# Simvastatin-induced myopathy

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**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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# Snacking

**Report Type**: Eating Behaviors

**About**: Eating behaviors can be quantified through the use of questionnaires. These quantification methods provide an entry point for studies into the genetics of these behaviors, such as the frequency of snacking. One study suggests that genetic variants may be associated with snacking behavior.[1]

**Genetics**: Snacking behavior is associated with variants in the LEPR gene, which encodes a leptin receptor. Leptin is a hormone that is essential for the regulation of food intake. The association of genotype with snacking behavior is based on a small study of European women. A group of obese women with a body mass index (BMI) greater than or equal to 33 kg/$m^2$ were defined as having "extreme snack behavior" because they scored in the top 5$^{th}$ percentile on a survey of eleven questions about snacking frequency. The genotypes of these women were compared to genotypes of randomly selected control women with a mean BMI of 26 kg/$m^2$. Increased snacking behavior was associated with homozygosity for the G allele at the tested marker.[1] Individuals who are homozygous for the G allele receive an outcome of "Increased", which indicates that they are more likely to experience increased snacking.

**Possible Outcomes**: Increased, Typical

**Recommendations**: N/A

**Markers Tested and Scientific Strength** LEPR [rs2025804]

The rs2025804 marker is rated "2".

"Scientific Strength" refers to the strength of research evidence for the genetic marker and the associated result. A rating of "4" indicates a study of over 2,000 people and at least one study that replicated the results. A rating of "3" indicates a study of over 400 people. A rating of "2" indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of "1" indicates that results are extremely preliminary.

**Limitations and Warnings**: The association between rs2025804 and snacking was detected in Caucasians and may or may not apply to other ethnicities. This association was only studied in women and may or may not apply to men.

**References**

1. de Krom M, van der Schouw YT, Hendriks J, et al. Common genetic variations in CCK, leptin, and leptin receptor genes are associated with specific human eating patterns. *Diabetes.* 2007;56:276-80.

# Sweet tooth

Report Type: Eating Behaviors

About: "Sweet tooth" can be described as the craving of sweet foods. Consumption of some of these foods can lead to an increase in blood glucose levels and the secretion of insulin. Entry of glucose into the pancreatic b-cell is the first step in glucose-induced insulin secretion. This step is facilitated by the glucose transporter type 2 (GLUT2), which is expressed in the pancreas, liver, small intestine, kidney and brain. GLUT2 is thought to be important in the postprandial state and in glucose homeostasis. Genetic variants in the SLC2A2 gene, which encodes GLUT2, have been shown to be associated with sweet tooth.

Genetics: An association between variants in the SLC2A2 gene and sweet tooth was shown in a study of Canadians. The T allele of rs5400 marker was associated with increased consumption of dietary sugar.[1] This result was observed in two independent populations within the study using two different methods of dietary assessment. The first population consisted of patients who were diagnosed with Type 2 diabetes within two months before the start of the study, did not require medication, and had an average BMI of 30.7 kg/m$^2$. Habitual food and beverage intake was assessed using a 3-day food record. Individuals with the T allele consumed a greater amount of sugar compared to individuals who were homozygous for the C allele.

The second population consisted of diabetes-free patients with an average BMI of 22.5 kg/m$^2$. A food frequency questionnaire was used to assess food and beverage intake. Individuals with the T allele consumed more sugar than individuals who were homozygous for the C allele. A specific analysis of sugar subtype showed that people with the T allele consumed more sucrose, fructose and glucose, but not lactose or maltose, than C allele homozygotes. In addition, this increased sugar intake resulted from increased consumption of sweetened beverages and sweets.

Possible Outcomes: Increased, Typical

Recommendations: N/A

Markers Tested and Scientific Strength: SLC2A2 [rs5400]

The rs5400 marker is rated “3”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs5400 with sweet tooth was detected in adults and may or may not apply to children and adolescents.

References

1. Eny KM, Wolever TM, Fontaine-Bisson B, El-Sohemy A. Genetic variant in the glucose transporter type 2 is associated with higher intakes of sugars in two distinct populations. *Physiological genomics.* 2008;33:355-60.

# 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<br>• Embolism of vein<br>• Thrombosis (vein) | N/A |

References

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# Genetic risk for decreased vitamin A

**Report Type**: Nutrition

**About**: Vitamin A consists of a many related compounds, including retinol, retinal and retinoic acid. It is critical for vision, immune system function, bone growth, reproduction and regulation of gene expression.[1,2,3,4] Genetic variants have been shown to be associated with levels of vitamin A.[5]

**Genetics**: Vitamin A levels are associated with variants in the BCMO1 gene, which encodes an enzyme that converts beta-carotene to retinal, the precursor of vitamin A. Screening of the BCMO1 gene identified two common variants that resulted in reduced activity of BCMO1 by almost 57 percent *in vitro*.[5] The *in vitro* results were confirmed using healthy female volunteers that were given a pharmacological dose of beta-carotene and assessed for beta-carotene metabolism. Female individuals who had the R267S (rs12934992) or A379V (rs7501331) allele showed approximately 69% reduction in beta-carotene metabolism as measured by retinyl palmitate:beta-carotene ratios.[5]

An outcome of "Inconclusive," means that there was not enough clinical evidence to determine how the patient's genotype relates to the efficiency of converting beta-carotene to vitamin A.

**Possible Outcomes**: Optimize Intake, Stay Balanced, Inconclusive

**Recommendations**: N/A

**Markers Tested and Scientific Strength**

| Gene/Locus[a] | Marker[b] | Associated Allele[c] | Scientific Strength[d] |
|---|---|---|---|
| BCMO1 | rs7501331 | T | 2 |
| BCMO1 | rs12934922 | T | 2 |

[a]Gene or locus containing the tested marker

[b]Marker tested

[c]"Associated Allele" refers to the allele that is associated with decreased vitamin A levels.

[d]"Scientific Strength" refers to the strength of research evidence for the genetic marker and the associated result. A rating of "4" indicates a study of over 2,000 people and at least one study that replicated the results. A rating of "3" indicates a study of over 400 people. A rating of "2" indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of "1" indicates that results are extremely preliminary.

**Limitations and Warnings**: This test reports on genetic predisposition for decreased vitamin A levels. Other tests are available to assess a patient's vitamin A plasma levels. An 'Optimize Intake' genetic result does not indicate that the patient's actual vitamin A plasma levels are too low, but rather that the patient may be genetically predisposed to have lower

vitamin A plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin A plasma levels are optimal.

The association of rs7501331 and rs12934922 with decreased vitamin A levels was detected in female patients from the United Kingdom and may or may not be applicable to males or other ethnicities.

References


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# Genetic risk for decreased vitamin B12

Report Type: Nutrition

About: Vitamin B12 contributes to brain and nervous system function and the health of red blood cells. It is also a critical component for DNA synthesis and regulation.[1] Symptoms of vitamin B12 deficiency can vary but may include fatigue, weakness, bloating, or numbness and tingling in the hands and feet. The recommended intake for adults is 2.4 micrograms per day. Genetic variants are associated with vitamin B12 levels.[2,3,4]

Genetics: Vitamin B12 plasma levels are associated with variants in the FUT2 gene, which encodes a protein involved in protein maturation. Multiple studies have found that individuals with the G allele of the rs602662 marker had lower plasma levels of vitamin B12 than individuals who were homozygous for the A allele.[2,3,4] A genome-wide association study (GWAS) with replication identified an association between rs602662 and vitamin B12 levels.[4] A second GWAS with replication that looked at a population of women also found an association between rs602662 and vitamin B12 levels.[3] Additionally, a meta-analysis came to the same conclusion, although it should be noted that the study included individuals from the second GWAS.[2] Individuals who have the G allele of rs602662 receive an outcome of “Optimize Intake”.

Possible Outcomes: Optimize Intake, Stay Balanced

Recommendations: N/A

Markers Tested and Scientific Strength: FUT2 [rs602662]

The rs602662 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: This test reports on genetic predisposition for decreased vitamin B12 levels. Other tests are available to directly assess a patient’s vitamin B12 plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin B12 plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin B12 plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin B12 plasma levels are optimal.

The association of rs602662 with vitamin B12 levels was detected in Caucasians and may or may not apply to other ethnicities.

References

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# Genetic risk due to decreased vitamin B2

**Report Type**: Nutrition

**About**: Vitamin B2, or riboflavin, is a cofactor of the enzyme MTHFR, which is involved in folate metabolism. Folate can lower plasma levels of homocysteine, which, at high levels, is a risk factor for cardiovascular disease and stroke.[1,2] An individual's genotype can indicate how riboflavin levels may affect levels of homocysteine.

**Genetics**: The rs1801133 marker is located in the MTHFR gene. In European individuals who were homozygous for the T allele at this marker, riboflavin was the second strongest predictor of homocysteine levels (after folate levels), with there being an inverse relationship between riboflavin and plasma homocysteine levels.[3,4] In individuals who were homozygous for the T allele, homocysteine levels were highest in people with low riboflavin or vitamin B2 levels. Furthermore, riboflavin supplementation reduced homocysteine levels in these individuals.[5,6] As high homocysteine levels are known to be a risk factor for cardiovascular disease and stroke,[1,2] individuals who are homozygous for the T allele receive an outcome of "Optimize Intake" of riboflavin. On the other hand, vitamin B2 supplementation had a relatively small impact on homocysteine levels in people who have a C allele; therefore, these individuals receive a "Stay Balanced" outcome.

**Possible Outcomes**: Optimize Intake, Stay Balanced

**Recommendations**: Please also see the genetic test results for related conditions: "Genetic risk for decreased folate" and "Methotrexate toxicity".

**Markers Tested and Scientific Strength**: MTHFR [rs1801133]

The rs1801133 marker is rated "3".

"Scientific Strength" refers to the strength of research evidence for the genetic marker and the associated result. A rating of "4" indicates a study of over 2,000 people and at least one study that replicated the results. A rating of "3" indicates a study of over 400 people. A rating of "2" indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of "1" indicates that results are extremely preliminary.

**Limitations and Warnings**: This test reports on genetic predisposition for increased homocysteine levels due to lower levels of vitamin B2. Other tests are available to assess a patient's levels of homocysteine and riboflavin in blood. An "Optimize Intake" genetic result does not indicate that the patient's actual blood levels of riboflavin are too low, but rather that the patient may be genetically predisposed to have lower levels of riboflavin in blood. Similarly, a "Stay Balanced" genetic result does not indicate that the patient's actual riboflavin levels in blood are optimal.

The association of rs1801133 with risk due to vitamin B2 levels was detected in Caucasians and may or may not apply to other ethnicities.

**References**

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# Genetic risk for decreased vitamin B6

**Report Type**: Nutrition

**About**: Vitamin B6 contributes to nervous system function and protein and sugar metabolism.[1] Vitamin B6 deficiency is rare in the United States because most people receive sufficient amounts of vitamin B6 from a healthy diet. Genetic variants are associated with levels of vitamin B6.[2,3]

**Genetics**: Vitamin B6 levels are associated with variants of the NBPF3 gene. In multiple studies, patients who had the C allele of the rs4654748 marker had lower levels of B6 than patients who were homozygous for the T allele. In a genome-wide association (GWA) study of Caucasian individuals, the association of rs4654748 with vitamin B6 levels was identified and replicated. A meta-analysis of the original and replicated groups showed that vitamin B6 levels were 1.45 ng/mL lower per C allele.[2] Another meta-analysis of three GWA studies looked at levels of plasma PLP, an active form of vitamin B6. This study found that individuals who were homozygous for the T allele at rs4654748 had higher plasma PLP levels than individuals with one or more C alleles.[3] Individuals who have the C allele receive an outcome of “Optimize Intake”.

**Possible Outcomes**: Optimize Intake, Stay Balanced

**Recommendations**: N/A

**Markers Tested and Scientific Strength**: NBPF3 [rs4654748]

The rs4654748 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

**Limitations and Warnings**: This test reports on genetic predisposition for decreased vitamin B6 levels. Other tests are available to directly assess a patient’s vitamin B6 plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin B6 plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin B6 plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin B6 plasma levels are optimal.

The association of rs4654748 with vitamin B6 levels was detected in Caucasians and may or may not apply to other ethnicities.

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# Genetic risk for decreased vitamin C

**Report Type**: Nutrition

**About**: Vitamin C, or L-ascorbic acid, must be acquired from dietary sources. Severe vitamin C deficiency ultimately leads to scurvy. Variations in vitamin C levels have been associated with a wide range of chronic complex diseases, such as atherosclerosis, type 2 diabetes and cancer.[1] These associations are thought to result from a contribution of vitamin C as an antioxidant, as well as its role in the synthesis of collagen and various hormones. Genetic variants have been shown to be associated with vitamin C levels.[2]

**Genetics**: Vitamin C plasma levels are associated with variants in the SLC23A1 gene, which encodes a protein that transports vitamin C into cells. A large study that examined circulating levels of L-ascorbic acid in Caucasians found that the A allele of the rs33972313 marker in SLC23A1 was associated with decreased levels of circulating L-ascorbic acid in a discovery cohort, four replication cohorts and a meta-analysis.[2] The rs33972313 marker was associated with reduction of L-ascorbic acid levels of -4.15 µmol/L per A allele in the discovery cohort and -5.98 µmol/L per A allele in the pooled analysis.[2]

**Possible Outcomes**: Optimize Intake, Stay Balanced

**Recommendations**: N/A

**Markers Tested and Scientific Strength**: SLC23A1 [rs33972313]

The rs33972313 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

**Limitations and Warnings**: This test reports on genetic predisposition for decreased vitamin C levels. Other tests are available to assess a patient’s vitamin C plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin C plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin C plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin C plasma levels are optimal.

The association of rs33972313 with vitamin C levels was detected in Caucasians and may or may not apply to other ethnicities.

References

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# Genetic risk for decreased vitamin D

**Report Type**: Nutrition

**About**: Vitamin D is important for the absorption and use of calcium.[1] Exposure to sunlight is an important determinant of a person's vitamin D level because there are few natural dietary sources of vitamin D. In addition to environmental factors, genetic variants have also been shown to be associated with plasma levels of vitamin D.[2,3]

**Genetics**: Vitamin D plasma levels are associated with variants in the GC gene, which encodes a vitamin D-binding protein. The G allele of the rs2282679 marker is associated with decreased plasma levels of 25-hydroxyvitamin D, the major circulating form of vitamin D. Individuals who have the G allele of the rs2282679 marker may have lower plasma levels of vitamin D than patients who are homozygous for the T allele. This result may be due to a reduced ability to transport vitamin D in the body.[2,3] Individuals who have the G allele of rs2282679 receive an outcome of "Optimize Intake".

**Possible Outcomes**: Optimize Intake, Stay Balanced

**Recommendations**: N/A

**Markers Tested and Scientific Strength**: GC [rs2282679]

The rs2282679 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

**Limitations and Warnings**: This test reports on genetic predisposition for decreased vitamin D levels. Other tests are available to assess a patient’s vitamin D plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin D plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin D plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin D plasma levels are optimal.

The association of rs2282679 with vitamin A levels was detected in Caucasians and may or may not apply to other ethnicities.

References

1. Holick MF. Vitamin D and bone health. *The Journal of nutrition.* 1996;126:1159S-64S.
2. Ahn J, Albanes D, Berndt SI, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. *Carcinogenesis.* 2009;30:769-76.

3. Wang TJ, Zhang F, Richards JB, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. *Lancet (London, England).* 2010;376:180-8.

# Genetic risk for increased vitamin E

**Report Type**: Nutrition

**About**: Vitamin E is a group of eight antioxidant molecules, with alpha-tocopherol being the most abundant in the body. Vitamin E functions in the immune system and regulates metabolic processes;[1,2] increased levels are associated with decreased frailty and disability in old age.[3] Genetic variants have been shown to be associated with increased vitamin E plasma levels.[4]

**Genetics**: Vitamin E plasma levels are associated with variants near the APOA5 gene, which encodes an apolipoprotein involved in the regulation of triglyceride plasma levels. Vitamin E absorption and distribution follows processes similar to those used in fatty acid digestion and metabolism.[4] In a genome-wide association study, individuals with the A allele of the rs12272004 marker, which is near the APOA5 gene, had increased plasma levels of alpha-tocopherol compared to individuals who were homozygous for the C allele. The association was identified in one population and replicated in two other, separate populations. A meta-analysis of all three studies confirmed the result.[4] Individuals who have the A allele receive an outcome of “Stay Balanced”.

**Possible Outcomes**: Optimize Intake, Stay Balanced

**Recommendations**: N/A

**Markers Tested and Scientific Strength**: Intergenic [rs12272004]

The rs12272004 marker is rated “4”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

**Limitations and Warnings**: This test reports on genetic predisposition for elevated vitamin E levels. Other tests are available to assess a patient’s vitamin E plasma levels. An ‘Optimize Intake’ genetic result does not indicate that the patient’s actual vitamin E plasma levels are too low, but rather that the patient may be genetically predisposed to have lower vitamin E plasma levels. Similarly, a ‘Stay Balanced’ genetic result does not indicate that the patient’s actual vitamin E plasma levels are optimal.

The association of rs12272004 with vitamin E levels was detected in Caucasians and may or may not apply to other ethnicities.

**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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# Weight loss-regain

Report Type: Body and Weight

About: Weight loss is beneficial to overweight and obese patients, but keeping excess weight off is also important for maintaining good health. The propensity to regain weight after it is lost varies among individuals, and genetic variants have been shown to be associated with weight regain.[1]

Genetics: Weight loss-regain is associated with variants in the ADIPOQ gene, which encodes adiponectin, a hormone that is often lower in obese patients. In one study of obese Spanish people, individuals were enrolled in an 8-week, low-calorie diet. Measurements were conducted at baseline and at 0, 32 and 60 weeks after the diet. Clinical manifestations of metabolic syndrome disappeared after the diet in individuals who were homozygous for the G allele at the rs17300539 marker in the ADIPOQ gene. Specifically, no differences associated with the genotype were observed at week 8 for insulin resistance, insulin values or triacylglyceride values. By week 32, individuals who were homozygous for the G allele had recovered the risk of metabolic co-morbidities; by week 60, the improvement in these individuals disappeared.[1] At week 60, the individuals who were homozygous for the G allele showed an average regain of 1.4±1.0 kg and increased insulin resistance, while the individuals who had the A allele showed no significant weight regain and no increased insulin resistance. Thus, individuals who are homozygous for the G allele receive an outcome of “More Likely to Regain Weight” and individuals with other genotypes receive an outcome of “Weight Loss Maintained”.

Possible Outcomes: More Likely to Regain Weight, Weight Loss Maintained

Recommendations: N/A

Markers Tested and Scientific Strength: ADIPOQ [rs17300539]

The rs17300539 marker is rated “2”.

“Scientific Strength” refers to the strength of research evidence for the genetic marker and the associated result. A rating of “4” indicates a study of over 2,000 people and at least one study that replicated the results. A rating of “3” indicates a study of over 400 people. A rating of “2” indicates a study of less than 400 people; studies in this category are preliminary but pass the criteria for statistical significance. A rating of “1” indicates that results are extremely preliminary.

Limitations and Warnings: The association of rs17300539 with weight loss regain was detected in a small study of Spanish individuals and may or may not apply to other ethnicities.

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