CV Health Genomic Markers

Genomics & Cardiovascular Risk: APO-E

Apolipoprotein E (apoE) plays a key role in the metabolism of cholesterol and triglycerides by helping to mediate the clearance of chylomicrons and VLDL remnants from dietary fat. The 3 major isoforms of apoE (apoE2, apoE3, and apoE4) are encoded by 3 common alleles at the APOE locus, giving rise to 6 common phenotypes (E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, and E4/E4). The differences between these genotypes influence the biological functions of apoE, disease risk, and treatment response. Total- and LDL-cholesterol concentrations increase in a step-wise fashion with sum of the APOE alleles (E2/2 < 2/3 < 2/4 < 3/3 < 4/3 < 4/4).

ApoE2

- Highest apoE levels
- Tendency toward lower LDL- C and higher HDL-C, but higher triglycerides, (TGs) esp. in response to dietary carbohydrates.
- Higher antioxidant activity3 and reduced risk of CHD, MI, stroke, and non-alcoholic fatty liver disease.

Treatment Considerations

- Minimize high-glycemic index foods (produce the largest TG response in E2s
- Lipid-lowering effect of a low-saturated fat and low-cholesterol diet may be least effective for E2s; However, MI risk may be increased with high saturated fat.
- Alcohol may reduce LDL-C in men (neutral in women) and increase HDL-C.
- Dietary fiber and exercise help improve the lipid profile.
- Fish oils may reduce TGs most effectively in E2 individuals.
- Some studies suggest most favorable lipid response to statins.
- Fibrates help reduce TGs and ApoB.
- Oral estrogens will increase TGs the most in E2s; transdermal ERT is safer.

ApoE3

- Intermediate apoE levels
- E3/E3 is the most common genotype and is considered neutral relative to E2 and E4.
- Only a moderate tendency toward high LDL-C and low HDL-C.
- Risk is intermediate between E2 and E4 for CHD, MI, and stroke.

Treatment Considerations

- A low saturated-fat and low-cholesterol diet has a moderate lipid-lowering effect in E3s; follow recommendations for E4 if dyslipidemia.
- Dietary fiber, fish oils, and exercise generally improve the lipid profile in this genotype.
- Alcohol appears to have a neutral effect on LDL-C.
- E3/E3 individuals generally respond well to statins. Statin mimetics include niacin, red rice yeast, and policosanol.
- HRT generally improves the lipid profile in all genotypes, including post-menopausal E3 carriers.

ApoE4

- Lowest apoE levels
- Tendency toward higher ApoB8, total- and LDL-cholesterol and lower HDL-C.
- Increased risk of CHD, MI, stroke, metabolic syndrome, obesity, and toxicity by heavy metals such as lead and mercury.

Treatment Considerations

- Reduce excess weight, which synergizes with E4 in affecting insulin and lipids.
- A low-saturated fat and low-cholesterol diet most effectively lowers LDL-C in E4s.
- Minimize high-glycemic index foods, which augments E4-associated CHD risk.
- Minimize alcohol (may raise LDL-C in men and reduce hippocampal volume when high Hcy).
- Fish oils lower TGs but may raise LDL-C the most in E4s (DHA more than EPA).
- Mixed studies on statins: E4 diabetics may have best lipid-lowering response to statins. Statins may also improve odds of survival after MI in E4 individuals.
- Mixed studies on benefits from fibrates.

Genomics & CV Risk: Factor II & Factor V Leiden

Factor II is also known as **prothrombin**. In the coagulation cascade, the conversion of Factor X to Xa stimulates the conversion of prothrombin to its active form, thrombin, which forms the essential part of a clot. The conversion of prothrombin to thrombin is also catalyzed by **Factor V,** as it combines with Factor X. A mutation in this gene is referred to as **Factor V Leiden**. Both of these polymorphisms significantly increase risk of clot formation.

Factor II

- Elevated levels of prothrombin, resulting in greater thrombin formation and coagulability.
- Increased risk of venous thrombosis and ocular vascular occlusions; thromboembolism risk is exacerbated by coexisting Factor V Leiden.
- Increased risk of CVD,5 carotid atherosclerosis, atrial fibrillation, and MI when other CV risk factors present.
- Increased risk of recurrent pregnancy loss.

Factor V Leiden

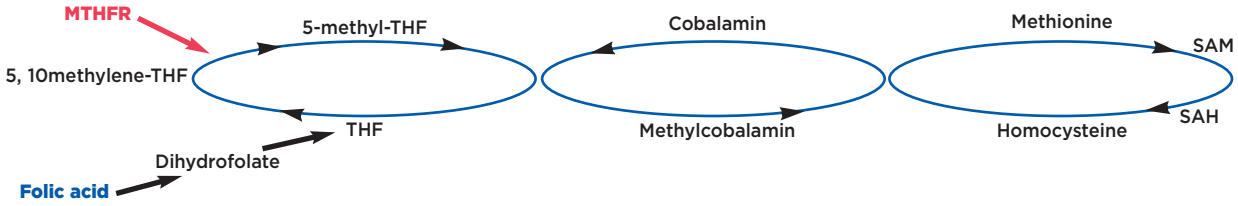
- Greater thrombin formation, due to impaired inactivation of the Factor V molecule.
- Increased risk of clot formation, thromboembolism, and ocular vascular occlusion.
- Coagulation risk increases with age, high Hcy, and coexisting SNPs in Factor II or MTHFR.
- Increased risk of MI when other CV risk factors present.
- Increased risk of CAD if coexisting MTHFR SNP.
- Increased risk of pregnancy complications and recurrent pregnancy loss.

Treatment Considerations

- Exercise caution with factors that increase coagulation risk (e.g., smoking, hypertension, obesity, surgery, immobilization, trauma, diabetes mellitus, pregnancy); anticoagulation may be indicated for pregnant women with combined Factor II and V Leiden.
- Avoid oral contraceptives and oral estrogens; conjugated equine estrogens dramatically raise coagulation risk in carriers of the SNPs.
- Platelet activation inhibitors help reduce coagulation risk (e.g., fish oils, garlic, onions, ginger, ginkgo biloba, thyme, rosemary, genestein, aspirin).
- Glycyrrhizin (licorice) inhibits conversion of prothrombin to thrombin; monitor blood pressure to prevent hypertension.
- Nattokinase (fermented soybean extract) and serrapeptase (from Serratia) potentiate fibrinolytic activity.

Genomics & Cardiovascular Risk: MTHFR

5,10-methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism, facilitating the formation of methyltetrahydrofolate, a required cofactor in the remethylation of homocysteine (Hcy) to methionine. Variants of the MTHFR polymorphisms, 677CT and 1298AT, result in reduced MTHFR enzyme activity, impaired methylation, and increased risk of various disorders, including cardiovascular. Of the two SNPs, 677CT is more clinically significant.



677CT -/- 1298 AC -/-	677CT -/- 1298 AC +/-	677CT -/- 1298 AC +/+	677CT +/- 1298 AC -/-	677CT +/- 1298 AC +/-	677CT +/+ 1298 AC -/-	677CT +/+ 1298 AC +/-
Baseline normal enzyme activity	Baseline normal enzyme activity	**30-40% reduced enzyme activity**	**30-40% reduced enzyme activity**	50-60% reduced enzyme activity	60-70% reduced enzyme activity	60-70% reduced enzyme activity

MTHFR polymorphisms have been associated with:

- Reduced ability to remethylate Hcy to methionine; impaired methylation
- Increased risk of increased homocysteine (and S-adenosylhomocysteine, or SAH), especially in conjunction with low B-vitamin status. Hcy may damage the endothelium and contribute to atherosclerosis.
- (CV): Increased risk of atherosclerosis, stroke, abdominal aortic aneurysm, essential hypertension, venous thrombosis8
- (Non-CV): Increased risk of diabetic depression, schizophrenia, autism, osteoporosis, certain cancers, and pregnancy-related disorders

Lifestyle considerations

- **Avoid smoking** (synergizes with the SNP to promote atherosclerosis)
- **Avoid excess coffee** (synergizes with SNP to increase Hcy)
- **Ensure adequate exercise**

Dietary considerations

- **Emphasize** dark green vegetables and other folate-rich foods (e.g., legumes, liver, wheat germ, fortified grains, and orange juice)
- **Mediterranean diet** lowers Hcy more effectively in carriers of the SNP.

Supplement considerations

- **Folic acid, vitamin B12, B6 (as p5p)**– Low levels promote homocysteinemia and hypertension in carriers of the SNP. Serum folate levels may also be lower in 677TT individuals.
- **Consider active sources of folate**, such as L-5-methyl-THF or Ca folinate.
- **Riboflavin (B2)** is the cofactor for MTHFR; insufficiency limits enzyme activity and exacerbates high Hcy.
- **Consider alternate methyl donors,** e.g., betaine (TMG) or DMG. (***Note:*** These will NOT compensate for deficient folate.)

Rule out folate antagonists

- **Folate absorption is reduced by:** sulfasalazine; cimetidine and antacids.
- **Folate antagonists include:** aminopterin, methotrexate, pyrimethamine, trimethoprim, triamterene.

Medication considerations

- **ACE Inhibitors** may lower BP more effectively in 677TT individuals.
- **Pravastatin** appears to protect against CHD only in 677CC (-/-) individuals. Other studies suggest that statins' effect on coronary function may not be influenced by SNP.
- **HRT's** effects on Hcy also not influenced by SNP.
- **Fibrates** may increase Hcy levels; effects appear independent of the SNP.

Genova Diagnostics®
Innovative Testing for Optimal Health
63 Zillicoa Street
Asheville, NC 28801
828.253.0621
www.GDX.net

n,ig,CVHealth_Genomic,120909