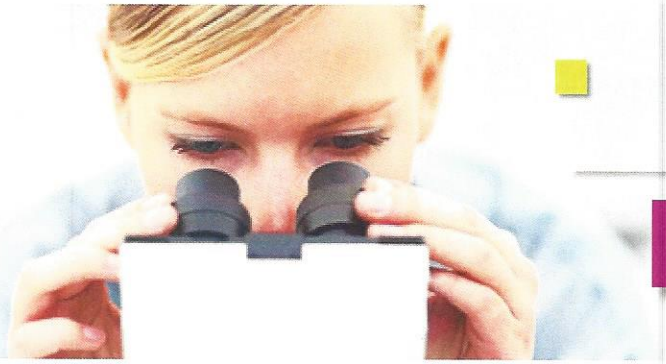
MTHFR Genotyping



Nutrient Correlation Wheel

Vitamin B3
Maintains proper methylation of genes that suppress tumor formation and growth.[3,4,5,6]

Vitamin B6
Cofactor for the enzyme (serine hydroxyl methyl transferase) that transfers methyl units.[7,8]

Vitamin B12
B12 is a key enzyme needed in the synthesis of S-adenosylmethionine (SAMe), the body's most important methyl donor. Methionine synthase, an enzyme that catalyzes the methylation cycle is B12 dependent.[9,10,11]

Folate
Methyl donor for many reactions in the body, including neurotransmitter synthesis and conversion of homocysteine to methionine; Precursor to SAMe; Required for proper DNA synthesis.[12,13,14]

Vitamin B2
Helps recycle folate into a usable methyl-donor form; **Precursor to FAD (flavin** adenine dinucleotide) which assists methylation reactions.[1,2,3]

Choline
A major source of methyl groups **(methyl donor); Deficiency linked** to DNA damage.[15,16,17]

Serine
Important methyl donor, especially in the case of folate **deficiency.**[18,19,20]

METHYLATION

Zinc
Deficiency can lower the ability to use methyl groups from methyl donors such as SAMe, thus causing global hypo-methylation of DNA.[32,33,34]

Glutathione
Deficiency impairs methylation reactions and hinders synthesis of the methyl donor SAMe.[21,22]

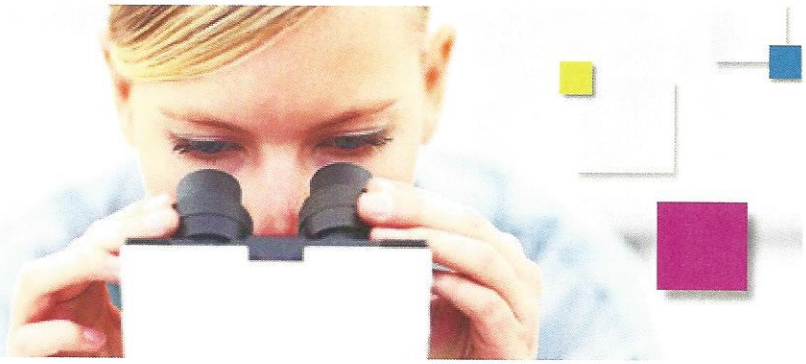
Vitamin C
Deficiency alters methylation patterns in cancer cells; Also a cofactor for methylating enzymes.[23,24]

Selenium
Inhibits a methylating enzyme (DNA methyltransferase) in cancer genes, effectively turning them off; Selenoproteins protect DNA and metabolize methionine.[30,31]

Magnesium
Its role in the methylation of genes that affect glucose metabolism may explain the link between magnesium **deficiency and diabetes.**[28,29]

Copper
Several key enzymes needed for methylation reactions are copper dependent.[25,26,27]

ApoE Genotyping



Approximately 45% of individuals carry one or more of the high risk variants within the APoE gene.

What is ApoE?

Apolipoprotein E is a component of plasma lipoproteins (eg.VLDL, HDL, chylomicrons) and determines an individual's genetic risk associated with the Apolipoprotein E gene. Apo E is involved in the metabolism of cholesterol and triglycerides, and variants in this gene can have clinically relevant implications for disease risk as well as one's response to statin therapy, dietary fat, and other risk factors (eg., smoking and alcohol consumption). Approximately 45% of individuals carry one or more of the high risk variants within the ApoE gene. The results of the genotyping of Apolipoprotein E have important implications in the treatment strategies for individual patients in reducing cardiovascular disease risk.

What does ApoE do?

- ApoE plays a role in the transport and metabolism of plasma lipoproteins (which carry cholesterol).
- The role of ApoE is to bind to cellular receptors and mediate clearance of the lipoproteins and their remnants from the bloodstream.
- ApoE functions mainly in the liver and brain but is also found in other tissues throughout the body.

Fig. 1. Odds Ratios for Coronary Disease With Apolipoprotein E Genotypes Using Individuals With the e3/e3 Genotype as the Reference Group, Based on Data From 21, 331 Cases and 47,467 Controls in Studies With 500 or More Cases.

Size of data markers is proportional to the inverse of the variance of the odds ratios (e3/e3 is represented by a square with arbitrary fixed size) and vertical lines represent 95% confidence intervals (CIs).

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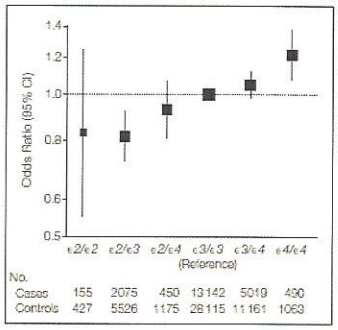


What does ApoE Genotype Mean for Cardiovascular Disease Risk?

There are 6 possible ApoE genotypes:

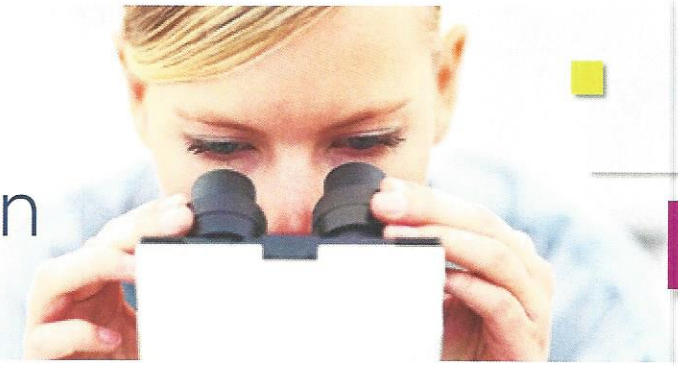
e2/e2	e2/e3
e3/e3	e3/e4
e4/e4	e2/e4

GENOTYPE	SUMMARY/RECOMMENDATION
e3/e3 or e2/e4	• e3 is considered normal with no associated risk factors. • e3/e3 is the most common genotype (55% of population) • Normal treatment & dietary guidelines as determined by lipid profiles
e2/e2 or e2/e3	• e2 carriers with high cholesterol and triglycerides tend to respond well to statin therapy • May not respond as well to low-fat diet alone • Moderate alcohol intake may have positive effects on cholesterol profiles in e2 carriers • e2 is often associated with lower levels of LDL cholesterol but higher triglycerides • e2 carriers (especially e2/e2) may be more likely to develop type III hyperlipoproteinemia. Monitor for symptoms. • Type III hyperlipoproteinemia is associated with increased cholesterol and triglycerides; yellow fatty skin lesions called xanthomas; early development of cardiovascular disease • Type III hyperlipoproteinemia is triggered by additional factors, including diabetes, hypothyroidism, obesity, and possibly other unknown genetic factors
e3/e4 or e4/e4	• e4 is associated with increased levels of LDL cholesterol and triglycerides Higher risk of early development of coronary heart disease and atherosclerosis • e4 carriers may not respond well to statin therapy • e4 carriers tend to respond best to very low fat diet due to higher sensitivity to fat intake • Risks associated with smoking and alcohol intake are higher for e4 carriers

How to use ApoE Genotyping

- ApoE genotyping is best used in conjunction with additional lipid profile monitoring
- ApoE genotyping is a useful tool to help determine the best dietary and pharmaceutical approach to maintaining healthy lipid levels
- Maintaining healthy lipid levels can decrease risk of cardiovascular disease, strokes, and other health problems

Factor V Leiden



What is factor V Leiden?

- Factor V Leiden refers to a mutation in the gene that manufactures a protein called factor V which is involved in the process of blood coagulation. The factor V protein is also called coagulation factor V, and sometimes proaccelerin or labile factor.

Risks associated with factor V Leiden

- People with the factor V Leiden gene have an increased risk of developing a type of blood clot called a deep venous thrombosis (DVT).

- The factor V protein functions as a cofactor that activates an enzyme called thrombin. Thrombin in turn cleaves fibrinogen to form fibrin, which functions to cross link and form the dense meshwork that makes up the majority of a blood clot when activated.

- Factor V Leiden thrombophilia also increases the risk that clots will break away from their original site and travel through the bloodstream. These clots can lodge in the lungs, where they are known as pulmonary emboli.

- Although factor V Leiden thrombophilia increases the risk of blood clots, only about 10 percent of individuals with the factor V Leiden mutation ever develop abnormal clots.

- Women with the factor V Leiden R506Q gene mutation (called R506Q) have increased risk of clotting in pregnancy in the form of deep vein thrombosis and pulmonary embolism. They also may have a small increased risk of preeclampsia, may have a small increased risk of low birth weight babies, may have a small increased risk of miscarriage and stillbirth due to either clotting in the placenta or umbilical cord. Please note: Many women with this mutation go through one or multiple pregnancies with no difficulties, while others may have complications or develop clots during pregnancy.

- If you have factor V Leiden and have developed blood clots, medications can lessen your risk of developing additional blood clots and help you avoid potentially serious complications.

Who should be tested?

- Those who have had an unexplained blood clot (thrombotic episode), especially under the age of 50.
- Those who have recurrent DVT/VTE (venous thrombo embolism) episodes.
- Those who have a strong family history of thrombosis.
- Women considering pregnancy.

Results R506Q Mutation

There are three possible outcomes:

Negative: zero copies of this genetic mutation

- This genotype indicates normal enzyme activity and is not associated with any increased risks of thrombosis (blood clots).
- The normal average risk of developing an abnormal blood clot is about 1 in 1,000 per year in the general population.

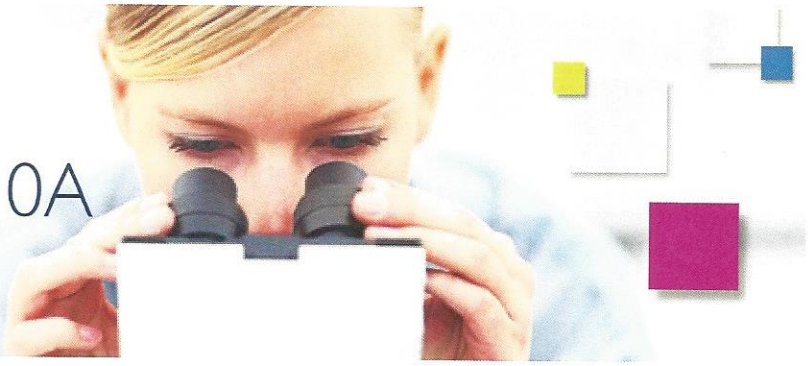
Heterozygous: one copy of this genetic mutation

- This result is associated with an increased risk of deep vein thrombosis (excessive blood clotting in veins).
- The presence of one copy of the factor V Leiden mutation (a heterozygous positive result) increases this risk 4-8 fold, from normal (1 in 1000) to between 1 in 250 to 1 in 125.
- Heterozygosity for factor V Leiden is associated with a two- to threefold increase in relative risk for pregnancy loss, and possibly other pregnancy complications such as preeclampsia, fetal growth retardation, and placental abruption. Please note: Many women with this mutation go through one or multiple pregnancies with no difficulties.

Homozygous Positive: Two copies of this genetic mutation

- This result indicates increased clotting activation (increased chance that blood clots begin to form) and is associated with an increased risk of deep vein thrombosis (excessive blood clotting in veins).
- The presence of two copies of the factor V Leiden mutation (a homozygous positive result) increases the risk of developing blood clots from 0.1% (normal risk of 1 in 1000) to about 8% chance (roughly 1 in 12) per year.
- Some women with the R506Q mutation in factor V Leiden have an increase in relative risk for pregnancy complications such as preeclampsia, fetal growth retardation, and placental abruption. Please note: Many women with this mutation go through one or multiple pregnancies with no difficulties.

Prothrombin G20210A



What is Prothrombin?

- Prothrombin is a protein that causes blood to coagulate and form blood clots. A genetic mutation (called G20210A) in the production of this protein is a risk factor for thrombosis (blood clots) including deep venous thrombosis (DVT). This mutation in the gene encoding the clotting factor prothrombin is found in about 1 in 50 persons in the US. It raises the risk of thrombosis significantly for both males and females in all age groups.
- The Prothrombin G20210A mutation increases circulating prothrombin levels. This appears to create a hypercoagulable state.

Risks associated with Prothrombin

- This gene provides instructions for making a protein called prothrombin (also called coagulation factor II). Coagulation factors are essential proteins for normal blood clotting. After an injury, clots protect the body by sealing off damaged blood vessels, preventing additional blood loss.
- This mutation causes the gene to be overactive and leads to the excess production of prothrombin, which may lead to high rates of blood clot formation.
- People who have prothrombin mutation G20210A have a 2-to-3 fold increase in the risk of DVT (Deep Vein Thrombosis). Persons who have this mutation plus the factor V Leiden mutation have a 10-to-20 fold increase in thrombotic risk.
- Other factors also increase the risk of blood clots in people with prothrombin thrombophilia (a disorder that causes overcoagulation of the blood). These factors include increasing age, obesity, trauma, surgery, smoking, the use of oral contraceptives (birth control pills) or hormone replacement therapy, and pregnancy.

Who should be tested?

- Those who have had a blood clot in one of the deep veins of the body (also called deep vein thrombosis or DVT)
- Those who have have a blood clot that has traveled to the lung (called a pulmonary embolism or PE)
- Those who have had a blood clot in an unusual site (such as the mesenteric or cerebral sinus vein)
- Those who have suffered a heart attack or stroke at a young age
- Those who have a history of recurrent pregnancy loss or stillbirth.

Results - F2 G20210A Mutation

There are three possible outcomes:

Negative: zero copies of this genetic mutation

- This genotype indicates normal enzyme activity and is not associated with any increased risks of thrombosis (blood clots).
- Normal risk of abnormal blood clots is 1 in 1,000 per year (0.10%)

Heterozygous: one copy of this genetic mutation

- This result is associated with an increased risk of deep vein thrombosis (excessive blood clotting in veins).
- Inheriting one copy of this gene mutation may increase that risk to 2 to 3 in 1,000. (0.2 – 0.3%) compared to normal (0.1%).
- The G20210A mutation is associated with an increased risk of myocardial infarction (heart attack) (4-fold in women, and a 1.5-fold increase in risk for men).
- This result is also associated with an increase in first trimester miscarriage and pregnancy complication rates compared to the general population. Please note: Many women with this mutation go through one or multiple normal pregnancies with no difficulties.

Homozygous Positive: Two copies of this genetic mutation

- This result is associated with increased risk of deep vein thrombosis (excessive blood clotting in veins).
- The homozygous positive subject has increased risk for blood clot formation by 10 fold over a ten year period.
- This result is also associated with an increased risk of myocardial infarction (heart attack) (4-fold in women, and a 1.5-fold increase in risk for men).
- Evidence suggests that increased prothrombin levels, which occur when a person has this genetic mutation, might affect critical aspects of placental development (e.g., cell adhesion, smooth muscle proliferation, and vasculogenesis). Please note: Many women with this mutation go through on or multiple normal pregnancies with no difficulties.
- This result is associated with an increase in first trimester miscarriage and pregnancy complication rates.