous thrombosis, but are not part of this test. Non-genetic factors known to increase the risk of venous thrombosis include age, obesity, trauma/surgery, smoking, pregnancy and airplane travel.[25]

According to the American College of Medical Genetics (ACMG) Consensus Statement on Factor V Leiden Mutation Testing, the MTHFR C677T only accounts for a third of hyperhomocysteinemia cases, and plasma measurements of homocysteine may be more informative than molecular methods.[7]

Dietary factors, such as folic acid intake, may influence the association between MTHFR and VTE.[19]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
453.9 Other venous embolism and thrombosis of unspecified site • Embolism of vein • Thrombosis (vein)	N/A

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Verapamil and QTc interval

(DC:TB-0235.001 06DEC2012)

Report Type: Pharmacogenetics

About: Verapamil is an L-type calcium-channel blocker that is used to treat hypertension and angina. Its interaction with calcium channels reduces the force and rate of muscle contraction, leading to decreased blood pressure and heart rate.[1]

Genetics: The nitric oxide synthase 1 (neuronal) adaptor protein, which is encoded by the NOS1AP gene, regulates the synthesis of nitric oxide, a known regulator of intracellular calcium.[2,3] Variants in the NOS1AP gene are associated with the prolongation of QTc interval in patients taking verapamil.[4]

When treated with verapamil, patients who were homozygous for the G allele at the tested marker in NOS1AP were more likely to display verapamil-induced QTc interval prolongation, compared to individuals who were not.[4] Individuals of any genotype on other calcium-channel blocker medications did not show this potentiation effect.[4] The association of this NOS1AP marker with verapamil-induced QTc interval prolongation has not yet been independently replicated. In some studies, a prolonged QTc has been shown to increase the risk for developing certain tachyarrhythmias that increase the risk of sudden cardiac death.[5,6] However, QTc interval length depends on many factors, including age, gender and other genes. In addition, QTc interval prolongation has been associated with certain medications and specific disease pathologies.[7,8]

Recommendations: NA

Possible Outcomes: Increased Risk of Prolongation, Typical Risk of Prolongation

Markers or Alleles Tested: NOS1AP [rs10494366]

Ethnic Distribution of Tested Alleles: NA

Limitations and Warnings: NA

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

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Verapamil vs. atenolol

(DC:TB-0232.001 06DEC2012)

Report Type: Pharmacogenetics

About: Verapamil is an L-type calcium-channel blocker that is used to treat hypertension and angina. Its interaction with calcium channels reduces the force and rate of muscle contraction, leading to decreased blood pressure and heart rate.[1]

Atenolol is a cardioselective beta(1)-adrenergic antagonist that is used to manage hypertension and chest pain caused by coronary heart disease. By inhibiting beta(1)-adrenergic receptors in the heart and smooth muscle of the vasculature, atenolol decreases resting heart rate, cardiac output and blood pressure.[2]

Genetics: Calcium-channel blockers, such as verapamil, bind to L-type calcium channels via the alpha1c-subunit, which is a major component of the channel pore and is encoded by the CACNA1C gene. Variants in CACNA1C are associated with a patient's response to different treatment strategies (beta-blockers versus calcium-channel blockers), but the mechanism is unknown.[3] Variants in CACNA1C have also been shown to be associated with blood pressure[4] and a reduction in blood pressure in response to calcium-channel blockers.[5,6]

Based on a study that included patients with hypertension and stable coronary artery disease, those individuals who were homozygous for the A allele at the tested marker in CACNA1C and were treated with verapamil were more likely to have decreased incidence of death, myocardial infarction or stroke compared to individuals with the same genotype who were treated with the beta-blocker atenolol. On the other hand, patients who were homozygous for the G allele and were treated with atenolol were more likely to have decreased incidence of death, myocardial infarction or stroke compared to individuals with the same genotype who were treated with verapamil. For heterozygous patients, no association of increased benefits with atenolol versus verapamil was found. It is important to note that all patients in this study had their blood pressure under control regardless of medication taken. Consequently, the mechanism that explains how different genotypes lead to the different outcomes in response to calcium-channel blockers and beta-blockers is not understood.[3] The association of this CACNA1C marker with benefits on verapamil or atenolol has not yet been independently replicated.

Recommendations: NA

Possible Outcomes: Likely Increased Benefit on Atenolol, Likely Increased Benefit on Verapamil, Likely Similar Benefit on Verapamil or Atenolol

Markers or Alleles Tested: CACNA1C [rs1051375]

Ethnic Distribution of Tested Alleles: NA

Limitations and Warnings: The results of this test are based on a study of patients with hypertenstion and stable coronary artery disease. Thus, they may not apply to patients being treated with verapamil or atenolol for other conditions.

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
995.29 Unspecified adverse effect of other drug, medicinal and biological substance Applies to: • Unspecified adverse effect of medicinal substance NEC properly administered	N/A

References

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Warfarin

(DC:TB-0230.002 31JUL2013)

Report Type: Pharmacogenetics

About: Warfarin is the most frequently used oral anticoagulant worldwide, prescribed for prophylaxis and treatment of thrombotic disorders and thromboembolic events. Such indications include venous thrombosis, pulmonary embolism, atrial fibrillation and cardiac valve replacement. Warfarin is highly efficacious, but its narrow therapeutic index and large interindividual dosing variability lead to a high incidence of adverse events. Improper warfarin dosing is the second leading cause of drug-related emergency room visitation[1] and the number one cited reason for drug-related mortality.[2]

Warfarin acts as an anticoagulant through its ability to inhibit reduction of vitamin K by the vitamin K epoxide reductase complex subunit 1 (VKORC1) enzyme complex. Reduced vitamin K is an essential cofactor of gamma-glutamyl carboxylase, the enzyme that activates coagulation factors II, VII, IX and X. By decreasing the amount of reduced vitamin K available, warfarin depresses the activation of factors II, VII, IX and X into functional, coagulant proteins, and, therefore, decreases the ability of blood to clot. The primary metabolizing enzyme of warfarin is cytochrome P450 2C9 (CYP2C9).[3]

In 2010, the United States Food and Drug Administration (FDA) released a table of dosing recommendations for initiation of warfarin therapy based on VKORC1 and CYP2C9 genotypes. This pharmacogenetics-based dosing table significantly improved accuracy of therapeutic dose prediction compared to the traditional strategy of empirically determined dose.[4]

Genetics: The A allele of the -1639G>A mutation in the VKORC1 gene has been shown to decrease hepatic expression of VKORC1 and, therefore, increase patient sensitivity to warfarin.[5,6,7] Research studies have shown that the therapeutic dose of warfarin in patients with two copies of the A allele was less than the dose of patients with two copies of the G allele, with a difference up to 2.0 to 4.5-fold.[7,8,9]

Individuals carrying *2 or *3 genetic variants of CYP2C9 clear warfarin at a 30% to 50% or 80% to 90% slower rate, respectively, and exhibit increased serum levels of warfarin compared to carriers of only the reference wild-type variant *1.[10,11] CYP2C9*2 and CYP2C9*3 variants may decrease the dose required for effective anticoagulation and may increase the time necessary to achieve stable, therapeutic effect.[9,12] The CYP2C9*6 variant may also reduce metabolic activity and the dose required for effective anticoagulation.[11,13]

Customizing initial warfarin dose to VKORC1 and CYP2C9 genotypes may decrease patient risk of bleeding complications and may reduce the time required to achieve a stable, therapeutic effect.[12,14,15]

Recommendations: The FDA-approved label for warfarin recommends initial dosing based on VKORC1 and CYP2C9 genotypes in addition to clinical factors.[16] The National Institutes of Health (NIH) Clinical Pharmacogenetics Implementation Consortium guidelines recommend initial dosing based on VKORC1 and CYP2C9 genotypes.[11]

Standard doses of warfarin may cause bleeding complications in patients whose genotypes indicate increased or substantially increased sensitivity to warfarin. These patients may require lower initial doses of warfarin. Increased laboratory monitoring may be appropriate.

Classes of drugs that potentially interact with warfarin include the following:[16] inhibitors or inducers of CYP2C9, CYP1A2 and/or CYP3A4, anticoagulants, antiplatelet agents, nonsteroidal anti-inflammatory agents, serotonin reuptake inhibitors, antibiotics, antifungals, and botanical (herbal) products and foods. This list is not complete. Consult the warfarin drug label[16] and the labels of all concurrently used drugs for more specifics about warfarin drug interactions.

Possible Outcomes: Substantially Increased Sensitivity, Increased Sensitivity, Typical Sensitivity

Markers or Alleles Tested: VKORC1 -1639G>A [rs9923231]; CYP2C9 [CYP2C9*2/rs1799853, CYP2C9*3/rs1057910, CYP2C9*6/rs9332131]

Ethnic Distribution of Tested Alleles

Frequency of VKORC1 and CYP2C9 alleles differs significantly between racial and ethnic groups.[17]

Gene	Allele	Caucasian	African American	Asian	Hispanic
VKORC1	-1639: G	59.4%	89.2%	33.3%	56.4%
VKORC1	-1639: A	40.6%	10.8%	66.7%	43.6%
CYP2C9	*1	78.8%	86.7%	92.2%	82.2%
CYP2C9	*2	15.1%	2.8%	2.9%	6.9%
CYP2C9	*3	5.7%	2.0%	3.9%	6.4%
CYP2C9	*6	0.0%	1.0%	0.0%	0.5%

Predicted Warfarin Sensitivity Status

	VKORC1 -1639G>A genotype		
CYP2C9 genotype (below)	G/G	G/A	A/A
*1/*1	Typical sensitivity	Typical sensitivity	Increased sensitivity
*1/*2	Typical sensitivity	Increased sensitivity	Increased sensitivity
*1/*3	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*1/*6	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*2/*2	Increased sensitivity	Increased sensitivity	Substantially increased sensitivity
*2/*3	Increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*2/*6	Increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*3/*3	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*3/*6	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity
*6/*6	Substantially increased sensitivity	Substantially increased sensitivity	Substantially increased sensitivity

Limitations and Warnings: Warfarin can cause major or fatal bleeding. Additional genetic variants within VKORC1, CYP2C9, and other genes not included in this test are known to affect warfarin sensitivity. Not all genetic factors influencing warfarin sensitivity have been identified. Regular monitoring of INR (international normalized ratio) should be performed on all treated patients.

Not all factors influencing warfarin response are known. Important non-genetic factors include age, sex, weight, height, race, ethnicity, comorbidities, warfarin indication, target INR, and use of tobacco and interacting medications.[11]

Compatible ICD-9 Codes: Insurance coverage is not required for genetic testing. The diagnostic code (ICD-9) information provided herein is for insurance information purposes only and does not guarantee insurance coverage for any genetic test, nor is it intended to be a definitive list of diagnosis codes that may be applicable for any individual patient. The testing laboratory will pursue reimbursement directly from the patient should the patient's insurance carrier refuse to provide coverage.

Primary ICD-9 Code(s)	Screening ICD-9 Code(s)
E934.2 Anticoagulants causing adverse effects in therapeutic use	N/A

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