Fagron genomics

Gene Comprehensive Nutrigenomic Report

Accession Number: ##########
Specimen Collected: ##/##/####
Specimen Received: ##/##/####
Report Generated: September 16, 2024
Specimen Type: Buccal Swab
Provider: ######## ########
Patient Name: ###### ######
Patient DOB: ##/##/####
Patient Gender: Female

Do not make any decisions about your health solely based on the information contained in this report.
Always consult with a licensed and experienced health practitioner when you receive this report.

Fagron Genomics US | 844-258-5564 | FagronGenomicsUS.com
Lab | 807 Las Cimas Pkwy, Suite 145 | Austin, TX 78746
Laboratory Director: James W. Jacobson, Ph.D

– 31 – Female

(-/-) No clinical abnormality | (+/-) Heterozygous result | (+/+) Homozygous result

rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result	Highly Recommended Therapeutics	Provider Discretion: As Needed Formula Recommendations	Lifestyle Recommendations	Laboratory Recommendations
Methylation | Foundation Panel							
Folate Metabolism							
rs1051266	SLC19A1	+/+	Methyltetrahydrofolate (B9), Riboflavin (B2), Niacinamide (B3)	**Methyl Folate Pro** twice daily			Complete Blood Count Serum and RBC Folate
rs2071010	FOLR1	-/-					
rs651933	FOLR2	+/-					
rs70991108	DHFR	+/-					
rs6495446	MTHFS	+/+					
rs1076991	MTHFD1	+/+					
rs1801131	MTHFR A1298C	+/+					
rs1801133	MTHFR C677T	-/-					
Vitamin B12 Metabolism							
rs526934	TCN1	-/-	Methylcobalamin, Adenosylcobalamin		Methyl B12 OR Methylation Pro Topical once daily		Serum Vitamin B12
rs1801222	CUBN	-/-					
rs1801198	TCN2	+/+					
rs1801394	MTRR A66G	+/+	Methylcobalamin (B12)	**Methyl B12** twice daily			Serum Vitamin B12 AND/OR Plasma Homocysteine
rs1802059	MTRR A664A	+/-					

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Methylation | Foundation Panel							
Methylation Capacity							
rs7087728	MAT1A	+/+	S-adenosyl-L-methionine (SAMe)	SAMe	Methyl Folate Pro, if Methionine Levels Are Low or Risk Alleles Are Present for MTHFR Be cautious with vitamin B12 supplementation with high activity MTR variant (G allele). Increased MTR activity could contribute to risk of hypermethioninemia.	Methionine Restricted Diet, if Methionine Levels Are High	Plasma Methylation Profile OR Plasma Amino Acid Profile OR Plasma Homocysteine
rs13043752	AHCY	-/-	S-adenosyl-L-methionine (SAMe), Methyltetrahydrofolate, Niacinamide, N-Acetyl Cysteine				

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Methylation | Foundation Panel							
Homocysteine Metabolism							
Remethylation							
rs1805087	MTR	+/+	Methyltetrahydrofolate, Methylcobalamin, Methionine				
rs3733890	BHMT	-/-	Choline, Trimethylglycine (Betaine)				
Catabolism							
rs234706	CBS	+/-	Methyltetrahydrofolate, Methylcobalamin, Pyridoxal 5'-Phosphate (B6), Choline, Trimethylglycine, Serine, N-Acetyl Cysteine		Methylation Complete Pro OR Methylation Pro Topical	Avoid Smoking and Heavy Alcohol Consumption Consider Anti-Inflammatory Diet and Lifestyle	Plasma Methylation Profile OR Plasma Homocysteine
Vitamin D Transport							
rs2282679	GC	+/-	High Dose Vitamin D, Vitamin K	**Maximize Vitamin D3+K2**	Bone Support Plus		Consider Checking Vitamin D Levels OR Comprehensive Micronutrient Testing
rs2228570	VDR	+/+					

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Methylation | Foundation Panel							
Mitochondria							
rs1467568	SIRT1	+/-	Pterostilbene, Resveratrol, Quercetin, NAD+, Coenzyme Q10, Pyrroloquinoline Quinone (PQQ), L-Carnitine, Ornithine, Magnesium, Calcium	**Daily Cell Recharge**		Exercise Regularly Caloric Restriction	Organic Acid Testing
rs8192678	PPARGC1A	+/-					
rs1937	TFAM	+/+					
CoQ10							
rs1800566	NQO1	-/-	Coenzyme Q10, Pyrroloquinoline Quinone (PQQ), Riboflavin				
rs2072183	NPC1L1	+/-	Coenzyme Q10, PQQ				
Oxidative Stress							
rs6721961	NFE2L2	-/-	Pterostilbene, Green Tea (Epigallocatechin Gallate), Turmeric, Sulforaphane		Intracellular Detox Complex	Consume Antioxidant Rich Diet	
rs4880	SOD2	+/-	High Dose Antioxidants, Curcumin, Sulforaphane, Vitamin C				

Summary for Foundation/Methylation/Wellness

Highly Recommended Therapeutics

- Methyl Folate Pro twice daily
- Methyl B12 twice daily
- SAMe
- Maximize Vitamin D3+K2
- Daily Cell Recharge

Provider Discretion: As Needed Formula Recommendations

- Methyl B12 OR Methylation Pro Topical once daily
- Methyl Folate Pro, if Methionine Levels Are Low or Risk Alleles Are Present for MTHFR
- Be cautious with vitamin B12 supplementation with high activity MTR variant (G allele). Increased MTR activity could contribute to risk of hypermethioninemia.
- Methylation Complete Pro OR Methylation Pro Topical
- Bone Support Plus
- Intracellular Detox Complex

Lifestyle Recommendations

- Methionine Restricted Diet, if Methionine Levels Are High
- Avoid Smoking and Heavy Alcohol Consumption
- Consider Anti-Inflammatory Diet and Lifestyle
- Exercise Regularly
- Caloric Restriction
- Consume Antioxidant Rich Diet

Laboratory Recommendations

- Complete Blood Count
- Serum and RBC Folate
- Serum Vitamin B12
- Serum Vitamin B12 AND/OR Plasma Homocysteine
- Plasma Methylation Profile OR Plasma Amino Acid Profile OR Plasma Homocysteine
- Plasma Methylation Profile OR Plasma Homocysteine
- Consider Checking Vitamin D Levels OR Comprehensive Micronutrient Testing
- Organic Acid Testing

VITAMIN B12

FOOD SOURCES


Eggs


Seafood – clams, trout, salmon, tuna


Meats – liver, beef, ham, chicken

Low-fat milk products


Swiss cheese

Low-fat yogurt


Nori/Seaweed


Fortified Foods


Nutritional Yeast

ABSORBABLE VITAMIN B12

METHYLCO-BALAMIN

ACTIVE FORM

FUNCTIONS (OR BENEFITS AS YOU AGE)

- Formation and maintenance of red blood cells (RBCs)
- Facilitates DNA synthesis
- Regulates homocysteine levels (decreases)
- Facilitates neurological functionting

DEFICIENCY & PATHWAY ALTERATIONS

- Increased production of homocysteine
- Decreased breakdown of homocysteine
- Circadian Rhythm Problems
- Cancers
- Memory-related disorders
- Cardiovascular diseases
- Fatigue
- Poor balance
- Mood disorders

VITAMIN D

FOOD SOURCES


Tuna

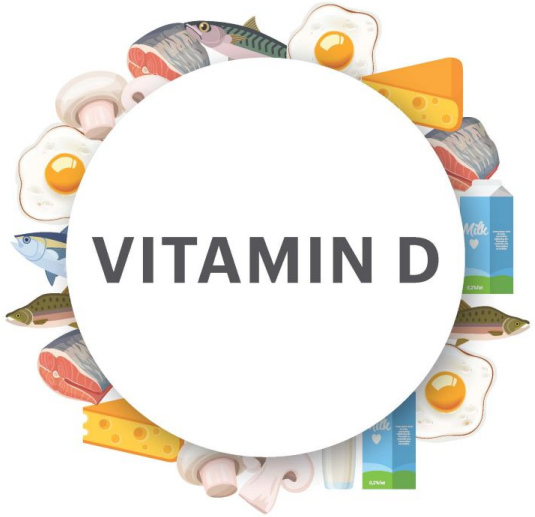

Mushrooms


Eggs


Mackerel


Cheese

Milk Products



BENEFITS AS YOU AGE


Lower Risk of Fractures


Improves Heart Function


Supports Immune System


Speeds Wound Healing

DEFICIENCY CAUSES

- Bone Pain
- Arthritis
- Obesity
- Backache
- Depression
- Diabetes
- Hypertension
- Osteoporosis
- Heart Disease
- Skin Conditions

Gene Information Key

rsID	Gene	"-" variant	"+" variant
rs13043752	AHCY	G	A
rs3733890	BHMT	G	A
rs234706	CBS	A	G
rs1801222	CUBN	G	A
rs70991108	DHFR	INS	DEL
rs2071010	FOLR1	G	A
rs651933	FOLR2	A	G
rs2282679	GC	T	G
rs7087728	MAT1A	A	G
rs1076991	MTHFD1	C	T
rs1801131	MTHFR: A1298C	T	G
rs1801133	MTHFR: C677T	G	A
rs6495446	MTHFS	T	C
rs1805087	MTR	G	A
rs1802059	MTRR: A664A	G	A
rs1801394	MTRR: A66G	A	G
rs6721961	NFE2L2	G	T
rs2072183	NPC1L1	G	C
rs1800566	NQO1	G	A
rs8192678	PPARGC1A	C	T
rs1467568	SIRT1	A	G
rs1051266	SLC19A1	T	C
rs4880	SOD2	A	G
rs526934	TCN1	A	G
rs1801198	TCN2	C	G
rs1937	TFAM	C	G
rs2228570	VDR	G	A

Definitions

DETOXIFICATION	Detoxification enzymes are responsible for clearing environmental chemicals and metabolites from our body. Accumulation of these chemicals and by-products can damage intracellular biochemical functions. Alterations in these systems can have a significant negative effect on the nervous system and immune systems functions. These polymorphisms can result in decreased "quality of life" and even decreased "life-span".
NFE2L2 rs6721961	The NFE2L2 (NFE2 like bZIP transcription factor 2) gene encodes a transcription factor, known as NRF2, that has a crucial role in the regulation of a network of antioxidant genes. NRF2 activates expression of genes with a conserved promoter sequence called the antioxidant response elements (ARE). Genes with an ARE include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX), etc. Therefore, NRF2 is a master regulator of oxidant and antioxidant balance. The polymorphism rs6721961 occurs in the promoter region of NFE2L2, and mechanistic studies have found that the variant encoded by the T allele has reduced promoter activity and mRNA levels. Consistent with these findings, carriers of the T allele have been shown to have lower total antioxidant capacity. T allele carriers had less SOD, CAT, GPX, and glutathione activity. Furthermore, T allele carriers are at increased risk for insulin resistance and vascular stiffness.
SOD2	The SOD2 (superoxide dismutase 2) gene encodes a mitochondrial enzyme that uses iron and manganese to covert superoxide, a byproduct of the mitochondrial electron transport chain, to hydrogen peroxide and oxygen. As a results, SOD2 clears mitochondrial reactive oxygen species (ROS), conferring protection against mitochondrial damage and cell death. The polymorphism rs4880 results in a valine substitution for an alanine residue in the enzyme at position 16. Mechanistic studies have shown that the G allele, which encodes a valine residue, has decreased basal activity of SOD2. Furthermore, SOD2 can be upregulated by inflammatory signals in cells carrying the G allele, but prolonged cellular stress resulted in an accumulation of toxic metabolic by-products, suggesting that the efficiency of cellular detoxification pathways was reduced with the G allele. Clinical studies have also found that the GG genotype is associated with increased risk for kidney dysfunction and hepatotoxicity in response to various pharmacological treatments.
ESSENTIAL VITAMINS	The polymorphisms in this panel will identify any potential weakness of absorption, conversion or delivery or your essential vitamins.
GC	The GC (group-specific component) gene encodes a carrier protein from the albumin gene family that transports vitamin D and its metabolites to target tissues. As a result, the product of the GC gene is also termed the vitamin D binding protein (VDBP). The polymorphism rs2282679 is located in intron 12, and it has a strong genome-wide association with 25-hydroxyvitamin D3 concentrations. The G allele variant is associated with lower levels of VDBP and vitamin D in the blood. Furthermore, since vitamin D is needed to maintain calcium and phosphorous homeostasis, the G allele of rs2282679 is associated with reduced calcium level.
VDR rs2228570	The VDR (vitamin D receptor) gene encodes a receptor for vitamin D3 that is highly expressed in the intestines. VDR is a member of the nuclear hormone receptor superfamily, so when activated by vitamin D, it can impact transcription of many genes involved in mineral metabolism, cell proliferation, and immune activation. The polymorphism rs2228570, sometimes termed FokI for the restriction enzyme that can detect it, results in a threonine substitution for a methionine residue in the first codon of the protein, altering the translation start site. As a result, translation of the receptor produced by the A allele, which does not contain the FokI restriction site (f) and encodes a methionine residue, is 427 amino acids in length, whereas the receptor produced by the G allele, which does contain the FokI restriction site (F) and encodes a threonine residue, is three amino acids shorter. Mechanistic studies indicate that the shorter variant encoded by the G allele has greater capacity to bind vitamin D and more transcriptional activity in response to vitamin D. Consistent with these findings, A allele carriers were less responsive to vitamin D supplementation, and A allele carriers were shown to have reduced calcium absorption and bone mineral density. Furthermore, vitamin D supplementation was less effective at reducing inflammatory markers in carriers of the A allele, and the A allele is associated with risk for celiac disease and type 2 diabetes.
HOMOCYSTEINE METABOLISM	
BHMT rs3733890	The BHMT (betaine-homocysteine S-methyltransferase) gene encodes an essential enzyme that consume betaine, or trimethylglycine, to convert homocysteine to dimethylglycine and methionine. Therefore, BHMT both detoxifies homocysteine and generates methionine needed to maintain methylation capacity. It is primarily expressed in the liver and kidneys. The polymorphism rs3733890 results in a glutamine substitution for an arginine residue at position 239. The A allele, which encodes a glutamine residue, results in more partitioning of choline, a precursor of betaine, for phosphatidylcholine synthesis via the cytidine diphosphate (CDP)-choline pathway, suggesting that less betaine is available for detoxification of homocysteine and regeneration of methionine. Likewise, carriers of the A allele have been shown to have reduced levels of betaine and dimethylglycine. Furthermore, folate was shown to be a less effective treatment to lower homocysteine levels in carrier of the A allele with hyperhomocysteinemia. Nevertheless, increased intake of choline in A allele carriers can increase flux to betaine synthesis to support BHMT activity. In summary, A allele carriers may benefit from increased choline or betaine intake, especially when managing high levels of homocysteine.
MTR	The MTR (5-methyltetrahydrofolate-homocysteine methyltransferase) gene encodes a metabolic enzyme that catalyzes the remethylation of homocysteine to methionine; therefore, the enzyme is also referred to as methionine synthase. The reaction requires both active vitamin B9 (methyltetrahydrofolate) and vitamin B12 (methylcobalamin), and the enzyme works in close coordination with 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR), which regenerates MTR to a functional state. The polymorphism rs1805087 results in a glycine substitution for an aspartic acid residue in the enzyme at position 919, which is located in the binding site for accessory proteins needed to regenerate the enzyme to its active form. Numerous studies indicate that the G allele variant, which encodes a glycine residue, results in increased enzyme function. For example, the G allele was associated with reduced levels of homocysteine and increased levels of DNA methylation, suggesting accelerated conversion of homocysteine to methionine. However, increased MTR activity also results in accelerated consumption of methylcobalamin, and predictably, the GG genotype has been associated with vitamin B12 deficiency.

HORMONE METABOLISM	The conversion of estrogen and its' metabolites is essential to effective safe estrogen treatment. These SNPs will identify your potential for increased production of possible carcinogenic forms of estrogen.
CBS rs234706	The CBS (cystathionine beta-synthase) gene encodes an enzyme that catalyzes the first step in the transsulfuration pathway. More specifically, CBS, a pyridoxal 5'-phosphate-dependent enzyme, consumes serine to convert homocysteine to cystathionine, which is further catabolized to generate substrate for glutathione synthesis. Therefore, homocysteine clearance and glutathione synthesis converge on the function of CBS. The polymorphism rs234706 results in a nucleotide substitution in exon 8. Carriers of the G allele have been found to have higher levels of homocysteine and lower levels of cystathionine and betaine, consistent with reduced CBS activity. Furthermore, individuals with the GG genotype had higher plasma homocysteine following the ingestion of a methionine load, and individuals with the GG genotype were less responsive to folate supplementation to lower homocysteine levels. Lastly, the GG genotype is associated with increased risk for coronary artery disease.
METHYLATION	Methylation is a primary biochemical process in the body that involves the addition of a "methyl" chemical group to a vitamin or neurotransmitter. The addition of the "methyl" group allows for very specific biochemical interactions. Poor "methylation" function alters the effectiveness, delivery and function of many vitamins and important chemicals in the cell.
AHCY rs13043752	The AHCY (adenosylhomocysteinase) gene encodes an enzyme that catalyzes the reversible hydrolysis of S-adenosylhomocysteine (SAH) to adenosine and homocysteine. Therefore, this enzyme, sometimes referred to as S-adenosylhomocysteine hydrolase (SAHH) regulates intracellular SAH concentrations, which acts as an inhibitor of most transmethylation enzymes. Deficiency in this protein can lead to increased levels of methionine. The polymorphism rs13043752 results in a tryptophan substitution for an arginine residue at position 38 in the enzyme. Mechanistic studies have found that the variant produced by the A allele, which encodes a tryptophan residue, has decreased enzyme activity, suggesting the A allele may result in a reduced methylation index or less methylation capacity.
CUBN rs1801222	The CUBN (cubilin) gene encodes a receptor for intrinsic factor-cobalamin (Cbl-IF) complexes, and it is essential for intestinal absorption of vitamin B12. The polymorphism rs1801222 results in a phenylalanine substitution for a cysteine residue at position 253 in the protein. The A allele, which encodes a phenylalanine residue, is associated with reduced plasma levels of vitamin B12 and increased levels of homocysteine. Additionally, the A allele has been associated with risk for neural tube defects.
DHFR rs70991108	The DHFR (dihydrofolate reductase) gene encodes an enzyme essential for converting folic acid, a synthetic form of folate that is common in supplements and fortified foods, to tetrahydrofolate, a usable form of folate. The polymorphism rs70991108 results in a 19-bp deletion in the first intron, and mechanistic studies indicate that the deletion reduces translation and stability of the enzyme. Individuals homozygous for the deletion had higher levels of circulating unmetabolized folic acid, compared to carriers of the full length gene. Furthermore, cognitive function was reduced in deletion carriers, suggesting the 19-bp deletion reduces DHFR activity and folate metabolism. Lastly, the deletion allele has been associated with neural tube defects, pre-term delivery, and hepatic toxicity in response to treatment with methotrexate, which competitively inhibits DHFR activity. In summary, individuals with the 19-bp deletion should prioritize natural forms of folate, instead of folic acid, to maintain productive folate metabolism.
FOLR1	The FOLR1 (folate receptor alpha) gene produces a folate receptor that is responsible for transporting folate and its derivatives into cells. Variations in this gene can affect the delivery of folate in the bloodstream to cells. A study found that individuals who were heterozygous for the polymorphism rs2071010 had elevated serum folate levels compared to those with the GG genotype, suggesting that the A allele may reduce FOLR1 function. Additionally, individuals with the AA genotype may be at increased risk for elevated homocysteine levels.
FOLR2	Folate Receptor 2 (FOLR2) is a member of the folate receptor (FOLR) family. Members of this gene family have a high affinity for folic acid. Polymorphisms in this gene allow for poor delivery of folic acid to the interior of cells. This can create a high plasma folic acid. This polymorphism does create a methylation deficiency. This polymorphism is associated with many disorders of pregnancy. This receptor is found in high quantities on the placenta, thymus and bone marrow. Can be affiliated with immune disorders.
MAT1A rs7087728	The MAT1A (methionine adenosyltransferase 1A) gene encodes an enzyme that transfers the adenosyl moiety of ATP to methionine to form S-adenosylmethionine (SAMe), the universal methyl donor. SAMe is essential to hundreds of biological reactions for modifying biomolecules, such as lipids, proteins, and nucleic acids. Additionally, SAMe is needed for epigenetic regulation, hormone and neurotransmitter synthesis, and detoxification. When SAMe donates a methyl group, S-adenosyl homocysteine is produced, and homocysteine needs to be processed through the methionine cycle or the transsulfuration pathway to prevent excess oxidative stress. The polymorphism rs7087728 occurs in the 3' untranslated region of MAT1A; therefore, the variation may alter mRNA stability. Individuals with the GG genotype had increased levels of urinary 8-OHdG, a marker of oxidative DNA damage. Unlike the response in A allele carriers, vitamin B6, which can support homocysteine clearance, was not effective at reducing levels of oxidative DNA damage in individuals with the GG genotype. This suggests that the DNA damage observed in individuals with the GG genotype may be due to decreased methylation due to reduced SAMe production. In summary, individuals with the GG genotype may be at increased risk for reduced MAT1A activity, SAMe production, and methylation capacity.
MTHFD1	The MTHFD1 (methylenetetrahydrofolate dehydrogenase, cyclohydrolase, and formyltetrahydrofolate synthetase 1) gene encodes an enzyme that is essential for folate metabolism. The enzyme catalyzes three sequential steps in folate metabolism, utilizing separate catalytic domains in the protein. It converts 1) tetrahydrofolate (THF) to 10-formylTHF 2) 10-formylTHF to 5,10-methenlyTHF, and 3) 5,10-methenlyTHF to 5,10-methyleneTHF, which can then be converted to the bioactive form of folate, 5-methylTHF (MTHF), by methylenetetrahydrofolate reductase (MTHFR). The polymorphism rs1076991 occurs in the promoter region of the gene, and mechanistic studies found that the variant encoded by the T allele had a 60% reduction in transcription rate, suggesting that T allele carriers produce significantly less enzyme and MTHF. Congruently, the T allele has also been associated with risk for heart attack.

MTHFR rs1801131	The MTHFR (methylenetetrahydrofolate reductase) gene encodes a metabolic enzyme that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (MTHF), the bioactive form of folate. Folate is a crucial mediator of one-carbon metabolism, which is necessary for a plethora of biochemical functions, such as nucleotide biosynthesis, amino acid metabolism, epigenetic maintenance, and oxidative defense. The polymorphism rs1801131, sometimes referred to as A1298C, results in an alanine substitution for a glutamate residue in the enzyme at position 429, which occurs near the binding site for an allosteric inhibitor, S-adenosyl-L-methionine (SAMe). Cell-based assays have shown that the enzyme produced by the G allele, which encodes an alanine residue, reduces MTHFR activity by about 30% compared to the enzyme produced by the T allele. Consistent with these findings, the GG genotype has been associated with increased risk for ischemic stroke and infertility due to decreased sperm production in men. Furthermore, individuals heterozygous for rs1801131 and rs1801133, another polymorphism in the MTHFR gene, have a more severe clinical phenotype that is similar to the AA genotype for rs1801133. Lastly, despite the prevalence of both minor alleles, the genotype combination rs1801131 GG and rs1801133 AA is nearly nonexistent in the population, suggesting it confers a significant genetic disadvantage.
MTHFR rs1801133	The MTHFR (methylenetetrahydrofolate reductase) gene encodes a metabolic enzyme that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (MTHF), the bioactive form of folate. Folate is a crucial mediator of one-carbon metabolism, which is necessary for a plethora of biochemical functions, such as nucleotide biosynthesis, amino acid metabolism, epigenetic maintenance, and oxidative defense. The polymorphism rs1801133, sometimes referred to as C677T, results in a valine substitution for an alanine residue in the enzyme at position 222, which occurs near the binding site for a cofactor and the substrate, FAD and 5,10-methylenetetrahydrofolate respectively. Mechanistic studies have shown that the enzyme produced by the A allele, which encodes a valine residue, has reduced thermal stability and 55% reduced activity compared to the enzyme produced by the G allele. Consistent with these results, carriers of the A allele were found to have decreased levels of folate and increased levels of homocysteine. As a result, carriers of the A allele are at risk for neural tubes defects, vascular disease, stroke, migraine, depression, and infertility. Furthermore, individuals heterozygous for rs1801133 and rs1801131, another polymorphism in the MTHFR gene, have a more severe clinical phenotype that is similar to the AA genotype for rs1801133. Lastly, despite the prevalence of both minor alleles, the genotype combination rs1801131 GG and rs1801133 AA is nearly nonexistent in the population, suggesting it confers a significant genetic disadvantage.
MTHFS	The MTHFS (methenyletetrahydrofolate synthase) gene encodes an enzyme that catalyzes the irreversible conversion of 5-formyltetrahydrofolate to 5,10-methenyltetrahydrofolate, a precursor of reduced forms of folate that are necessary for one-carbon metabolism. The polymorphism rs6495446 occurs in the second intron, and the C allele has been associated with increased gene expression, suggesting that C allele carriers may have increased MTHFS activity. Increased MTHFS activity can result in increased folate turnover and ultimately, folate depletion, often leading to an accumulation of homocysteine. The C allele has also been associated with risk of chronic kidney disease (CKD), a condition that frequently presents with elevated levels of homocysteine. Lastly, the risk of CKD was compounded in individuals homozygous for the C allele (CC genotype).
MTRR Ala637	Methionine Synthase Reductase is an enzyme responsible for the production of methionine, a very important amino acid. Polymorphisms in this enzyme require an increased amount of Methyl B12 to help this reaction.
MTRR rs1801394	The MTRR (5-methyltetrahydrofolate-homocysteine methyltransferase reductase) gene encodes an enzyme that regenerates methionine synthase, an enzyme encoded by the MTR gene, to a functional state. As a results, MTRR is also known as methionine synthase reductase, and it has a key role maintaining folate-methionine homeostasis. The polymorphism rs1801394 results in a methionine substitution for an isoleucine residue in the enzyme at position 22, and biochemical studies have found that the enzyme encoded by the G allele has a lower affinity for its target, methionine synthase, than the enzyme encoded by the A allele. These results suggest that carriers of the G allele, which produces a protein containing a methionine residue, may have reduced regeneration of methionine synthase and reduced conversion of homocysteine to methionine. Congruently, numerous studies have shown that G allele carriers have elevated homocysteine levels, which can be mediated by supplementation with folate. The G allele was also found to be a risk factor for neural tube defects and Down syndrome. Lastly, risk of neural tube defects was increased in G allele carriers who were also deficient in vitamin B12.
SLC19A1	The SLC19A1 (solute carrier family 19 member 1) gene encodes a folate transporter known as reduced folate carrier (RFC). RFC mediates cellular uptake of folate and folate derivatives, including antifolate pharmaceuticals. Folate is an essential nutrient that supplies a methyl group to support important biochemical functions, such as DNA synthesis and substrate methylation. For example, folate, with the help of vitamin B12, supplies the methyl group needed to convert homocysteine to methionine. The polymorphism rs1051266 results in an arginine substitution for a histidine residue in the transporter at position 27, which occurs in a transmembrane domain. Individuals with the CC genotype were found to have lower levels of plasma folate compared to individuals with the TT genotype, suggesting that the C allele, which encodes the arginine variant, produces a less efficient transporter. Additionally, individuals with the CC genotype for rs1051266 and the TT genotype for rs1801133, a variant in the MTHFR gene, were found to have higher levels of homocysteine. The C allele has been associated with delayed memory ability and increased susceptibility for neural tube defects. Lastly, carriers of the C allele may be less responsive to treatment with methotrexate, and individuals with the CC genotype may be at increased risk for ischemic stroke.
TCN1	The TCN1 (transcobalamin 1) gene encodes various isoforms of a carrier protein that binds vitamin B12 (cobalamin). The isoforms are differentially glycosylated, and they dimerize to form a vitamin B12-binding protein called haptocorrin. Haptocorrin protects vitamin B12 from the acidic environment of the stomach and transports it to the small intestine, where it can be bound by intrinsic factor. It is also estimated that haptocorrin carriers 70-80% of vitamin B12 in circulation. However, unlike transcobalamin encoded by the TCN2 gene, haptocorrin mainly delivers vitamin B12 to the liver. The polymorphism rs526934 occurs in the eighth intron, and carriers of the G allele have been shown to have lower vitamin B12 levels compared to individuals with the AA genotype.
TCN2	The TCN2 (transcobalamin 2) gene encodes a carrier protein that binds vitamin B12 (cobalamin) and delivers it to all tissues. Around 30% of circulating vitamin B12 is bound to TCN2. The polymorphism rs1801198 results in an arginine substitution for a proline residue in the protein at position 259, which occurs in the binding region for vitamin B12. In individuals with adequate vitamin B12 status, carriers of the G allele, which encodes an arginine residue, had less vitamin B12-bound TCN2 than C allele carriers. A large meta-analysis also reported that individuals with the GG genotype had significantly lower concentrations of vitamin B12-bound TCN2 and higher concentrations of homocysteine, a functional indicator of vitamin B12 status, compared to individuals with the CC genotype. Lastly, carriers of the C allele were shown to have lower levels of methylmalonic acid, which is converted to succinyl CoA in a vitamin B12-dependent reaction, suggesting that G allele carriers may have reduced levels of vitamin B12.

MITOCHONDRIA	The mitochondrial enzymes are responsible for energy production from the mitochondria. The mitochondria is known as the "powerhouse" of the cell and produces over 90% of the energy for a cell. The mitochondrial respiratory chain (also known as the electron transport chain) is where these 4 protein complexes are found. Polymorphic alterations in these enzymes reduce the energy output of the mitochondria and leads to symptoms of chronic fatigue, cognitive deficiency, exercise intolerance, low metabolic rate, muscle weakness, poor healing and higher rates of sleep disorders and mood abnormalities.
NPC1L1 rs2072183	The NPC1L1 (NPC1 like intracellular cholesterol transporter 1) gene encodes a transmembrane protein that has a crucial role in the intestinal absorption of cholesterol, vitamin E, and CoQ10. The polymorphism rs2072183 results in a nucleotide substitution in exon 2. Carriers of the minor, C allele were shown to be less responsive to CoQ10 supplementation, suggesting that intestinal absorption may be reduced.
NQO1 rs1800566	The NQO1 (NAD(P)H quinone dehydrogenase 1) gene encodes a riboflavin-dependent enzyme that protects against oxidative stress. Moreover, it regenerates the antioxidant capacity of CoQ10 by reducing it. The polymorphism rs1800566 results in a serine substitution for a proline residue at position 187, which occurs in the FAD-binding site. The A allele, which encodes a serine residue, produces a variant with reduced stability due to reduced ability to bind FAD, a necessary co-factor. Because CoQ10 is sensitive to oxidative stress, molecular studies suggest that NOQ1 has a role in maintaining CoQ10 status, and a clinical study found an association with NOQ1 and CoQ10 status and response to supplementation. Lastly, molecular studies have found that NOQ1 function is also dependent on adequate levels of riboflavin.
PPARGC1A rs8192678	The PPARGC1A (PPARG coactivator 1 alpha) gene encodes a transcriptional coactivator, termed PGC-1?, that enhances mitochondrial biogenesis and function. PGC-1? activity leads to the transcription of TFAM, which translocates to the mitochondrial matrix where it stimulates mitochondrial DNA replication and expression of other mitochondrial gene needed for replication. The polymorphism rs8192678 results in a serine substitution for a glycine at position 487, and the T allele encodes a serine residue. Individuals with the TT genotype were found to have reduced mitochondrial DNA copy number, less endurance exercise capacity, and increased risk of metabolic dysfunction, suggesting that mitochondrial content is decreased. Additionally, carriers of the T allele may have increased risk of polycystic ovary syndrome (PCOS), which often coincides with metabolic dysfunction.
SIRT1 rs1467568	The SIRT1 (sirtuin 1) gene encodes a nicotinamide adenine dinucleotide (NAD+) and zinc-dependent histone deacetylase. SIRT1 is an important epigenetic regulator that responds to metabolic and oxidative stress to activate genes related to mitochondrial biogenesis and ATP production. SIRT1 activates PGC-1? through the SIRT1/PGC-1? axis, which responds to the cytosolic ratio of NAD+ to NADH. The polymorphism rs1467568 occurs in the eighth intron, and studies have found that G allele carriers may be at risk for increased BMI and obesity. Studies have also shown that SIRT1 expression was lower in overweight or obese individuals than it was in lean individuals. Together, these results suggest that G allele carriers may have reduced SIRT1 expression, restricting the SIRT1/PGC-1? axis and mitochondrial biogenesis. Furthermore, studies have found that physical activity and calorie restriction, known activators of SIRT1, can effectively address excess weight in G allele carriers. Lastly, BMI was noticeably higher in G allele carriers with low vitamin E, indicating that antioxidants may support SIRT1 and mitochondrial activity in G allele carriers as well.
TFAM rs1937	The TFAM (transcription factor A, mitochondrial) gene codes a transcription factor that promotes the expression of genes essential for mitochondrial DNA replication and repair. The polymorphism rs1937 results in a threonine substitution for a serine residue at position 12, which occurs in the mitochondrial signaling sequence. Individuals with the GG genotype were found to have reduced endurance exercise capacity and decreased longevity, suggesting that ability of the mitochondria to produce sufficient energy may be decreased. Furthermore, the GG genotype was associated with increased risk for Alzheimer disease.

Disclaimers

TESTING:

Testing Performed By: AC

METHODOLOGY AND LIMITATIONS DISCLAIMER:

Testing for genetic variation/mutation on listed genes was performed using ProFlex PCR and Real-Time PCR with TaqMan® allele-specific probes on the QuantStudio 12K Flex. All genetic testing is performed by GX Sciences, LLC d/b/a Fagron Genomics US (“Fagron Genomics US”) (807 Las Cimas Pkwy, Suite 145, Austin, TX. 78746). This test will not detect all the known alleles that result in altered or inactive tested genes. This test does not account for all individual variations in the individual tested. Test results do not rule out the possibility that this individual could be a carrier of other mutations/variations not detected by this gene mutation/variation panel. Rare mutations surrounding these alleles may also affect our detection of genetic variations. Thus, the interpretation is given as a probability. Therefore, this genetic information shall be interpreted in conjunction with other clinical findings and familial history for the administration of specific nutrients. Patients should receive appropriate genetic counseling to explain the implications of these test results. Details of assay performance and algorithms leading to clinical recommendations are available upon request. The analytical and performance characteristics of this laboratory developed test (LDT) were determined by Fagron Genomics US’s laboratory (Laboratory Director: James Jacobson, PhD) pursuant to Clinical Laboratory Improvement Amendments (CLIA) requirements (CLIA #: 45D2144988).

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Fagron Genomics US SNP References

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