Estrogenomic Profile

GENOVA DIAGNOSTICS

63 Zillicoa Street
Asheville, NC 28801

Patient: **SAMPLE PATIENT**
Age: 44
Sex: F
MRN:

Order Number:
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Collected: January 14, 2008

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 APO E2/3 genotype is common, accounting for 10-15% of most populations
- APO E2 is associated with lower LDL cholesterol and higher HDL-C, but higher triglycerides (as found in Metabolic Syndrome) compared to the other genotypes
- APO E2 also confers a lower risk of atherosclerosis, myocardial infarction, stroke, and osteoporosis, and higher antioxidant activity

Treatment Options

- The cholesterol-lowering effect of a low saturated fat and low cholesterol diet is least effective with E2 individuals
- Minimize high-glycemic index foods, which produce the largest triglyceride (TG) response in E2 carriers
- Dietary fiber, fish oils, and exercise generally improve the lipid profile in this genotype; fish oils reduce TGs most effectively in E2 individuals
- Alcohol may reduce LDL-C in men (neutral in women)
- E2 individuals generally respond the most favorably to statins and would therefore likely respond to statin mimetics such as inositol hexaniacinate, red rice yeast, and policosanol
- Gemfibrozil may be particularly effective at lowering TGs and total cholesterol
- HRT improves 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.

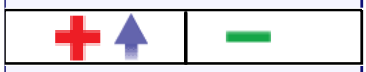
(You inherit one chromosome from each parent)

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

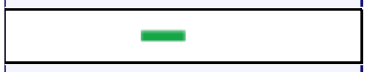
GENOVATIONS™

CYP1B1 — *Cytochrome p450 1B1 : DETOXIFICATION*

Location:
Chromosome 2
L432V
Your Genotype:



N453S
Your Genotype:



CYP1B1 is a Phase I detoxification enzyme responsible for the 4-hydroxylation of estrogen as well as the activation of environmental toxins such as polycyclic aromatic hydrocarbons, PCBs, and aflatoxin B1.

Health Implications

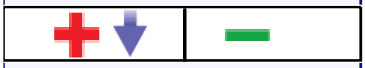
· Hyper-induction of CYP1B1 upon exposure to substrates or inducers
· Increased production of 4-hydroxyestrogens and potentially carcinogenic compounds
· Tendency for lower 2:16α-hydroxyestrone ratio (higher risk of breast cancer)
· Increased risk of breast cancer, especially if xenobiotic exposure (e.g., PAHs), high body mass index, estrogen therapy >= 4 yrs, or coexisting CYP1A1 polymorphism (I462V)
· Possible increased risk of cancer of the ovary, uterus, prostate, and lung (esp. if exposed to second-hand smoke)

Treatment Options

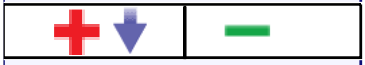
· Minimize exposure to xenobiotics (e.g., PAHs) and xenoestrogens (e.g., organochlorines), which increase CYP1B1 activity
· Maintain a diet rich in antioxidants (colorful fruits and vegetables), consider supplementation
· Consider redirecting estrogen metabolism away from 4-hydroxylation with cruciferous vegetables and/or agents such as indole 3-carbinol (I3C), diindolylmethane (DIM), fish oils, or rosemary
· Caution using long-term estrogen therapy, especially conjugated equine estrogens, which are preferentially 4-hydroxylated. Combined estrogen/progestin therapy produces the greatest breast density in carriers of the SNP
· Carcinogen-induced DNA damage may be minimized by agents such as curcumin, black cohosh, genistein, and DHEA

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

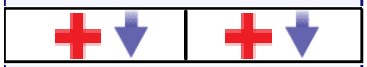
· Heterozygosity for both 677 (-/+) and 1298 (-/+) results in 50-60% reduction in MTHFR enzyme activity, low folate status, and increased risk of elevated homocysteine (and S-adenosylhomocysteine, or SAH)
· MTHFR polymorphism-induced SAH elevations may disrupt neurotransmitter metabolism as well as synthesis of DNA, carnitine, and coenzyme Q10
· Increased risk of autism, depression, neural tube defects, cardiovascular disease, diabetic retinopathy, osteoporosis, and some cancers
· Low folate status significantly increases risk of associated disorders

Treatment Options

· Ensure adequate intake of folate-rich green vegetables
· Consider supplementation with folic acid (or folinic acid or 5-methyltetrahydrofolate), vitamins B2, B3, B6 (pyridoxal 5-phosphate), B12 (or methylcobalamin), and betaine (trimethylglycine)

COMT — Catechol-O-MethylTransferase : METHYLATION

Location:
Chromosome 22.11q
V158M
Your Genotype:



COMT is a key enzyme in the deactivation of catechol compounds such as catecholamines, estrogens, various chemicals, and toxins. COMT modulates the neurotransmitter functions of dopamine and norepinephrine.

Health Implications

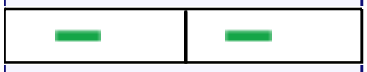
- 3-4-fold reduction in COMT activity with increased bioavailability of catecholamines and impaired methylation of catechol estrogens
- Increased risk of nervousness, anxiety, or panic disorder
- Reduced pain threshold and increased risk of fibromyalgia

Treatment Options

- Ensure adequate B6, B12, folate, magnesium, and methionine to support formation of S-adenosylmethionine and prevent elevated homocysteine
- Ensure adequate anti-oxidants to prevent oxidation of dopamine and pro-carcinogenic 4-hydroxyestrogens
- Exercise caution using MAO inhibitors, tricyclics, mirtazapine (Remeron®) or stimulants - especially in patients with bipolar disorder
- Inferior anti-depressant response to mirtazapine (Remeron®)

TNF-a — Tumor Necrosis Factor a : INFLAMMATION

Location:
Chromosome 6
-308G-A
Your Genotype:



TNF-α is a pro-inflammatory cytokine secreted from activated macrophages that plays an important role in host defense. Excessive TNF-α release can lead to inflammatory reactions and oxidative stress.

Health Implications

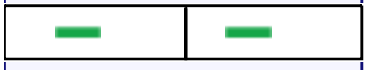
- Decreased production of TNF-α, decreased inflammatory tendency and oxidative stress
- Decreased risk of autoimmune disease, osteoporosis, insulin resistance
- May be associated with increased risk of some cancers because of TNF-α's anti-neoplastic properties

Treatment Options

- Risk of inflammatory disorders is minimal
- Diet and lifestyle associated with minimizing cancer risks is prudent

IL-6 — InterLeukin-6 : INFLAMMATION

Location:
Chromosome 7
-174G - C
Your Genotype:



IL-6 is a TH-2 cytokine that promotes maturation of antibody-producing B-cells. IL-6 mediates inflammatory and stress-induced responses.

Health Implications

- Higher baseline levels of IL-6; increased risk of inflammation
- Increased stress response, with stimulation of HPA axis and cortisol
- Increased risk of osteoporosis, atherosclerosis, stroke, auto-immune disease, and Type II diabetes (in some populations)

Treatment Options

- Stress management; support adrenal function
- Avoid trans fats, ensure adequate intake of Ω-3 fatty acids
- IL-6 release is reduced by a Mediterranean-style diet, N-acetyl cysteine, anti-oxidants, Siberian ginseng, curcumin, conjugated linoleic acid, estrogen, progesterone, DHEA, and COX-2 inhibitors

VDR — Vitamin D Receptor : HORMONAL BONE FORMATION

Location:
Chromosome 12
BsmI RFLP
Your Genotype:

VDR is an intracellular hormone receptor that specifically binds the active form of vitamin D and interacts with target-cell nuclei to produce effects.

Health Implications

· Slight impairment of vitamin D receptor with resistance to vitamin D3
· Slightly increased risk of impaired calcium absorption, increased bone loss, lower bone mineral density, and enhanced bone lead accumulation
· Moderately reduced risk of prostate cancer

Treatment Options

· Carriers of the (+) allele benefit from vitamin D supplementation
· Ensure adequate calcium (Ca) intake; studies suggest minimum of 900 mg/day
· Vitamin K may help to compensate for the higher risk of bone loss
· Caffeine intake >300 mg/day may accelerate bone loss, especially when low calcium intake
· Favorable bone response to etidronate and raloxifene and HRT

CYP1A1 — Cytochrome p450 1A1 : DETOXIFICATION

Location:
Chromosome 15
***2A (MSPI)**
Your Genotype:

***2C (I462V)**
Your Genotype:

CYP1A1 is a Phase I detoxification enzyme responsible for the 2-hydroxylation of estrogen as well as the activation of common environmental toxins, such as polycyclic aromatic hydrocarbons (PAHs).

Health Implications

· Baseline "normal" CYP1A1 enzyme activity
· "Normal" degree of procarcinogen activation upon exposures to substrates
· Possible decreased risk of endometriosis

Treatment Options

· Regardless of CYP1A1 genotype, it is recommended to minimize exposure to PAHs (e.g. smoke and well-done meats), PCBs (e.g., contaminated fish or waste), and dioxins (e.g., chlorine bleaching, PVC plastics, incineration)
· Maintain a diet rich in antioxidants (colorful fruits and vegetables)

GSTM1 — Glutathione S-Transferase mu-1 : DETOXIFICATION

Location:
Chromosome 1

Your Genotype:

ABSENT

The GSTM1 gene is either PRESENT or ABSENT (also called Null). If either copy is present, it is termed PRESENT. If both copies are absent, it is termed ABSENT.

GST is responsible for Phase II detoxification of xenobiotics, carcinogens, and products of oxidative stress. GSTM1 is located primarily in the liver.

Health Implications

· GSTM1 enzyme activity is absent, with reduced detoxification capacity
· Increased risk of toxic burden, oxidative stress, atopic asthma, lung problems, cancer, chemical sensitivity, and coronary artery disease
· Decreased risk of cancer, only with high intake of cruciferous vegetables

Treatment Options

· Eat cruciferous vegetables and allium foods to reduce cancer risk
· Eat a diet rich in antioxidants (colorful foods), consider supplementation
· Ensure availability of glutathione precursors and cofactors
· Limit glutathione depletion with α-lipoic acid, milk thistle, or taurine
· Minimize exposure to xenobiotics, including PAHs and toxic metals

GSTP1 — Glutathione S-Transferase pi-1 : DETOXIFICATION

Location:
Chromosome 11
A114V
Your Genotype:

—	—

I105V
Your Genotype:

—	—

GST is responsible for Phase II detoxification of xenobiotics, carcinogens, steroids, heavy metals, and products of oxidative stress. GSTP1 is located primarily in the brain and lungs.

Health Implications

· Polymorphisms are associated with either higher or lower enzyme activity, depending on specific environmental exposures; therefore, the (-/-) genotype may still increase risk for some disorders. The I105V snp is the more significant of the two.

· The I105V genotype (-/-) is associated with slightly increased risk of some cancers (especially if exposed to cigarette smoke), also atopy, xenobiotic-induced asthma, and COPD

Treatment Options

· Ensure availability of glutathione precursors and cofactors, e.g., methionine-rich foods, NAC, L-glutamine, glycine, Mg, B6

· Eat a diet rich in antioxidants (colorful foods), consider supplementation

· Minimize exposure to xenobiotics, including polycyclic aromatic hydrocarbons (e.g., cigarette smoke) and toxic metals

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

Treatment Options

· 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

Treatment Options

· 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

Treatment Options

· 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

Treatment Options

· None indicated

This test has been developed and its performance characteristics determined by Genova Diagnostics, Inc. It has not been cleared or approved 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%.