KASHI CLINICAL LABORATORIES

CARDIAC HEALTH PANEL

Genetic Analysis Report

PATIENT
PFirst PLast
DOB: 01/01/72

ORDERING PROVIDER
Example Organization

LABORATORY INFORMATION

Lab ID:	N8C9841
Collection Date:	01/11/10
Test Date:	01/21/10
Report Date:	01/22/10

GENE MARKER	NORMAL/ WILD TYPE	TEST RESULT	RISK ALLELE	ASSOCIATION	COMMENT
9p21	G/G	C/G	◐	Plaque development in coronary arteries	Up to 25% increased risk of coronary heart disease or atherosclerosis
eNOS/NOS3	G/G	G/T	◐	Nitric Oxide Synthesis	May have reduced ability to synthesize nitric oxide
AGT	C/C	C/C	❍	Blood Pressure	No increased risk of coronary heart disease
MTHFR C677T / A1298C	CC/AA	CT/CC	▼	Conversion of homocysteine to methionine	One copy of the C677T risk alelle and two copies of the A1298C risk allele were detected which indicates 48% enzymatic activity. This genotype is unlikely to exhibit higher levels of homocysteine and is not associated with an increased risk for thrombosis
Factor II	G/G	G/A	◐	Clotting	Increased risk for thrombophilia, and venous thromboembolism, and possibly stroke
Factor V	G/G	G/G	❍	Clotting	No increased risk for thrombophilia, venous thromboembolism, and stroke
APOE	E2/E2 E2/E3 E3/E3	E3/E4	◐	Lipid transportation and Cholesterol levels	Increased risk for cardiovascular disease associated with increased triglycerides, total cholesterol levels, and LDL
SLCO1B1*5	T/T	C/T	◐	Statin metabolization	Mild decrease in ability to metabolize statins. Less likely to respond to statin therapy. Consider routine creatine kinase monitoring

GENOTYPE RISK KEY:
❍ No Risk ◐ Risk Allele Heterozygous ● Risk Allele Homozygous
▼ Decreased Enzyme Activity ▼ Decreased Enzyme Activity (no risk associated)

SCIENTIFIC DETAILS OF GENETIC MARKERS

❖ 9p21

9p21 is one of the first identified and most researched risk factors associated with coronary artery disease. 9p21 is thought to reduce plaque formation in coronary arteries[1]. Plaque build-up can lead to a condition called atherosclerosis in which the artery walls harden and the arteries vessels narrow. Both changes are dangerous for the cardiovascular system. Studies have shown that one copy of the risk allele increases the risk for development of coronary artery disease (CAD), and two copies of the risk allele double the risk for development of CAD[1].

❖ AGT

The AGT gene produces the precursor to angiotensin II, a protein that causes blood vessels to tighten and blood pressure to increase. Higher angiotensin II levels frequently result in higher blood pressure[2]. The risk allele for this gene is associated with higher amounts of angiotensin and therefore an increased risk for poor cardiovascular health mainly in Caucasians[3].

❖ eNOS/NOS3

This gene produces an important enzyme responsible for keeping the levels of nitric oxide in balance. Nitric oxide (NO) helps the blood vessels to relax and decrease blood pressure[4]. This enzyme also helps lower the amount of blood clots that form in blood vessels. The risk allele is associated with a form of the enzyme that does not work properly, resulting in lower levels of NOS. This risk allele may increase the risk of ischemic heart disease, ischemic stroke, and myocardial infarction in young patients[6].

❖ MTHFR C677T and A1298C

This gene makes an enzyme called MTHFR that turns folic acid into folate, the chemical the body uses for many processes such as amino acid breakdown. MTHFR is also important because it keeps homocysteine amounts in a normal range. When homocysteine is high there is increased risk of ischemic stroke, thrombotic and cardiovascular disease[7]. People with the C677T or A1298C risk alleles can have low levels of folate and high levels of homocysteine[8-10]. Because diet and environment can also affect levels of folate, this condition does not always lead to high levels of homocysteine. People with the C677T risk allele have more trouble maintaining normal amounts of folate and homocysteine.

❖ Factor II Prothrombin

This gene helps to make an enzyme called thrombin that causes the blood to clot[11-13]. The risk allele for this gene can increase the risk of forming blood clots in someone age 55 or older. Blood clots can cause strokes, which can lead to severe vascular injury and sometimes death.

❖ Factor V

The Factor V gene makes a protein called Human factor V[14] which helps in forming blood clots. Having the risk allele for this gene means that factor V is always working therefore increasing the likelihood of more blood clots[13-15]. Blood clots can cause strokes which can lead to severe vascular injury and sometimes death.

❖ ApoE

The APOE gene makes a protein called apolipoprotein E (ApoE). There are three different types of this protein, called ApoE2, ApoE3, and ApoE4. The job of these proteins in the body is to help cholesterol and fat get into cells[16]. Some of the ApoE proteins are better at this transport process than others. Of the three types of proteins, ApoE4 has the hardest time transporting fat and cholesterol from the blood into the cell, thus leaving more fat and cholesterol circulating in the blood. The ApoE4 risk allele increases the risk of heart disease[17]. Two copies of the risk allele ApoE2 may increase the risk of developing type III hyperlipidemia, however this happens in less than 10% of cases[16].

❖ SLCO1B1*5

This gene encodes for a protein called organic anion transporting polypeptide B1 (OATPB1), which helps the liver absorb certain chemicals[18]. One type of chemical that needs the help of the OATPB1 protein to be absorbed is a type of drug called statins[18]. The risk allele for OATPB1 reduces the liver's ability to absorb statins. This means less of the drug enters into the blood stream and therefore it has less clinical effect. In people who have this risk allele high dose statin drugs may be harmful and should be avoided[18].

TREATMENT CONSIDERATIONS

1. **9p21**
   Due to the association with increased plaque formation, treatment should focus on decreasing any factors that cause injury to blood vessels. Blood vessels are most frequently damaged as a result of inflammation. Consuming fish rich in n-3 polyunsaturated fatty acids (PUFA) at least twice a week is beneficial for decreasing vascular damage[19]. Fish containing high levels of these fatty acids, such as omega 3 and omega 6, are herring, salmon, mackerel and tuna. Fish oil supplements are also a source of the omega 3 and 6 fatty acids which make up PUFA. Resveratrol has also been shown in some studies to have protective effects on blood vessels[20].

2. **MTHFR**
   Supplementation with methylated B vitamins is a consideration, including B-6 (in the form of P-5-P), methylated folate, and B-12. Increase foods in the diet that are high in folate; for instance green leafy vegetables such as kale, chard, spinach, lettuce, broccoli, asparagus, and also some beans such as lentils.

3. **Factor V Leiden and Factor 2 Prothrombin**
   Omega 3 fatty acids help make blood platelets less likely to stick together; and fish oils are a good source of omega 3 fatty acids[21]. Fish oils should never be taken with blood thinners without a doctor's supervision.

4. **ApoE and SLCO1B1*5**
   Fiber binds bile in the small intestines causing the body to use cholesterol to make more bile, and thus lowering cholesterol levels[22]. The daily recommended amount of fiber is 25-38 grams; the average American consumes about 15 grams a day through food[23]. Supplementation should depend on diet, and fiber should always be taken with lots of water in order to avoid constipation. For ApoE - to lower triglycerides, the best recommendation is to decrease simple carbs in the diet[24].

CARDIAC HEALTH GLOSSARY

- **Genotype** – The entire set of genes in a cell
- **Allele** – Any of the alternative forms of a gene that may occur
- **Risk Allele** – A significant gene variant that can have an influence on health
- **Phenotype** – The observable properties of an organism that are produced by the interaction of the genotype and the environment
- **Receptor** – A structure on the surface of a cell (or inside a cell) that selectively receives and binds a specific substance
- **Mutation** – A permanent change in the nucleotide sequence of a gene
- **Wild Type** – The common or "normal" version of a gene

This test detects only specific targeted genetic variations and there is a possibility that other genetic variants not detected by this test may be present. The DNA variants tested for in this report have been scientifically determined to be possible risk factors for the reported condition. The content of this report is provided for informational purposes only, not as a diagnostic tool. The report does not supersede the judgment of a qualified medical provider. This test is not a substitute for a comprehensive consideration of all factors that influence the maintenance of a healthy body. Genetic risk factors are not guarantees that you will develop a condition, and in many cases, the presence of a particular DNA variant may only play a minor role in your risk for disease, compared with environmental and lifestyle factors. This test is not FDA approved. The test's performance characteristics have been established and maintained by Kashi Clinical Laboratories under CLIA and CAP compliance.

Reported and Reviewed By:

Zahra Mehdizadeh Kashi, Ph.D., HCLD
CEO and Laboratory Director

SCIENTIFIC REFERENCES

1. Roberts R and Stewart A. 9p21 and the genetic Revolution for Coronary Artery Disease. Clinical Chemistry. 2012; 58(1):104-112.
2. Catt KJ et al. Angiotensin II blood levels in human hypertension. The Lancet. 1971; 297:459-464.
3. Wang WZ. Association between T174M polymorphism in the angiotensinogen gene and risk of coronary artery disease: a meta-analysis. J Geriatr Cardiol. 2013: 10:59-65.
4. Cosentino F and Luscher TF. Maintenance of vascular integrity: role of nitric oxide and other bradykinin mediators. Eur Heart J. 1995; 16 Suppl K:4-12.
5. Tesauro M et. Al. Intracellular processing of endothelial nitric oxide synthase isoforms associated with differences in severity of cardiopulmonary diseases: cleavage of proteins with aspartate vs. glutamate at position 298. Proc Natl Acad Sci USA. 2006:2832-2835.
6. Wang M et al. Association of G894T polymorphism in endothelial nitric oxide synthase gene with the risk of ischemic stroke: A meta-analysis. Biomed Rep. 2013: (1)1:144-150.
7. Refsum H et al. The Hordaland Homocysteine Study: A community-Based Study of Homocysteine, Its Determinants, and Associations with Disease. J Nutr. 2006; 136:1731S-174OS.
8. Frost P et. Al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet. 1995; 10-111-113.
9. Cotlarciuc I et al. Effect of genetic variants associated with plasma homocysteine levels on stroke risk. Stroke. 2014; 45(7):1920-4.
10. Weisberg I et al. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. Mol Genet Metab. 1998; 64:169-72
11. Poort SR et.al. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. Nov 15, 1996:88(10):3698-703.
12. Simone B et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetethraydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. Eur J Epidemiol. 2013; 28(8):621-47.
13. Gohil, R et al. The Genetics of Venous Thromboembolism: A meta-analysis involving 120,000 cases and 180,000 controls. Journal of Thrombosis and Haemostasis. 2009; 102: 360-370.
14. Kujovich J et. al GeneReviews; 1999 "Factor V Leiden Thrombophilia".
15. Bertina RM et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994; 369(6475):64-7.
16. Mahley RW et al. Apolipoprotein E: Far More Than a Lipid Transport Protein. Annu Rev Genomics Hum Genet. 2000; 1:507-537.
17. Howard BV et al. Association of Apolipoprotein E Phenotype with Plasma lipoproteins in African-American and White Young Adults. Am J Epidemiol. 1998: 148(9):859-868.
18. Niemi M et al. Organic Anion Transporting Protein 181:a Genetically Polymorphic Transporter of Major Importance for Hepatic Drug Uptake. Pharm Review. 2011; 63(1): 157-181.
19. Saita E et al. Anti-inflammatory Diet for Atherosclerosis and Coronary Artery Disease: Antioxidant Foods. Clinical Medicine Insights: Cardiology. 2014:8(S3) 61-65.
20. Enguo Fan, Lijuan Zhang, Sha Jiang, and Yuhua Bai. Journal of Medicinal Food. December 2008, 11(4): 610-614.https://doi.org/10.1089/jmf.2007.0091
21. Hosogoe N et al. Add-on Antiplatelet Effects of Eicosapentaenoic Acid with Tailored Dose Setting in Patients on Dual Antiplatelet Therapy. Int Heart J. 2017 Ag 3; 58 (4): 481-485.
22. Ho, H. T. et al. A systematic review and meta-analysis of randomized controlled trials of the effect of konjac glucomannan, a viscous soluble fiber, on LDL cholesterol and the new lipid targets non-HDL cholesterol and apolipoprotein B. Am J Clin Nutr. 2017; 105(5):1239-1247.
23. Zelman, K. April 07, 2016. Fiber: How Much Do I Need? WebMD. https://www.webmd.com/diet/guide/fiber-how-much-do-you-need#1. [2017, October 2]
24. Nordmann A et al. Effects of Low-Carbohydrate vs Low-fat Diets on Weight loss and Cardiovascular Risk Factors. Arch Intern Med. 2006; 166:285-293.