CardioGenomicPlus Profile (Buccal Cells)

GENOVATIONS™

63 Zillicoa Street
Asheville, NC 28801

Patient: **SAMPLE PATIENT**
DOB:
Sex:
MRN:

Apo E

Location:
Chromosome 19
APOE
APO E2: cys / cys
APO E3: cys / arg
APO E4: arg / arg
Your Genotype:

2	3

The two SNPs lead to 3 possible variants for each chromosome, known as ApoE2, E3, & E4.

Apolipoprotein E : CHOLESTEROL REGULATION

Apolipoprotein E (Apo E) plays a key role in lipid metabolism by helping to remove dietary cholesterol (chylomicrons and VLDL) from the bloodstream.

Health Implications

- The E2/E3 genotype is common, accounting for 10-15% of most populations.
- ApoE2 is associated with lower LDL-C and higher HDL-C, but also higher triglycerides (TGs).
- Slightly increased risk of type 2 diabetes and diabetic nephropathy
- ApoE2 is generally associated with lowest risk of atherosclerosis, MI and stroke; however, CAD and MI risk may increased with elevated TGs.
- Tendency toward higher plasma C-reactive protein despite lower CV risk.
- ApoE2 associated with reduced risk of osteoporosis and higher antioxidant activity.
- The APOE-ε2ε3 genotype and the APOE-ε2 allele are associated with serum uric acid levels in Chinese subjects, indicating that individuals carrying the APOE-ε2 allele have a higher risk of hyperuricemia than non-carriers.

Clinical Management Considerations

- The cholesterol-lowering effect of a low saturated fat and low cholesterol diet is least effective with E2 individuals.
- Minimize sugar and high-glycemic index foods, which produce the largest TG response in E2 carriers.
- Fish oils may reduce TGs the most effectively in E2 carriers.
- Alcohol may reduce LDL-C in men (neutral in women), but may increase risk of hemorrhagic stroke in men (at least in Asians).
- Lipid response to statins, and triglyceride response to fibrates, are usually the best in E2 > E3 > E4; studies are mixed.
- Gemfibrozil may help lower TGs and total cholesterol.
- HT appears to improve the lipid profile in this genotype, although oral estrogen may significantly increase TGs.

Key

- \- \- Neither chromosome carries the genetic variation.
- \+ \- One chromosome (of two) carries the genetic variation.
- \+ \+ Both chromosomes carry the genetic variation.

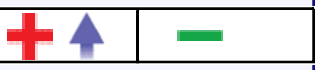
(You inherit one chromosome from each parent)

- \+ ↑ Gene activity increased
- \+ ↓ Gene activity decreased

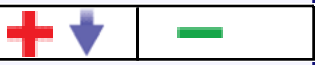
GENOVA DIAGNOSTICS

CETP — Cholesterol Ester Transfer Protein : CHOLESTEROL REGULATION

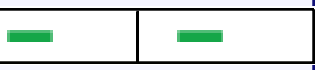
Location:
Chromosome 16
TAQ1B
Your Genotype:



RSA I405V
Your Genotype:



D442G
Your Genotype:



CETP is a plasma glycoprotein that plays a major role in regulating levels of LDL- and HDL-cholesterol. Higher CETP activity tends to increase LDL-C, while decreasing HDL-C.

Health Implications

· Highest CETP activity, increased LDL-C, small dense LDL particles and triglycerides (TGs); lower HDL and Apo-A1 in Taq1B (+) individuals

· HDL-C is significantly reduced in these individuals who are smokers (> 20 cigarettes/day), have elevated triglycerides, or are overweight

· Increased risk of coronary artery disease, hypertension, and cardiac events, including early MI in smokers

Clinical Management Considerations

· A low-cholesterol, low saturated fat diet helps decrease LDL and VLDL

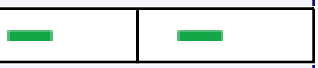
· Bile sequestrants (e.g. cholestyramine), fiber, plant sterols, garlic, weight reduction, and exercise training help lower plasma CETP and cholesterol levels, LDL, and TGs; gemfibrozil lowers TGs

· Alcohol may have less positive effect on HDL-C in Taq1B carriers; avoid smoking

· Statins may be the most effective among individuals with this Taq1B genotype

SELE — E-Selectin : CHOLESTEROL METABOLISM

Location:
Chromosome 1q23
S128R
Your Genotype:



E-selectin facilitates adhesion and infiltration of neutrophils through the endothelium into the arterial intima after NFκB-mediated inflammation, a critical and early event in the development of atherosclerosis.

Health Implications

· Normal adhesion activity of E-selectin

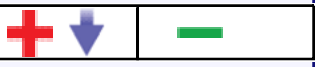
· Low risk of atherosclerosis and coronary artery disease

Clinical Management Considerations

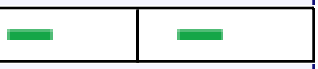
· Ensure healthy anti-oxidant status to preventive up-regulation of E-selectin activity from oxidative stress

MTHFR — 5,10-methyltetrahydrofolate reductase : METHYLATION

Location:
Chromosome 1
C677T
Your Genotype:



A1298C
Your Genotype:



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.

Health Implications

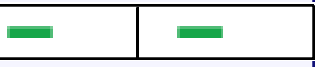
- Heterozygosity for 677 (-/+) results in 30-40% reduction in MTHFR enzyme activity, which may moderately limit methylation reactions in the body
- High homocysteine and disease risks are primarily associated with the (+/+) genotype
- Possible marginally increased risk of essential hypertension and stroke; studies are mixed
- Possible slight increased risk of birth defects in the offspring, e.g., neural tube defects, cleft lip and/or palate, and Down syndrome; studies are mixed
- Possible slight increased risk of gastric and esophageal cancer, the latter of which may be reversed with adequate folate intake

Clinical Management Considerations

- Ensure adequate intake of dark-green leafy vegetables and other B vitamin-rich foods
- Consider supplementation with folic acid (or 5-methyltetrahydrofolate, which bypasses the MTHFR step), vitamins B2, B3, B6 (pyridoxal 5-phosphate), B12 (or methylcobalamin), and betaine (trimethylglycine)

GNB3 — Guanine Nucleotide-binding Protein ²-3 : HYPERTENSION

Location:
Chromosome 12
C825T
Your Genotype:



G-proteins regulate cell-to-cell signal transduction in ~80% of cellular receptors. GNB3 influences cellular signal transduction and ion transport.

Health Implications

- Lowest activity of G-proteins and "normal" signal transduction
- Decreased risk of hypertension, atherosclerosis, obesity, and depression

Clinical Management Considerations

- Sibutramine (SNRI) produces greater satiety and weight loss
- Less favorable response to anti-depressant medications
- Decreased immune response to Hepatitis B vaccination, Hepatitis C response to interferon(a)/ribavirin, and anti-retroviral therapy in HIV

AGTR1 — Angiotensin II Receptor-1- HYPERTENSION

Location:
Chromosome 3
A1166C
Your Genotype:

AGTR1 mediates the effects of angiotensin II including: contractility, vasoconstriction, vascular hypertrophy, inflammation & oxidative stress.

Health Implications

- Increased sensitivity to AGT II, with increased risk/ severity of HTN
- Increased risk of pre-eclampsia, especially if AGT (+/+)
- Increased severity of coronary artery disease and kidney disease HTN, faster disease progression in chronic renal disease

Clinical Management Considerations

- Favorable BP response to resistance training and exercise
- Reduction in arterial stiffness with ACE inhibitors; less favorable response to Ca channel blockers
- Low-Sodium diet may improve BP response to losartan
- Nutrients that minimize the effects of AGT II include: fish oils, borage seed oil, magnesium, potassium, L-arginine and taurine

GP3A PL(A) — Platelet Glycoprotein IIIa : COAGULATION

Location:
Chromosome 17
PL(A1)/ PL(A2)
Your Genotype:

A1	A1

The GP3A polymorphism is a L33P change that results from the substitution of cytosine for thymidine at position 1565. Clinical studies commonly refer to this change as PL(A1) -> PL(A2).

GP3A is a protein component of the platelet fibrinogen receptor IIbIIIa, playing a pivotal role in platelet aggregation and thrombus formation.

Health Implications

- Decreased platelet aggregability and decreased risk of clot formation
- Greater risk of perioperative bleeding due to longer bleeding time

Clinical Management Considerations

- Aspirin and oral platelet antagonists are most effective in this genotype
- This genotype may be less sensitive to platelet - inhibiting effects of estrogen

PAI-1 — Plasminogen Activation Inhibitor-1 : COAGULATION

Location:
Chromosome 7
Del/Ins (4G/5G)
Your Genotype:

4G	5G
✚ ▲	▬

The PAI-1 polymorphism represents a single base-pair guanine (hence 5G->4G) in the promoter region. 5G is the norm and 4G is the variant or polymorphism.

PAI-1, present in platelets and vascular endothelium, decreases activation of plasminogen, inhibiting fibrinolytic activity and increasing clots.

Health Implications

- Higher PAI-1 levels and moderately increased risk of thrombosis
- Possible increased risk of periodontitis, asthma and allergic disease, and PCOS
- Slightly increased risk of obesity, especially in post-menopausal women

Clinical Management Considerations

- Evaluate insulin resistance; thiazolidinediones and metformin tend to reduce PAI-1
- PAI-1 is reduced by weight reduction and regular exercise
- Avoid smoking, which increases PAI-1 and risk of restenosis
- Minimize stressors, high intake of saturated fat, and alcohol
- ARBs reduce PAI-1 levels and ACE inhibitors are particularly effective in hypertensive patients with genotype
- Hormone therapy and DHEA supplementation reduces PAI-1, decreasing clots post-menopausally
- Nattokinase dissolves fibrin and inactivates PAI-1

FACTOR II — Factor II (Prothrombin) : COAGULATION

Location:
Chromosome 11
G20210A
Your Genotype:

▬	▬

Factor II is also known as prothrombin, which is converted to its active form, thrombin, and forms the essential part of a blood clot.

Health Implications

- Normal levels of prothrombin
- No increased risk of venous thromboembolism

Clinical Management Considerations

- None indicated

FACTOR V	*Factor V (Leiden) : COAGULATION*
Location: Chromosome 1 **R506Q** **Your Genotype:**	Factor V combines with Factor X to convert prothrombin to thrombin, the essential part of a blood clot. Factor Va is held in check by Protein C.
— —	**Health Implications** · Normal inactivation of Factor V by activated Protein C · No increased risk of venous thromboembolism **Clinical Management Considerations** · None indicated

This test has been developed and its performance characteristics determined by Genova Diagnostics, Inc. It has not been cleared by the U.S. Food and Drug Administration.

Commentary is provided to the practitioner for educational purposes, and should not be interpreted as diagnostic or treatment recommendations. Diagnosis and treatment decisions are the responsibility of the practitioner.

The accuracy of genetic testing is not 100%. Results of genetic tests should be taken in the context of clinical representation and familial risk. The prevalence and significance of some allelic variations may be population specific.

Any positive findings in your patient's test indicate genetic predisposition that could affect physiologic function and risk of disease. We do not measure every possible genetic variation. Your patient may have additional risk that is not measured by this test. Negative findings do not imply that your patient is risk-free.

DNA sequencing is used to detect polymorphisms in the patient's DNA sample. The sensitivity and specificity of this assay is <100%.