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

– 36 – 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
Women's Health							
Vitamin Conversion and Delivery							
rs1051266	SLC19A1	+/-	Methyltetrahydrofolate (B9), Riboflavin (B2), Niacinamide (B3)		Methyl Folate Pro once daily		Complete Blood Count Serum and RBC Folate
rs2071010	FOLR1	-/-					
rs651933	FOLR2	-/-					
rs1076991	MTHFD1	+/-					
rs1801131	MTHFR A1298C	-/-					
rs1801133	MTHFR C677T	+/-					
rs526934	TCN1	-/-	Methylcobalamin, Adenosylcobalamin		Methylation Pro Topical OR Methylation Complete Pro once daily		
rs1801198	TCN2	+/-					
Vitamin D Transport							
rs2282679	GC	-/-	Vitamin D, Vitamin K				
rs2228570	VDR	-/-					

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Hormone Metabolism							
rs4646	CYP19A1	+/-	High Activity of Aromatase, Higher Risk of Endometriosis and Estrogen Dominance		Estro Zen if Estrogen Dominant	Testosterone Therapy May Produce High Levels of Estrogen	Sex Hormones and Metabolites Panel including Estrogen, Progesterone, and Testosterone
Estrogen Metabolism and Clearance							
rs2606345	CYP1A1	+/-	Increased Levels of 4-Hydroxy Estrogen, Endometriosis and Osteoporosis				
rs1800440	CYP1B1	-/-					
rs4680	COMT	+/-	Difficulty with Clearing Estrogen Metabolites, Calcium-D-Glucarate				
rs1695	GSTP1	-/-					
Testosterone Metabolism							
rs824811	SRD5A1	-/-	Be Cautious with Testosterone and DHEA therapy due to potential increase in DHT				
Follicular Sensitivity							
rs6165	FSHR	+/-	Decreased FSH Sensitivity Higher Risk of PCOS, Estrogen Dominance and Premature Ovarian Failure D-Chiro-Inositol		DCI Cell Recovery and Metabolic Stimulator Pro	Monitor for PCOS and Premature Ovarian Failure May Need Supplemental Progesterone during Pregnancy	Sex Hormones and Metabolites Panel including Estrogen, Progesterone, and Testosterone

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Metabolic Risk Factor							
rs4704397	PDE8B	+/-	Iodine, Selenium, Increased Risk of Hypothyroidism		Advanced Thyroid Support		Thyroid Panel Urinary Iodine OR Comprehesive Micronuritent/Mineral Analysis
rs2235544	DIO1	+/-	Selenium		Advanced Thyroid Support OR Seleniomethionine (200 mcg/day) if Free Triiodothyronine (T3) Is Low		Thyroid Panel (Watch for T3 Insufficiency) Whole Blood Selenium OR Comprehensive Micronutrient Testing
rs510432	ATG5	+/+	Curcumin, Lithium Orotate, D-Chiro-Inositol, Catechins, Resveratrol, Caffeine, 12+ Hour Fasting, Sulforaphane, Ginseng	**May Benefit from Intracellular Detox Complex** **May Benefit from Metabolic Stimulator Pro** OR **DCI Cell Recovery**	Metformin May Be Beneficial if Insulin Resistance Is Present	May Have Reduced Blood Sugar Control Increasing Risk of Polycystic Ovary Syndrome and Gestational Diabetes Intermittent Fasting (12-15 Hours) Exercise Regularly	Routine Blood Sugar, Insulin, and HbA1c
rs26538	ATG12	-/-					
rs10210302	ATG16L1	+/+					

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Hypertension Risk							
rs4343	ACE	+/-	Increased Risk of Salt Retention and Hypertension			Increased Risk of Hypertension and Preeclampsia Recommend Salt Restriction After Age 40	
rs699	AGT	+/+					
Caffeine Metabolism							
rs762551	CYP1A2	+/+	Caffeine Metabolism: Slow Metabolizer (CC genotype), Intermediate Metabolizer (CA genotype), Rapid Metabolizer (AA genotype)		**Be Cautious with High Intake of Caffeine** due to Reduced Caffeine Metabolism Caffeine Sensitivity May Increase Risk of Hypertension		
Clot Risk							
rs6025	F5	-/-	Increased Risk of Thrombosis				
rs3211719	F10	-/-					

Summary for Women's Health

Highly Recommended Therapeutics

- May Benefit from Intracellular Detox Complex
- May Benefit from Metabolic Stimulator Pro OR DCI Cell Recovery

Provider Discretion: As Needed Formula Recommendations

- Methyl Folate Pro once daily
- Methylation Pro Topical OR Methylation Complete Pro once daily
- Estro Zen if Estrogen Dominant
- DCI Cell Recovery and Metabolic Stimulator Pro
- Advanced Thyroid Support
- Advanced Thyroid Support OR Seleniomethionine (200 mcg/day) if Free Triiodothyronine (T3) Is Low
- Metformin May Be Beneficial if Insulin Resistance Is Present
- Be Cautious with High Intake of Caffeine due to Reduced Caffeine Metabolism
- Caffeine Sensitivity May Increase Risk of Hypertension

Lifestyle Recommendations

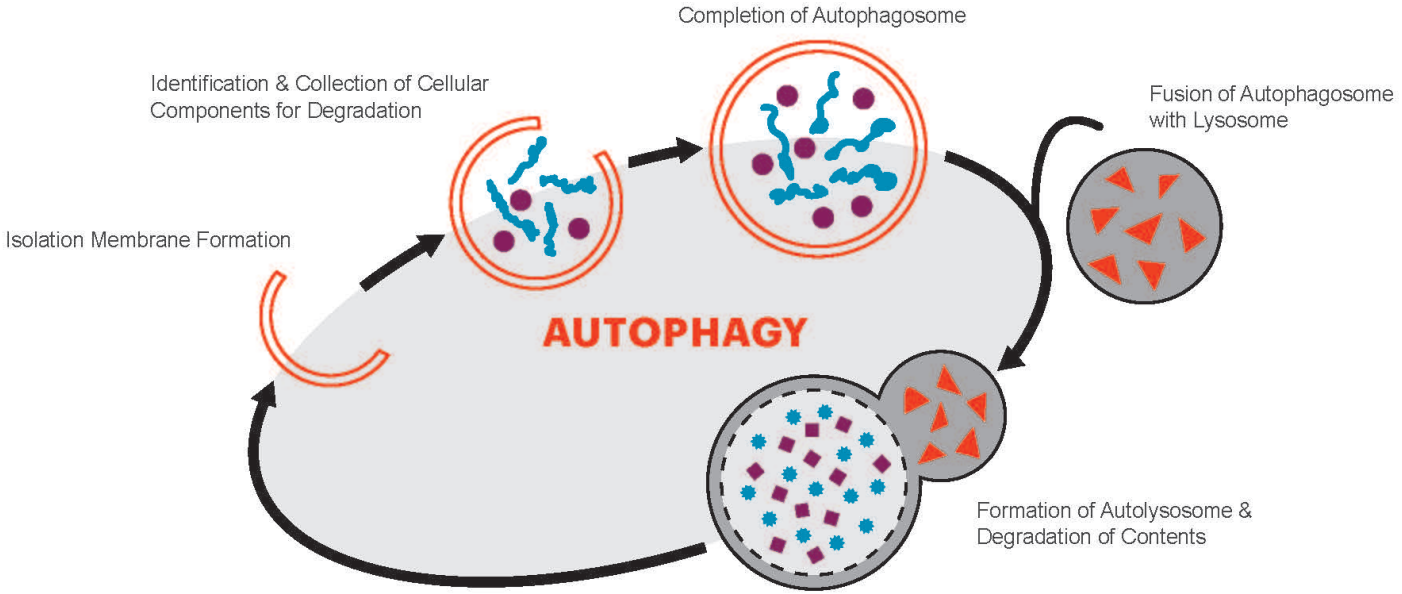
- Testosterone Therapy May Produce High Levels of Estrogen
- Monitor for PCOS and Premature Ovarian Failure
- May Need Supplemental Progesterone during Pregnancy
- May Have Reduced Blood Sugar Control Increasing Risk of Polycystic Ovary Syndrome and Gestational Diabetes
- Intermittent Fasting (12-15 Hours)
- Exercise Regularly
- Increased Risk of Hypertension and Preeclampsia
- Recommend Salt Restriction After Age 40

Laboratory Recommendations

- Complete Blood Count
- Serum and RBC Folate
- Sex Hormones and Metabolites Panel including Estrogen, Progesterone, and Testosterone
- Thyroid Panel
- Urinary Iodine OR Comprehesive Micronuritent/Mineral Analysis
- Thyroid Panel (Watch for T3 Insufficiency)
- Whole Blood Selenium OR Comprehensive Micronutrient Testing
- Routine Blood Sugar, Insulin, and HbA1c

AUTOPHAGY

VARIANTS IN THE ATG GENES HAVE BEEN ASSOCIATED WITH CELLULAR BLOCKAGE



DEFECTS LEAD TO:

- Neurodegenerative Diseases
- Aging
- Heart Disease
- Developmental Disorders
- Type II Diabetes
- Insulin Resistance
- Fatty Liver
- Cancers

WAYS TO INCREASE

Intermittent fasting or low-calorie diet

Routine Exercise

Ketogenic diets (high fat, low carbs)

Medications & Supplements
D-Chiro Inositol (B8)
Metformin

IODINE

WAYS TO INCREASE LEVELS

Seafood – fish (tuna, cod), shrimp

Vegetables/Legumes – green peas, lima beans, corn

Seaweed

Iodized salt

Dairy products

Eggs

Whole grains (unless gluten free)

Supplements

Fruits – prunes, bananas

FUNCTIONS

Synthesizes thyroid hormones (T3 & T4) for metabolic pathways

Role in growth & development

Role in immune response

DEFICIENCY VS HIGH INTAKE

Deficiency

- Developmental issues
- Improper thyroid hormone production
- Fertility issues

High intake

- Thyroid disorders
- Acute poisoning
  - Burning in mouth & throat
  - Fever
  - Abdominal pain
  - Nausea
  - Vomiting
  - Diarrhea

SELENIUM

WAYS TO INCREASE LEVELS

Brazil nuts

Low-fat milk products

Meats & seafood – fish (tuna, halibut, sardines), ham, shrimp, beef, liver, chicken, turkey

Boiled eggs

Wheat germ, Brewer's yeast

Whole grains (unless gluten free)

Supplements

FUNCTIONS

Role in proper thyroid function & thyroid hormone metabolism

Role in DNA synthesis

Role in reproduction

Protection from infection & oxidative damage

DEFICIENCY VS HIGH INTAKE

Deficiency

- Cardiovascular disorders
- Developmental issues
- Thyroid disorders
- Joint & bone issues
- Infertility issues
- Cancers

High intake

- Metallic taste in mouth
- Garlic odor of breath
- Hair and nail loss or brittleness
- Nervous system abnormalities
- Nausea
- Diarrhea
- Skin rashes
- Fatigue
- Irritability

ESTROGEN METABOLISM & CLEARANCE

A 2-PART PROCESS THAT INVOLVES THE BREAKDOWN OF ESTROGREN BY CYP1B1, CYP1A1 & COMT

CYP1B1 & CYP1A1 genes have been associated with increased levels of pro-carcinogenic 4-OHE1, endometriosis & osteoporosis
COMT & GSTP1 genes have been associated with difficult clearance of estrogen metabolites (i.e. E1, E2, E3)
CYP1B1 has been correlated with weight gain, breast tenderness/fullness, swelling & a much worse PMS

RELEVANT FUNCTIONS OF ESTROGEN:

- Estradiol (E2): main estrogen produced in premenopausal women
- Estriol (E3): main estrogen produced during pregnancy
- Estrone (E1): main estrogen made after menopause

RELEVANT FUNCTIONS OF ESTROGEN:


Role in reproduction


Helps regulate the menstrual cycle


Helps control inflammation


Role in the development of secondary sexual characteristics (i.e. breasts, wider hips & hair)


Maintains bone density


Role in brain functioning

SYMPTOMS OF EXCESS ESTROGEN


Weight gain


PMS


Fibrocystic breasts


Heavy periods


Fibroids


Loss of sex drive


Fatigue


Mood changes

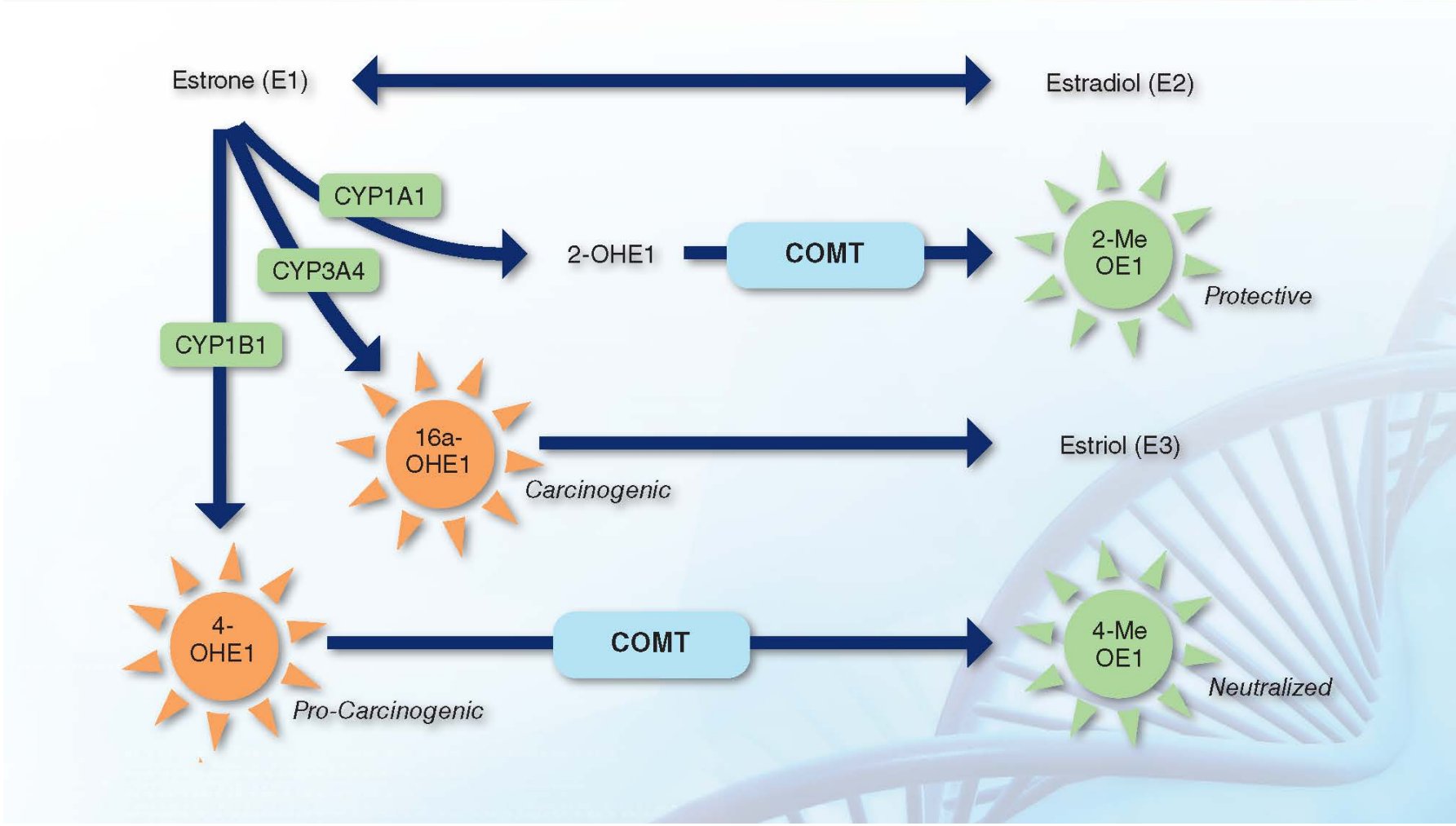
WAYS TO IMPROVE

Di-indolymethane (DIM) & Calcium-D Glucarate


Cruciferous Vegetables (ex. cabbage, broccoli, cauliflower, kale, collards & brussel sprouts)


Supplements

Phase I and II - Estrogen Metabolism

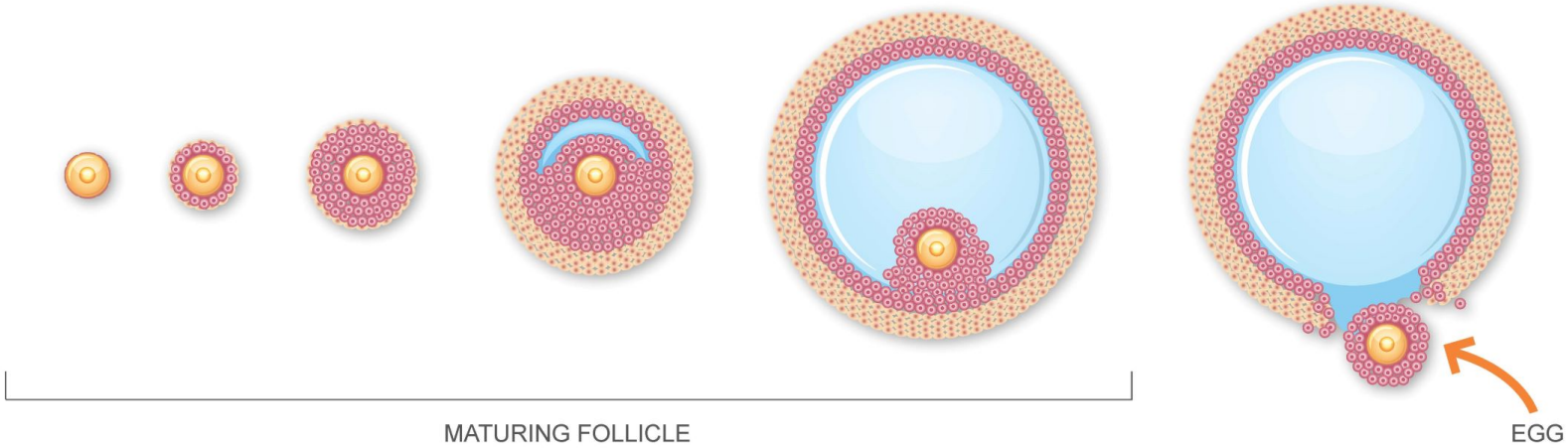


FOLLICULAR SENSITIVITY

THE FSHR GENE HAS BEEN ASSOCIATED WITH DISRUPTION IN DEVELOPMENT & RELEASE OF EGGS

Variants show an increased risk for PCOS, estrogen dominance, premature ovarian failure & poor ovarian response

FOLLICULAR STAGE OF MENSTRUATION



FSHR GENE

- Follicle stimulating hormone, FSH, causes the growth of a follicle
- Follicle: Cluster of cells that contains one immature egg
- Growth of follicles causes the lining of the uterus to thicken for possible pregnancy

WAYS TO IMPROVE

Progesterone supplementation (during pregnancy)

D-chiro-Inositol

METABOLIC RISK FACTOR

METABOLISM

THE BODY'S CONVERSION OF FOOD TO ENERGY WHICH IS REGULATED BY THE THYROID HORMONE

ATG GENES

Reduced clearance of cellular blockage, insulin resistance, diabetes, PCOS and fatty liver disease

FOXE1 GENE

Responsible for the production of thyroid hormone (TH)

Variants have been associated with:

Increased risk for hypothyroidism

DIO2 GENE

Variants have been associated with:

Responsible for selenium-dependent conversion of thyroid hormones

RECOMMENDATIONS & WAYS TO IMPROVE

Iodine and Selenium

Routine thyroid screenings

Intermittent fasting or low-calorie diet

Routine exercise

Ketogenic diets (high fat, low carbs)

Medications & supplements: D-Chiro Inositol or Metformin

HYPERTENSION RISK FACTOR

HIGH BLOOD PRESSURE

- Ranges
  - Normal: 120/80
  - Range of concern: 140/90 or higher
- Risk factors: high salt diet, high alcohol intake, stress, little potassium intake, alcohol & tobacco use, obesity, genetics/family history, age, lack of physical activity
- Uncontrolled high blood pressure has been associated with an increased risk for cardiovascular diseases and stroke

AGT & ACE GENES

Variants have been associated with an increased risk for:

Salt retention

Kidney issues

Preeclampsia

Poor sports performance

Hypertension & other cardiovascular issues

LIFESTYLE CHANGES

Limit salt intake

Angiotensin II Receptor Blockers (“sartans”)

Weight management & routine exercise

Mediterranean diet

Quit smoking

Heart-healthy diet/ Low-sodium diet/ DASH diet

DASH DIET

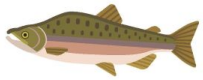
FOOD TO EAT

Fruits & vegetables

Egg whites

Whole grains (unless gluten free)

Nuts & nut butters



Lean, skinless meat & fish (salmon, trout, herring)

Legumes

Low-fat or fat-free dairy products

Olive oils high in polyphenols

BENEFITS

Improves heart health

Improves and/ or reduces risk for hypertension, heart disease and stroke

FOODS TO AVOID AND/OR LIMIT

Red meat

Fried foods

Sweets

Processed meats - deli meat, hotdogs, sausage, bacon

Sugar-sweetened beverages

Fats/oils - Butter, margarine, tropical oils (coconut, palm)

High-salt foods

Gene Information Key

rsID	Gene	"-" variant	"+" variant
rs4343	ACE	A	G
rs699	AGT	A	G
rs26538	ATG12	T	C
rs10210302	ATG16L1	C	T
rs510432	ATG5	T	C
rs4680	COMT	G	A
rs4646	CYP19A1	A	C
rs2606345	CYP1A1	C	A
rs762551	CYP1A2	A	C
rs1800440	CYP1B1	T	C
rs2235544	DIO1	C	A
rs3211719	F10	A	G
rs6025	F5	C	T
rs2071010	FOLR1	G	A
rs651933	FOLR2	A	G
rs6165	FSHR	T	C
rs2282679	GC	T	G
rs1695	GSTP1	A	G
rs1076991	MTHFD1	C	T
rs1801131	MTHFR: A1298C	T	G
rs1801133	MTHFR: C677T	G	A
rs4704397	PDE8B	G	A
rs1051266	SLC19A1	T	C
rs824811	SRD5A1	A	G
rs526934	TCN1	A	G
rs1801198	TCN2	C	G
rs2228570	VDR	G	A

Definitions

AUTOPHAGY	
ATG12	Autophagy-related 12 protein is part of the core autophagy machinery inside the cell. Autophagy, a form of cellular "recycling" is necessary for many cell functions. ATG12 is specifically involved in turning off the innate immune response. Mutations in the ATG12 gene are predicted to lead to increased activity of the innate immune response, and overall inflammation.
ATG16L1 rs10210302	The ATG16L1 (autophagy related 16 like 1) gene encodes a protein that is part of a major protein complex essential for autophagy, a process of digesting cellular components for nutrient sensing and cellular regulation. The polymorphism rs10210302 occurs in the promoter region of the gene, and a comprehensive study has linked the T allele with Crohn's disease, an inflammatory bowel disease.
ATG5	The ATG5 (autophagy-related 5) gene is an important intracellular mediator of the autophagy response, which is essential for maintaining homeostasis. The polymorphism rs510432 occurs in the promoter region of ATG5, and individuals homozygous for the C allele have been shown to have increased mRNA expression of ATG5. Additionally, individuals homozygous for the C allele are at an increased risk for developing childhood asthma, but they have a reduced risk for developing sepsis. Individuals who are heterozygous or homozygous for the T allele have been shown to have reduced levels of C-reactive protein.
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".
GSTP1	The GSTP1 (glutathione S?transferase pi 1) gene encodes a cytosolic enzyme that has a keystone role in cellular detoxification. It conjugates cytotoxic and carcinogenic substances to glutathione for elimination, thereby aiding in antioxidant defense and preserving DNA integrity. The polymorphism rs1695 results in a valine substitution for an isoleucine residue in the enzyme at position 105, which is a region of the protein that is known to undergo several post-translational modifications. Mechanistic studies have shown that the protein produced by the G allele, which encodes a valine residue, has reduced substrate binding capacity and enzymatic activity. Numerous clinical studies have shown that the GG genotype is a risk factor for asthma, especially when individuals are exposed to environmental toxins, such as cigarette smoke or traffic-related air pollution. Additionally, the G allele is associated with increased risk for heart failure, and the frequency of the G allele is decreased in populations of older, living adults, suggesting it does not confer increased longevity.
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.
ESTROGEN METABOLISM AND CLEARANCE	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
CYP19A1	The CYP19A1 (cytochrome P450 family 19 subfamily A member 1) gene encodes a monooxygenase enzyme termed aromatase. Aromatase catalyzes the last step in the conversion of androgens to estrogen. The polymorphism rs4646 occurs in the 3' untranslated region, suggesting that it might affect gene expression by altering mRNA stability. Furthermore, the C allele has been associated with higher circulating estrogen levels, indicating increased aromatase activity.
CYP1A1 rs2606345	The CYP1A1 (cytochrome P450 family 1 subfamily A member 1) gene encodes a monooxygenase enzyme that catalyzes 2-hydroxylation to metabolize estrogen to 2-OH estradiol catechol and 2-OH estrone catechol, which have weak estrogenic activities. The polymorphism rs2606345 occurs in the first intron, and studies have found that women with the CC genotype had lower concentrations of estradiol and higher concentrations of 2-hydroxy estrogen metabolites. Furthermore, premenopausal women with the CC genotype may experience more vasomotor symptoms such as hot flashes and night sweats than A allele carriers. Lastly, women carrying the C allele were shown to have increased risk of depressive symptoms at midlife than women with the AA genotype.

CYP1B1	The CYP1B1 (cytochrome P450 family 1 subfamily B member 1) gene encodes a monooxygenase that has a key role in metabolizing drugs, cholesterol, steroids and other lipids. More specifically, it catalyzes the breakdown of estradiol to 4-hydroxyestradiol, an estrogen metabolite that can cause DNA damage. The polymorphism rs1800440 results in a serine substitution for an asparagine residue in the enzyme at position 453. Women with the CC genotype had a 3-fold greater chance of experiencing hot flashes for more than 1 year compared to those with the TT genotype.
HEALTH PRECAUTIONS	
ACE	The ACE (angiotensin-converting enzyme) gene encodes a protein that plays a crucial role in regulating blood pressure and maintaining electrolyte balance. It converts angiotensin I to the active form, angiotensin II, which leads to vasoconstriction and elevated blood pressure. The polymorphism rs4343 confers an insertion/deletion of a small DNA sequence in the gene. Carriers of the G allele display increased ACE activity and elevated plasma levels of angiotensin II. Additionally, carriers of the G allele are more prone to blood pressure spikes when consuming high-salt diets than individuals with the AA genotype. Heterozygous individuals display an intermediate phenotype.
AGT	The AGT (angiotensinogen) gene produces angiotensinogen—a precursor of angiotensin which is involved in blood pressure regulation. In response to a drop in blood pressure, angiotensinogen is transformed into angiotensin I by renin, an enzyme secreted and stored in the kidneys. The polymorphism rs699 results in a threonine substitution for a methionine residue in angiotensinogen at position 259. The G allele results in elevated levels of angiotensin in plasma, leading to increased blood pressure and risks associated with hypertension.
CYP1A2	The CYP1A2 (cytochrome P450 family 1 subfamily A member 2) gene encodes a monooxygenase enzyme that mainly functions in the liver. It catalyzes the metabolism of about 10% of clinically used drugs that are metabolized by CYP enzymes, including caffeine. Additionally, it metabolizes some endogenous compounds, such as melatonin and estradiol. The A allele of rs762551 was found to have higher CYP1A2 enzyme activity with exposure to smoking or heavy coffee consumption. In contrast, the C allele was found to be associated with lower enzyme activity. rs762551 was also associated with caffeine consumption. Specifically, the AA genotype may predispose an individual to have higher coffee intake.
Factor V	The F5 gene encodes for coagulation factor V, an essential component of the blood coagulation cascade. Specifically, it serves as a cofactor for the prothrombinase activity of factor Xa that results in the activation of prothrombin to thrombin. The polymorphism rs6025 is a well-known missense mutation known as the Leiden mutation. The T allele of rs6025 encodes for a variant in which glutamine is substituted for arginine at position 506. Carriers of the T allele are at an elevated risk for venous thromboembolism and related conditions with the risk being even higher in individuals homozygous for the T allele.
Factor X	The F10 (coagulation factor X) gene encodes a vitamin K-dependent factor in the blood coagulation cascade. Factor X (FX) plays an important role in blood clotting, as both the intrinsic and extrinsic coagulation pathways converge on FX activation. FX is translated as a preproprotein, which is processed to a mature and activated version that converts prothrombin to thrombin. The polymorphism rs3211719 occurs in intron 1, and genome-wide association studies have found that the G-allele is associated with decreased prothrombin time and increased levels of factor VII, which initiates the extrinsic coagulation pathway. Additional studies have shown that the G allele is associated with increased factor VII antigen and factor VII coagulant activity, suggesting that clotting propensity is increased.
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.
FSHR	The FSHR (follicle stimulating hormone receptor) gene encodes a G-protein coupled receptor for follicle stimulating hormone (FSH), a hormone responsible for the growth of follicles and eggs in women. FSHR is expressed in the ovaries, and its signaling is necessary for the proliferation of granulosa cells, maturation of ovarian follicles, and development of mature eggs. The polymorphism rs6165 results in a threonine substitution for an alanine residue at position 307, which occurs in the extracellular domain of the receptor. The polymorphism rs6165 is in near perfect linkage disequilibrium with rs6166, meaning that the alleles are nonrandomly associated and inherited together. Therefore, the C allele, which encodes an alanine residue, for rs6165 also indicates the inheritance of a serine residue at position 680, which occurs in the cytoplasmic domain of the receptor. Functional studies have found that women carrying the C allele have ovaries that are less responsive to stimulation with FSH, suggesting that FSHR is less sensitive. Clinical studies also suggest that the C allele may be associated with polycystic ovarian syndrome (PCOS), as well as higher gonadotrophic hormones, testosterone, and high frequency of hyperandrogenism--all clinical features of PCOS. Lastly, women carrying the C allele may have an increased chance of being resistant to ovarian stimulation.
SRD5A1 rs824811	The SRD5A1 (steroid 5 alpha-reductase 1) gene encodes an enzyme that converts testosterone into the more potent androgen, dihydrotestosterone (DHT). High levels of DHT may be associated with male pattern hair loss and polycystic ovarian syndrome (PCOS). The polymorphism rs824811 occurs in the fourth intron. Carriers of the C allele have been shown to have reduced levels of testosterone and increased levels of testosterone metabolites downstream of SRD5A1 activity, suggesting that C allele carriers may have increased SRD5A1 activity and increased production of DHT.
METABOLIC RISK FACTOR	The polymorphisms in this category relate to increase risk of developing metabolic syndromes including diabetes, fatty liver, hypothyroidism and insulin resistance.
DIO1 rs2235544	The DIO1 (iodothyronine deiodinase 1) gene encodes an enzyme that converts prohormone thyroxine (T4) to bioactive thyroid hormone, triiodothyronine (T3), by cleaving iodine residues. Deiodinases are selenium-containing enzymes, and DIO1 the main enzymes responsible for T3 levels in the bloodstream. The polymorphism rs2235544 occurs in the third intron, and numerous studies have found that carriers of the A allele have decreased deiodinase activity. Therefore, A allele carriers have reduced conversion of thyroxine (T4) to triiodothyronine (T3). Furthermore, for treatment of hypothyroidism, carriers of the A allele had better outcomes when receiving a combination of T3 and T4, whereas C allele carriers had better outcomes when receiving only T4.

PDE8B rs4704397	The PDE8B (phosphodiesterase 8B) gene encodes a enzyme that catalyzes the hydrolysis of cAMP, a second messenger crucial for cellular energy sensing. The polymorphism rs4704397 occurs in the first intron, and numerous studies have found that the A allele is associated with increased levels of TSH, consistent with hypothyroidism. Additionally, the A allele has been associated with sub-clinical hypothyroidism, hypothyroidism, and infertility.
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.
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.
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.
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.
NEUROTRANSMITTERS	Neurotransmitters are chemicals that are used to produce specific effects in the nervous system. These specific neurotransmitter genomics assess a person's risk for anxiety, depression and dysphoria.
COMT rs4680	The COMT (catechol-O-methyltransferase) gene encodes an enzyme that deactivates catecholamines, including neurotransmitters (adrenaline, noradrenaline and dopamine), by catalyzing the transfer of a methyl groups from S-adenosyl-methionine to a hydroxyl group on a catechol. Therefore, COMT has a crucial role in catecholamine neurotransmission and the metabolism of catechol hormones and xenobiotics. The polymorphism rs4860 results in a methionine substitution for a valine residue at position 108 for soluble COMT, which is prevalent in peripheral tissues, or position 158 for membrane-bound COMT, which is prevalent in the brain. The enzyme produced by the A allele, which encodes a methionine residue, reduces COMT activity due to thermal instability. Moreover, the A allele variant can have a three-to-fourfold reduction in enzyme activity compared to the G allele variant, and the A allele has been associated with a disadvantage processing aversive stimuli, reduced appetite, OCD, and anxiety. Furthermore, COMT metabolizes estrogen, and a study found that girls with the AA genotype had higher levels of free estradiol and earlier pubertal development than girls with the GG genotype, suggesting that the A allele may be associated with less efficient estrogen clearance. However, individuals with the GG genotype may have increased homocysteine levels when combined with a MTHFR variant.

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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This test was developed and its performance characteristics determined by Fagron Genomics US. It has not been cleared or approved by the FDA. The laboratory is regulated under CLIA and qualified to perform high-complexity testing. This test is used for clinical and educational purposes. It should not be regarded as investigational or for research. The Reference SNP Cluster IDs (rsIDs) for the alleles being tested were obtained from the Single Nucleotide Polymorphism Database (dbSNP) (Build 142). These products are not approved by the Food and Drug Administration and are not intended to diagnose, treat, cure, or prevent disease. These recommendations are for report purposes only and an individual is not required to use such products. These are recommendations only and do not replace the advisement of your own healthcare practitioner.

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Fagron Genomics US SNP References

DETOXIFICATION SNP References

GSTP1

• Melén, E., Nyberg, F., Lindgren, C. M., Berglind, N., Zucchelli, M., Nordling, E., Hallberg, J., Svartengren, M., Morgenstern, R., Kere, J., Bellander, T., Wickman, M., & Pershagen, G. (2008). Interactions between glutathione S-transferase P1, tumor necrosis factor, and traffic-related air pollution for development of childhood allergic disease. Environmental Health Perspectives, 116(8), 1077–1084. https://doi.org/10.1289/ehp.11117 • Katsarou, M.-S., Giakoumaki, M., Papadimitriou, A., Demertzis, N., Androutsopoulos, V., & Drakoulis, N. (2018). Genetically driven antioxidant capacity in a Caucasian Southeastern European population. Mechanisms of Ageing and Development, 172, 1–5. https://doi.org/10.1016/j.mad.2017.08.010 • Mukhammadiyeva, G. F., Bakirov, A. B., Karimov, D. O., Ziatdinova, M. M., Valova, Y. V., Borisova, A. I., & Distanova, A. A. (2022). Analysis of the GSTP1 rs1695 polymorphism association with the development of asthma and phenotypic manifestations. The Journal of Asthma: Official Journal of the Association for the Care of Asthma, 59(6), 1065–1069. https://doi.org/10.1080/02770903.2021.1910295 • Palmer, C. N. A., Doney, A. S. F., Lee, S. P., Murrie, I., Ismail, T., Macgregor, D. F., & Mukhopadhyay, S. (2006). Glutathione S-transferase M1 and P1 genotype, passive smoking, and peak expiratory flow in asthma. Pediatrics, 118(2), 710–716. https://doi.org/10.1542/peds.2005-3030 • Moyer, A. M., Salavaggione, O. E., Wu, T.-Y., Moon, I., Eckloff, B. W., Hildebrandt, M. A. T., Schaid, D. J., Wieben, E. D., & Weinshilboum, R. M. (2008). Glutathione S-Transferase P1: Gene Sequence Variation and Functional Genomic Studies. Cancer Research, 68(12), 4791–4801. https://doi.org/10.1158/0008-5472.CAN-07-6724 • Hollman, A. L., Tchounwou, P. B., & Huang, H.-C. (2016). The Association between Gene-Environment Interactions and Diseases Involving the Human GST Superfamily with SNP Variants. International Journal of Environmental Research and Public Health, 13(4), 379. https://doi.org/10.3390/ijerph13040379 • do Nascimento, M. R., Silva de Souza, R. O., Silva, A. L., Lima, E. S., Gonçalves, M. S., & de Moura Neto, J. P. (2021). GSTP1 rs1695 and rs1871042, and SOD2 rs4880 as molecular markers of lipid peroxidation in blood storage. Blood Transfusion = Trasfusione Del Sangue, 19(4), 309–316. https://doi.org/10.2450/2020.0062-20 • Tamer, L., Caliko?lu, M., Ates, N. A., Yildirim, H., Ercan, B., Saritas, E., Unlü, A., & Atik, U. (2004). Glutathione-S-transferase gene polymorphisms (GSTT1, GSTM1, GSTP1) as increased risk factors for asthma. Respirology (Carlton, Vic.), 9(4), 493–498. https://doi.org/10.1111/j.1440-1843.2004.00657.x • Simeunovic, D., Odanovic, N., Pljesa-Ercegovac, M., Radic, T., Radovanovic, S., Coric, V., Milinkovic, I., Matic, M., Djukic, T., Ristic, A., Risimic, D., Seferovic, P., Simic, T., Simic, D., & Savic-Radojevic, A. (2019). Glutathione Transferase P1 Polymorphism Might Be a Risk Determinant in Heart Failure. Disease Markers, 2019, 6984845. https://doi.org/10.1155/2019/6984845 • Scarfò, M., Sciandra, C., Ruberto, S., & Santovito, A. (2021). GSTT1, GSTP1 and XPC genes are associated with longevity in an Italian cohort. Annals of Human Biology, 48(5), 443–447.

https://doi.org/10.1080/03014460.2021.1985170 • Dai, X., Bui, D. S., & Lodge, C. (2021). Glutathione S-Transferase Gene Associations and Gene-Environment Interactions for Asthma. Current Allergy and Asthma Reports, 21(5), 31. https://doi.org/10.1007/s11882-021-01005-y

DEVELOPMENTAL SNP References

ATG12

• Levine, B. & Kroemer, G. Autophagy in the Pathogenesis of Disease. Cell (2008). doi:10.1016/j.cell.2007.12.018 • Antunes, F. et al. Autophagy and intermittent fasting: the connection for cancer therapy? Clinics (Sao Paulo, Brazil) (2018). doi:10.6061/clinics/2018/e814s • Takagi, A., Kume, S., Maegawa, H. & Uzu, T. Emerging role of mammalian autophagy in ketogenesis to overcome starvation. Autophagy (2016). doi:10.1080/15548627.2016.1151597 • Smith, G. S., Walter, G. L. & Walker, R. M. Clinical Pathology in Non-Clinical Toxicology Testing. in Haschek and Rousseaux's Handbook of Toxicologic Pathology (2013). doi:10.1016/B978-0-12-415759-0.00018-2 • Mizushima, N. Autophagy: Process and function. Genes and Development (2007). doi:10.1101/gad.1599207 • Anton, R. F. et al. Pharmacogenomics. Nat. Genet. 16, 268–278 (2008). • Yuan, J. et al. Polymorphisms in autophagy related genes and the coal workers' pneumoconiosis in a Chinese population. Gene 632, 36–42 (2017). •

Lindberg, S. Autophagy: Definition, Diet, Fasting, Cancer, Benefits, and More. Healthline (2014). Available at: https://www.healthline.com/health/autophagy#bottom-line.

ESSENTIAL VITAMINS SNP References

GC or DBP

• Ahn, J., Yu, K., Stolzenberg-Solomon, R., Simon, K. C., McCullough, M. L., Gallicchio, L., Jacobs, E. J., Ascherio, A., Helzlsouer, K., Jacobs, K. B., Li, Q., Weinstein, S. J., Purdue, M., Virtamo, J., Horst, R., Wheeler, W., Chanock, S., Hunter, D. J., Hayes, R. B., … Albanes, D. (2010). Genome-wide association study of circulating vitamin D levels. Human Molecular Genetics, 19(13), 2739–2745. https://doi.org/10.1093/hmg/ddq155 • Jiang, X., O'Reilly, P. F., Aschard, H., Hsu, Y.-H., Richards, J. B., Dupuis, J., Ingelsson, E., Karasik, D., Pilz, S., Berry, D., Kestenbaum, B., Zheng, J., Luan, J., Sofianopoulou, E., Streeten, E. A., Albanes, D., Lutsey, P. L., Yao, L., Tang, W., … Kiel, D. P. (2018). Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. Nature Communications, 9(1), 260. https://doi.org/10.1038/s41467-017-02662-2 • Malik, S., Fu, L., Juras, D. J., Karmali, M., Wong, B. Y. L., Gozdzik, A., & Cole, D. E. C. (2013). Common variants of the vitamin D binding protein gene and adverse health outcomes. Critical Reviews in Clinical Laboratory Sciences, 50(1), 1–22. https://doi.org/10.3109/10408363.2012.750262 • Wang, T. J., Zhang, F., Richards, J. B., Kestenbaum, B., van Meurs, J. B., Berry, D., Kiel, D. P., Streeten, E. A., Ohlsson, C., Koller, D. L., Peltonen, L., Cooper, J. D., O'Reilly, P. F., Houston, D. K., Glazer, N. L., Vandenput, L., Peacock, M., Shi, J., Rivadeneira, F., … Spector, T. D. (2010). Common genetic determinants of vitamin D insufficiency: A genome-wide association study. Lancet (London, England), 376(9736), 180–188.

https://doi.org/10.1016/S0140-6736(10)60588-0

VDR rs2228570

• Arai, H., Miyamoto, K., Taketani, Y., Yamamoto, H., Iemori, Y., Morita, K., Tonai, T., Nishisho, T., Mori, S., & Takeda, E. (1997). A vitamin D receptor gene polymorphism in the translation initiation codon: Effect on protein activity and relation to bone mineral density in Japanese women. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 12(6), 915–921. https://doi.org/10.1359/jbmr.1997.12.6.915 • Ebrahimof, S., Angoorani, P., Shab-Bidar, S., Abedidni, S., Jahangir, F., & Hedayati, M. (2022). The interactive effect of vitamin D3 supplementation and vitamin D receptor polymorphisms on weight and body composition in overweight women with hypovitaminosis D: A randomized, double-blind, placebo-controlled clinical trial. Canadian Journal of Physiology and Pharmacology. https://doi.org/10.1139/cjpp-2022-0192 • Li, L., Wu, B., Liu, J.-Y., & Yang, L.-B. (2013). Vitamin D receptor gene polymorphisms and type 2 diabetes: A meta-analysis. Archives of Medical Research, 44(3), 235–241. https://doi.org/10.1016/j.arcmed.2013.02.002 • Neyestani, T. R., Djazayery, A., Shab-Bidar, S., Eshraghian, M. R., Kalayi, A., Shariátzadeh, N., Khalaji, N., Zahedirad, M., Gharavi, A., Houshiarrad, A., Chamari, M., & Asadzadeh, S. (2013). Vitamin D Receptor Fok-I polymorphism modulates diabetic host response to vitamin D intake: Need for a nutrigenetic approach. Diabetes Care, 36(3), 550–556. https://doi.org/10.2337/dc12-0919 • Whitfield, G. K., Remus, L. S., Jurutka, P. W., Zitzer, H., Oza, A. K., Dang, H. T., Haussler, C. A., Galligan, M. A., Thatcher, M. L., Encinas Dominguez, C., & Haussler, M. R. (2001). Functionally relevant polymorphisms in the human nuclear vitamin D receptor gene. Molecular and Cellular Endocrinology, 177(1–2), 145–159. https://doi.org/10.1016/s0303-7207(01)00406-3 • Uitterlinden, A. G., Fang, Y., Van Meurs, J. B. J., Pols, H. A. P., & Van Leeuwen, J. P. T. M. (2004). Genetics and biology of vitamin D receptor polymorphisms. Gene, 338(2), 143–156. https://doi.org/10.1016/j.gene.2004.05.014 • T, S., P, B., & S, S. (2023). A meta-analysis suggests the association of reduced serum level of vitamin D and T-allele of Fok1 (rs2228570) polymorphism in the vitamin D receptor gene with celiac disease. Frontiers in Nutrition, 9. https://doi.org/10.3389/fnut.2022.996450 • Abrams, S. A., Griffin, I. J., Hawthorne, K. M., Chen, Z., Gunn, S. K., Wilde, M., Darlington, G., Shypailo, R. J., & Ellis, K. J. (2005). Vitamin D receptor Fok1 polymorphisms affect calcium absorption, kinetics, and bone mineralization rates during puberty. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 20(6), 945–953. https://doi.org/10.1359/JBMR.050114 • Ames, S. K., Ellis, K. J., Gunn, S. K., Copeland, K. C., & Abrams, S. A. (1999). Vitamin D receptor gene Fok1 polymorphism predicts calcium absorption and bone mineral density in

children. Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research, 14(5), 740–746. https://doi.org/10.1359/jbmr.1999.14.5.740

ESTROGEN METABOLISM AND CLEARANCE SNP References

CYP1A1 rs2606345

• Sowers, M. R., Wilson, A. L., Kardia, S. R., Chu, J., & McConnell, D. S. (2006). CYP1A1 and CYP1B1 polymorphisms and their association with estradiol and estrogen metabolites in women who are premenopausal and perimenopausal. The American Journal of Medicine, 119(9 Suppl 1), S44-51. https://doi.org/10.1016/j.amjmed.2006.07.006 • Crandall, C. J., Crawford, S. L., & Gold, E. B. (2006). Vasomotor symptom prevalence is associated with polymorphisms in sex steroid-metabolizing enzymes and receptors. The American Journal of Medicine, 119(9 Suppl 1), S52-60. https://doi.org/10.1016/j.amjmed.2006.07.007 •

Kravitz, H. M., Janssen, I., Lotrich, F. E., Kado, D. M., & Bromberger, J. T. (2006). Sex steroid hormone gene polymorphisms and depressive symptoms in women at midlife. The American Journal of Medicine, 119(9 Suppl 1), S87-93. https://doi.org/10.1016/j.amjmed.2006.07.010

FSHR

• Kim, J. J., Choi, Y. M., Hong, M. A., Chae, S. J., Hwang, K., Yoon, S. H., Ku, S. Y., Suh, C. S., & Kim, S. H. (2017). FSH receptor gene p. Thr307Ala and p. Asn680Ser polymorphisms are associated with the risk of polycystic ovary syndrome. Journal of Assisted Reproduction and Genetics, 34(8), 1087–1093. https://doi.org/10.1007/s10815-017-0953-z • Alviggi, C., Conforti, A., Santi, D., Esteves, S. C., Andersen, C. Y., Humaidan, P., Chiodini, P., De Placido, G., & Simoni, M. (2018). Clinical relevance of genetic variants of gonadotrophins and their receptors in controlled ovarian stimulation: A systematic review and meta-analysis. Human Reproduction Update, 24(5), 599–614. https://doi.org/10.1093/humupd/dmy019 • Valkenburg, O., Uitterlinden, A. G., Piersma, D., Hofman, A., Themmen, A. P. N., de Jong, F. H., Fauser, B. C. J. M., & Laven, J. S. E. (2009). Genetic polymorphisms of GnRH and gonadotrophic hormone receptors affect the phenotype of polycystic ovary syndrome. Human Reproduction (Oxford, England), 24(8), 2014–2022. https://doi.org/10.1093/humrep/dep113 • Simoni, M., Nieschlag, E., & Gromoll, J. (2002). Isoforms and single nucleotide polymorphisms of the FSH receptor gene: Implications for human reproduction. Human Reproduction Update, 8(5), 413–421. https://doi.org/10.1093/humupd/8.5.413 • Song, D., Huang, X.-L., Hong, L., Yu, J.-M., Zhang, Z.-F., Zhang, H.-Q., Sun, Z.-G., & Du, J. (2019). Sequence variants in FSHR and CYP19A1 genes and the ovarian response to controlled ovarian stimulation. Fertility and Sterility, 112(4), 749-757.e2. https://doi.org/10.1016/j.fertnstert.2019.05.017 • Simoni, M., Tempfer, C. B., Destenaves, B., & Fauser, B. C. J. M. (2008). Functional genetic polymorphisms and female reproductive disorders: Part I: Polycystic ovary syndrome and ovarian response. Human Reproduction Update, 14(5), 459–484. https://doi.org/10.1093/humupd/dmn024 • Perez Mayorga, M., Gromoll, J., Behre, H. M., Gassner, C., Nieschlag, E., & Simoni, M. (2000). Ovarian response to follicle-stimulating hormone (FSH) stimulation depends on the FSH receptor genotype. The Journal of Clinical Endocrinology and Metabolism, 85(9), 3365–3369. https://doi.org/10.1210/jcem.85.9.6789 • Overbeek, A., Kuijper, E. a. M., Hendriks, M. L., Blankenstein, M. A., Ketel, I. J. G., Twisk, J. W. R., Hompes, P. G. A., Homburg, R., & Lambalk, C. B. (2009). Clomiphene citrate resistance in relation to follicle-stimulating hormone receptor Ser680Ser-polymorphism in polycystic ovary syndrome.

Human Reproduction (Oxford, England), 24(8), 2007–2013. https://doi.org/10.1093/humrep/dep114

General SNP References

CYP1A2

• Sachse, C., Brockmöller, J., Bauer, S., & Roots, I. (1999). Functional significance of a C?A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. British Journal of Clinical Pharmacology, 47(4), 445–449. https://doi.org/10.1046/j.1365-2125.1999.00898.x • Tornio, A., & Backman, J. T. (2018). Cytochrome P450 in Pharmacogenetics: An Update. Advances in Pharmacology (San Diego, Calif.), 83, 3–32. https://doi.org/10.1016/bs.apha.2018.04.007 • Djordjevic, N., Ghotbi, R., Bertilsson, L., Jankovic, S., & Aklillu, E. (2008). Induction of CYP1A2 by heavy coffee consumption in Serbs and Swedes. European Journal of Clinical Pharmacology, 64(4), 381–385. https://doi.org/10.1007/s00228-007-0438-6 • Djordjevic, N., Ghotbi, R., Jankovic, S., & Aklillu, E. (2010). Induction of CYP1A2 by heavy coffee consumption is associated with the CYP1A2 -163C>A polymorphism. European Journal of Clinical Pharmacology, 66(7), 697–703.

https://doi.org/10.1007/s00228-010-0823-4

HEALTH PRECAUTIONS SNP References

ACE

• Rigat, B., Hubert, C., Alhenc-Gelas, F., Cambien, F., Corvol, P., & Soubrier, F. (1990). An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. The Journal of Clinical Investigation, 86(4), 1343–1346. https://doi.org/10.1172/JCI114844 • Dengel, D. R., Brown, M. D., Ferrell, R. E., & Supiano, M. A. (2001). Role of angiotensin converting enzyme genotype in sodium sensitivity in older hypertensives. American Journal of Hypertension, 14(12), 1178–1184. https://doi.org/10.1016/s0895-7061(01)02204-x • Chung, C.-M., Wang, R.-Y., Chen, J.-W., Fann, C. S. J., Leu, H.-B., Ho, H.-Y., Ting, C.-T., Lin, T.-H., Sheu, S.-H., Tsai, W.-C., Chen, J.-H., Jong, Y.-S., Lin, S.-J., Chen, Y.-T., & Pan, W.-H. (2010). A genome-wide association study identifies new loci for ACE activity: Potential implications for response to ACE inhibitor. The Pharmacogenomics Journal, 10(6), 537–544. https://doi.org/10.1038/tpj.2009.70 •

Abdollahi, M. R., Huang, S., Rodriguez, S., Guthrie, P. A. I., Smith, G. D., Ebrahim, S., Lawlor, D. A., Day, I. N. M., & Gaunt, T. R. (2008). Homogeneous assay of rs4343, an ACE I/D proxy, and an analysis in the British Women's Heart and Health Study (BWHHS). Disease Markers, 24(1), 11–17. https://doi.org/10.1155/2008/813679

CYP1B1

• Crandall, C. J., Diamant, A. L., Maglione, M., Thurston, R. C., & Sinsheimer, J. (2020). Genetic Variation and Hot Flashes: A Systematic Review. The Journal of Clinical Endocrinology and Metabolism, 105(12), e4907–e4957. https://doi.org/10.1210/clinem/dgaa536 • Hefler, L. A., Grimm, C., Heinze, G., Schneeberger, C., Mueller, M.

W., Muendlein, A., Huber, J. C., Leodolter, S., & Tempfer, C. B. (2005). Estrogen-metabolizing gene polymorphisms and age at natural menopause in Caucasian women. Human Reproduction (Oxford, England), 20(5), 1422–1427. https://doi.org/10.1093/humrep/deh848

DIO1 rs2235544

• Sterenborg, R. B. T. M., Steinbrenner, I., Li, Y., Bujnis, M. N., Naito, T., Marouli, E., Galesloot, T. E., Babajide, O., Andreasen, L., Astrup, A., Åsvold, B. O., Bandinelli, S., Beekman, M., Beilby, J. P., Bork-Jensen, J., Boutin, T., Brody, J. A., Brown, S. J., Brumpton, B., … Medici, M. (2024). Multi-trait analysis characterizes the genetics of thyroid function and identifies causal associations with clinical implications. Nature Communications, 15(1), 888. https://doi.org/10.1038/s41467-024-44701-9 • Panicker, V., Cluett, C., Shields, B., Murray, A., Parnell, K. S., Perry, J. R. B., Weedon, M. N., Singleton, A., Hernandez, D., Evans, J., Durant, C., Ferrucci, L., Melzer, D., Saravanan, P., Visser, T. J., Ceresini, G., Hattersley, A. T., Vaidya, B., Dayan, C. M., & Frayling, T. M. (2008). A common variation in deiodinase 1 gene DIO1 is associated with the relative levels of free thyroxine and triiodothyronine. The Journal of Clinical Endocrinology and Metabolism, 93(8), 3075–3081. https://doi.org/10.1210/jc.2008-0397 • Wolff, T. M., Dietrich, J. W., & Müller, M. A. (2022). Optimal Hormone Replacement Therapy in Hypothyroidism—A Model Predictive Control Approach. Frontiers in Endocrinology, 13, 884018. https://doi.org/10.3389/fendo.2022.884018 • Taylor, P. N., Porcu, E., Chew, S., Campbell, P. J., Traglia, M., Brown, S. J., Mullin, B. H., Shihab, H. A., Min, J., Walter, K., Memari, Y., Huang, J., Barnes, M. R., Beilby, J. P., Charoen, P., Danecek, P., Dudbridge, F., Forgetta, V., Greenwood, C., … UK0K Consortium. (2015). Whole-genome sequence-based analysis of thyroid function. Nature Communications, 6, 5681. https://doi.org/10.1038/ncomms6681 • Porcu, E., Medici, M., Pistis, G., Volpato, C. B., Wilson, S. G., Cappola, A. R., Bos, S. D., Deelen, J., den Heijer, M., Freathy, R. M., Lahti, J., Liu, C., Lopez, L. M., Nolte, I. M., O'Connell, J. R., Tanaka, T., Trompet, S., Arnold, A., Bandinelli, S., … Naitza, S. (2013). A meta-analysis of thyroid-

related traits reveals novel loci and gender-specific differences in the regulation of thyroid function. PLoS Genetics, 9(2), e1003266. https://doi.org/10.1371/journal.pgen.1003266

F10

• Ken-Dror, G., Drenos, F., Humphries, S. E., Talmud, P. J., Hingorani, A. D., Kivimäki, M., Kumari, M., Bauer, K. A., Morrissey, J. H., & Ireland, H. A. (2010). Haplotype and genotype effects of the F7 gene on circulating factor VII, coagulation activation markers and incident coronary heart disease in UK men. Journal of Thrombosis and Haemostasis: JTH, 8(11), 2394–2403. https://doi.org/10.1111/j.1538-7836.2010.04035.x • Kanai, M., Akiyama, M., Takahashi, A., Matoba, N., Momozawa, Y., Ikeda, M., Iwata, N., Ikegawa, S., Hirata, M., Matsuda, K., Kubo, M., Okada, Y., & Kamatani, Y. (2018). Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. Nature Genetics, 50(3), 390–400. https://doi.org/10.1038/s41588-018-0047-6 • Thareja, G., Belkadi, A., Arnold, M., Albagha, O. M. E., Graumann, J., Schmidt, F., Grallert, H., Peters, A., Gieger, C., Consortium, T. Q. G. P. R., & Suhre, K. (2023). Differences and commonalities in the genetic

architecture of protein quantitative trait loci in European and Arab populations. Human Molecular Genetics, 32(6), 907–916. https://doi.org/10.1093/hmg/ddac243

F5

• Simone, B., De Stefano, V., Leoncini, E., Zacho, J., Martinelli, I., Emmerich, J., Rossi, E., Folsom, A. R., Almawi, W. Y., Scarabin, P. Y., den Heijer, M., Cushman, M., Penco, S., Vaya, A., Angchaisuksiri, P., Okumus, G., Gemmati, D., Cima, S., Akar, N., … Boccia, S. (2013). 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. European Journal of Epidemiology, 28(8), 621–647. https://doi.org/10.1007/s10654-013-9825-8 • Klarin, D., Emdin, C. A., Natarajan, P., Conrad, M. F., INVENT Consortium, & Kathiresan, S. (2017). Genetic Analysis of Venous Thromboembolism in UK Biobank Identifies the ZFPM2 Locus and Implicates Obesity as a Causal Risk Factor. Circulation. Cardiovascular Genetics, 10(2), e001643. https://doi.org/10.1161/CIRCGENETICS.116.001643 • Juul, K., Tybjaerg-Hansen, A., Schnohr,

P., & Nordestgaard, B. G. (2004). Factor V Leiden and the risk for venous thromboembolism in the adult Danish population. Annals of Internal Medicine, 140(5), 330–337. https://doi.org/10.7326/0003-4819-140-5-200403020-00008

PDE8B rs4704397

• Arnaud-Lopez, L., Usala, G., Ceresini, G., Mitchell, B. D., Pilia, M. G., Piras, M. G., Sestu, N., Maschio, A., Busonero, F., Albai, G., Dei, M., Lai, S., Mulas, A., Crisponi, L., Tanaka, T., Bandinelli, S., Guralnik, J. M., Loi, A., Balaci, L., … Naitza, S. (2008). Phosphodiesterase 8B Gene Variants Are Associated with Serum TSH Levels and Thyroid Function. American Journal of Human Genetics, 82(6), 1270–1280. https://doi.org/10.1016/j.ajhg.2008.04.019 • Agretti, P., De Marco, G., Di Cosmo, C., Bagattini, B., Ferrarini, E., Montanelli, L., Vitti, P., & Tonacchera, M. (2014). Frequency and effect on serum TSH of phosphodiesterase 8B (PDE8B) gene polymorphisms in patients with sporadic nonautoimmune subclinical hypothyroidism. Journal of Endocrinological Investigation, 37(2), 189–194. https://doi.org/10.1007/s40618-013-0036-7 • Mansuri, T., Jadeja, S. H. D., Singh, M., Begum, R., & Robin, P. (2020). Phosphodiesterase 8B Polymorphism rs4704397 Is Associated with Infertility in Subclinical Hypothyroid Females: A Case-Control Study. International Journal of Fertility & Sterility, 14(2), 122–128. https://doi.org/10.22074/ijfs.2020.6015 • Taylor, P. N., Porcu, E., Chew, S., Campbell, P. J., Traglia, M., Brown, S. J., Mullin, B. H., Shihab, H. A., Min, J., Walter, K., Memari, Y., Huang, J., Barnes, M. R., Beilby, J. P., Charoen, P.,

Danecek, P., Dudbridge, F., Forgetta, V., Greenwood, C., … UK0K Consortium. (2015). Whole-genome sequence-based analysis of thyroid function. Nature Communications, 6, 5681. https://doi.org/10.1038/ncomms6681

HORMONE METABOLISM SNP References

CYP19A1

• Yip, L., Zaloumis, S., Irwin, D., Severi, G., Hopper, J., Giles, G., Harrap, S., Sinclair, R., & Ellis, J. (2009). Gene-wide association study between the aromatase gene (CYP19A1) and female pattern hair loss. The British Journal of Dermatology, 161(2), 289–294. https://doi.org/10.1111/j.1365-2133.2009.09186.x • Haiman, C. A., Dossus, L., Setiawan, V. W., Stram, D. O., Dunning, A. M., Thomas, G., Thun, M. J., Albanes, D., Altshuler, D., Ardanaz, E., Boeing, H., Buring, J., Burtt, N., Calle, E. E., Chanock, S., Clavel-Chapelon, F., Colditz, G. A., Cox, D. G., Feigelson, H. S., … Ziegler, R. G. (2007). Genetic variation at the CYP19A1 locus predicts circulating estrogen levels but not breast cancer risk in postmenopausal women. Cancer Research, 67(5), 1893–1897. https://doi.org/10.1158/0008-5472.CAN-06-4123

SRD5A1 rs824811

• Kinter, K. J., Amraei, R., & Anekar, A. A. (2024). Biochemistry, Dihydrotestosterone. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557634/ • Price, D. K., Chau, C. H., Till, C., Goodman, P. J., Leach, R. J., Johnson-Pais, T. L., Hsing, A. W., Hoque, A., Parnes, H. L., Schenk, J. M., Tangen, C. M., Thompson, I. M., Reichardt, J. K. V., & Figg, W. D. (2016). Association of androgen metabolism gene polymorphisms with prostate cancer risk and androgen concentrations: Results from the Prostate Cancer Prevention Trial. Cancer, 122(15), 2332–2340. https://doi.org/10.1002/cncr.30071

HYPERTENSION SNP References

AGT

• Nakajima, T., Jorde, L. B., Ishigami, T., Umemura, S., Emi, M., Lalouel, J.-M., & Inoue, I. (2002). Nucleotide diversity and haplotype structure of the human angiotensinogen gene in two populations. American Journal of Human Genetics, 70(1), 108–123. https://doi.org/10.1086/338454 • Jeunemaitre, X., Soubrier, F., Kotelevtsev, Y. V., Lifton, R. P., Williams, C. S., Charru, A., Hunt, S. C., Hopkins, P. N., Williams, R. R., & Lalouel, J. M. (1992). Molecular basis of human hypertension: Role of angiotensinogen. Cell, 71(1), 169–180. https://doi.org/10.1016/0092-8674(92)90275-h

INFLAMMATORY SNP References

ATG16L1

• Wellcome Trust Case Control Consortium. (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature, 447(7145), 661–678. https://doi.org/10.1038/nature05911 • Levine, B., & Kroemer, G. (2008). Autophagy in the Pathogenesis of Disease. Cell, 132(1), 27–42. https://doi.org/10.1016/j.cell.2007.12.018

ATG5

• Grosjean, I., Roméo, B., Domdom, M.-A., Belaid, A., D'Andréa, G., Guillot, N., Gherardi, R. K., Gal, J., Milano, G., Marquette, C. H., Hung, R. J., Landi, M. T., Han, Y., Brest, P., Von Bergen, M., Klionsky, D. J., Amos, C. I., Hofman, P., & Mograbi, B. (n.d.). Autophagopathies: From autophagy gene polymorphisms to precision medicine for human diseases. Autophagy, 18(11), 2519–2536. https://doi.org/10.1080/15548627.2022.2039994 • Martin, L. J., Gupta, J., Jyothula, S. S. S. K., Butsch Kovacic, M., Biagini Myers, J. M., Patterson, T. L., Ericksen, M. B., He, H., Gibson, A. M., Baye, T. M., Amirisetty, S., Tsoras, A. M., Sha, Y., Eissa, N. T., & Hershey, G. K. K. (2012). Functional variant in the autophagy-related 5 gene promotor is associated with childhood asthma. PloS One, 7(4), e33454. https://doi.org/10.1371/journal.pone.0033454 • Shao, Y., Chen, F., Chen, Y., Zhang, W., Lin, Y., Cai, Y., Yin, Z., Tao, S., Liao, Q., Zhao, J., Mai, H., He, Y., He, J., & Cui, L. (2017). Association between genetic polymorphisms in the autophagy-related 5 gene promoter and the risk of sepsis. Scientific Reports, 7, 9399. https://doi.org/10.1038/s41598-017-09978-5 • Tamargo-Gómez, I., Fernández, Á. F., & Mariño, G. (2020). Pathogenic Single Nucleotide Polymorphisms on Autophagy-Related Genes. International Journal of Molecular Sciences, 21(21), 8196. https://doi.org/10.3390/ijms21218196

METHYLATION SNP References

FOLR1

• Zhu, S., Ni, G., Sui, L., Zhao, Y., Zhang, X., Dai, Q., Chen, A., Lin, W., Li, Y., Huang, M., & Zhou, L. (2021). Genetic Polymorphisms in Enzymes Involved in One-Carbon Metabolism and Anti-epileptic Drug Monotherapy on Homocysteine Metabolism in Patients With Epilepsy. Frontiers in Neurology, 12, 683275. https://doi.org/10.3389/fneur.2021.683275 • Laanpere, M., Altmäe, S., Kaart, T., Stavreus-Evers, A., Nilsson, T. K., & Salumets, A. (2011). Folate-metabolizing gene variants and pregnancy outcome of IVF. Reproductive Biomedicine Online, 22(6), 603–614. https://doi.org/10.1016/j.rbmo.2011.03.002 • Song, X., Wei, J., Shu, J., Liu, Y., Sun, M., Zhu, P., & Qin, J. (2022). Association of polymorphisms of FOLR1 gene and FOLR2 gene and maternal folic acid supplementation with risk of ventricular septal defect: A case-control study. European Journal of Clinical Nutrition, 76(9), 1273–1280. https://doi.org/10.1038/s41430-022-01110-9

FOLR2

• 5-Methyl-tetrahydrofolate. National Center for Biotechnology Information. PubChem Compound Database (2004). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/135483998. • Strausberg, R. L. et al. Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. Proc. Natl. Acad. Sci. U. S. A. (2002). doi:10.1073/pnas.242603899 • Nakashima-Matsushita, N. et al. Selective expression of folate receptor beta and its possible role in methotrexate transport in synovial macrophages from patients with rheumatoid arthritis. Arthritis Rheum. (1999). doi:10.1002/1529-0131(199908)42:8<1609::AID-ANR7>3.0.CO;2-L • Moore, L. D., Le, T. & Fan, G. DNA methylation and its basic function. Neuropsychopharmacology (2013). doi:10.1038/npp.2012.112 • Tanaka, T. et al. Genome-wide Association Study of Vitamin B6, Vitamin B12, Folate, and Homocysteine Blood Concentrations. Am. J. Hum. Genet. (2009). doi:10.1016/j.ajhg.2009.02.011 • Abu Seman, N., Wan Mohamud, W. N., Östenson, C. G., Brismar, K. & Gu, H. F. Increased dna methylation of the slc30a8 gene promoter is associated with type 2 diabetes in a malay population. Clin. Epigenetics (2015). doi:10.1186/s13148-015-0049-5 • Ducker, G. S. & Rabinowitz, J. D. One-Carbon Metabolism in Health and Disease. Cell Metabolism (2017). doi:10.1016/j.cmet.2016.08.009 • Voutilainen, S., Rissanen, T. H., Virtanen, J., Lakka, T. A. & Salonen, J. T. Low dietary folate intake is associated with an excess incidence of acute coronary events: The Kuopio Ischemic Heart Disease Risk Factor Study. Circulation (2001). doi:10.1161/01.CIR.103.22.2674 • Link, R. 15 Healthy Foods That Are High in Folate (Folic Acid). Healthline (2020). Available at: https://www.healthline.com/nutrition/foods-high-in-folate-folic-acid#6.-Citrus-fruits. • Office of Dietary Supplements - Folate. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ • Scaglione, F. & Panzavolta, G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica (2014). doi:10.3109/00498254.2013.845705 • Henderson, G. B. Folate-binding proteins. Annu. Rev. Nutr. (1990). doi:10.1146/annurev.nutr.10.1.319 • Ragoussis, J., Senger, G., Trowsdale, J. & Campbell, I. G. Genomic organization of the human folate receptor genes on chromosome 11q13. Genomics (1992). doi:10.1016/S0888-7543(05)80236-8 • Freisheim, J. H., Price, E. M. & Ratnam, M. Folate coenzyme and antifolate transport proteins in normal and neoplastic cells. Adv. Enzyme Regul. (1989). doi:10.1016/0065-2571(89)90091-5 • Ratnam, M., Marquardt, H., Duhring, J. L. & Freisheim, J. H. Homologous membrane folate binding proteins in human placenta: cloning and sequence of a cDNA. Biochemistry (1989). • Shen, F., Ross, J. F., Wang, X. & Ratnam, M. Identification of a novel folate receptor, a truncated receptor, and receptor type beta in hematopoietic cells: cDNA cloning, expression, immunoreactivity, and tissue specificity. Biochemistry (1994). doi:10.1021/bi00171a021 • Page, S. T., Owen, W. C., Price, K. & Elwood, P. C. Expression of the Human Placental Folate Receptor Transcript is Regulated in Human Tissues. Journal of Molecular Biology 229, 1175–1183 (1993). • Suzuki, Y., Yoshitomo-Nakagawa, K., Maruyama, K., Suyama, A. & Sugano, S. Construction and characterization of a full length-enriched and a 5'-end-enriched cDNA library. Gene (1997). doi:10.1016/S0378-1119(97)00411-3

MTHFD1

• Ding, Y. P., Pedersen, E. K. R., Johansson, S., Gregory, J. F., Ueland, P. M., Svingen, G. F. T., Helgeland, Ø., Meyer, K., Fredriksen, Å., & Nygård, O. K. (2016). B vitamin treatments modify the risk of myocardial infarction associated with a MTHFD1 polymorphism in patients with stable angina pectoris. Nutrition, Metabolism and Cardiovascular Diseases, 26(6), 495–501. https://doi.org/10.1016/j.numecd.2015.12.009 • Carroll, N., Pangilinan, F., Molloy, A. M., Troendle, J., Mills, J. L., Kirke, P. N., Brody, L. C., Scott, J. M., & Parle-McDermott, A. (2009). Analysis of the MTHFD1 promoter and risk of neural tube defects. Human Genetics, 125(3), 247–256. https://doi.org/10.1007/s00439-008-0616-3

MTHFR rs1801131

• van der Put, N. M., Gabreëls, F., Stevens, E. M., Smeitink, J. A., Trijbels, F. J., Eskes, T. K., van den Heuvel, L. P., & Blom, H. J. (1998). A second common mutation in the methylenetetrahydrofolate reductase gene: An additional risk factor for neural-tube defects? American Journal of Human Genetics, 62(5), 1044–1051. https://doi.org/10.1086/301825 • Shen, O., Liu, R., Wu, W., Yu, L., & Wang, X. (2012). Association of the methylenetetrahydrofolate reductase gene A1298C polymorphism with male infertility: A meta-analysis. Annals of Human Genetics, 76(1), 25–32. https://doi.org/10.1111/j.1469-1809.2011.00691.x • Ogino, S., & Wilson, R. B. (2003). Genotype and haplotype distributions of MTHFR677C>T and 1298A>C single nucleotide polymorphisms: A meta-analysis. Journal of Human Genetics, 48(1), 1–7. https://doi.org/10.1007/s100380300000 • Frosst, P., Blom, H. J., Milos, R., Goyette, P., Sheppard, C. A., Matthews, R. G., Boers, G. J., den Heijer, M., Kluijtmans, L. A., & van den Heuvel, L. P. (1995). A candidate genetic risk factor for vascular disease: A common mutation in methylenetetrahydrofolate reductase. Nature Genetics, 10(1), 111–113. https://doi.org/10.1038/ng0595-111 • Ducker, G. S., & Rabinowitz, J. D. (2017). One-Carbon Metabolism in Health and Disease. Cell Metabolism, 25(1), 27–42. https://doi.org/10.1016/j.cmet.2016.08.009 • Donnelly, J. G. (2000). The 1298(A-->C) mutation of methylenetetrahydrofolate reductase should be designated to the 1289 position of the gene. American Journal of Human Genetics, 66(2), 744–745. https://doi.org/10.1086/302784 • Weisberg, I. S., Jacques, P. F., Selhub, J., Bostom, A. G., Chen, Z., Curtis Ellison, R., Eckfeldt, J. H., & Rozen, R. (2001). The 1298A-->C polymorphism in methylenetetrahydrofolate reductase (MTHFR): In vitro expression and association with homocysteine. Atherosclerosis, 156(2), 409–415. https://doi.org/10.1016/s0021-9150(00)00671-7 • Wei, L. K., Au, A., Menon, S., Griffiths, L. R., Kooi, C. W., Irene, L., Zhao, J., Lee, C., Alekseevna, A. M., Hassan, M. R. A., & Aziz, Z. A. (2017). Polymorphisms of MTHFR, eNOS, ACE, AGT, ApoE, PON1, PDE4D, and Ischemic Stroke: Meta-Analysis. Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association, 26(11), 2482–2493. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.05.048

MTHFR rs1801133

• Wei, L. K., Au, A., Menon, S., Griffiths, L. R., Kooi, C. W., Irene, L., Zhao, J., Lee, C., Alekseevna, A. M., Hassan, M. R. A., & Aziz, Z. A. (2017). Polymorphisms of MTHFR, eNOS, ACE, AGT, ApoE, PON1, PDE4D, and Ischemic Stroke: Meta-Analysis. Journal of Stroke and Cerebrovascular Diseases: The Official Journal of National Stroke Association, 26(11), 2482–2493. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.05.048 • Christensen, B., Arbour, L., Tran, P., Leclerc, D., Sabbaghian, N., Platt, R., Gilfix, B. M., Rosenblatt, D. S., Gravel, R. A., Forbes, P., & Rozen, R. (1999). Genetic polymorphisms in methylenetetrahydrofolate reductase and methionine synthase, folate levels in red blood cells, and risk of neural tube defects. American Journal of Medical Genetics, 84(2), 151–157. https://doi.org/10.1002/(sici)1096-8628(19990521)84:2<151::aid-ajmg12>3.0.co;2-t • Frosst, P., Blom, H. J., Milos, R., Goyette, P., Sheppard, C. A., Matthews, R. G., Boers, G. J., den Heijer, M., Kluijtmans, L. A., & van den Heuvel, L. P. (1995). A candidate genetic risk factor for vascular disease: A common mutation in methylenetetrahydrofolate reductase. Nature Genetics, 10(1), 111–113. https://doi.org/10.1038/ng0595-111 • Hazra, A., Kraft, P., Lazarus, R., Chen, C., Chanock, S. J., Jacques, P., Selhub, J., & Hunter, D. J. (2009). Genome-wide significant predictors of metabolites in the one-carbon metabolism pathway. Human Molecular Genetics, 18(23), 4677–4687. https://doi.org/10.1093/hmg/ddp428 • Hong, H.-H., Hu, Y., Yu, X.-Q., Zhou, L., Lv, M.-Q., Sun, Y., Ren, W.-J., & Zhou, D.-X. (2017). Associations of C677T polymorphism in methylenetetrahydrofolate reductase (MTHFR) gene with male infertility risk: A meta-analysis. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 212, 101–109. https://doi.org/10.1016/j.ejogrb.2017.03.004 • Kowa, H., Yasui, K., Takeshima, T., Urakami, K., Sakai, F., & Nakashima, K. (2000). The homozygous C677T mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for migraine. American Journal of Medical Genetics, 96(6), 762–764. https://doi.org/10.1002/1096-8628(20001204)96:6<762::aid-ajmg12>3.0.co;2-x • Ogino, S., & Wilson, R. B. (2003). Genotype and haplotype distributions of MTHFR677C>T and 1298A>C single nucleotide polymorphisms: A meta-analysis. Journal of Human Genetics, 48(1), 1–7. https://doi.org/10.1007/s100380300000 • Shadrina, M., Bondarenko, E. A., & Slominsky, P. A. (2018). Genetics Factors in Major Depression Disease. Frontiers in Psychiatry, 9, 334. https://doi.org/10.3389/fpsyt.2018.00334 • van der Put, N. M., Steegers-Theunissen, R. P., Frosst, P., Trijbels, F. J., Eskes, T. K., van den Heuvel, L. P., Mariman, E. C., den Heyer, M., Rozen, R., & Blom, H. J. (1995). Mutated methylenetetrahydrofolate reductase as a risk factor for spina bifida. Lancet (London, England), 346(8982), 1070–1071. https://doi.org/10.1016/s0140-6736(95)91743-8 • Weisberg, I. S., Jacques, P. F., Selhub, J., Bostom, A. G., Chen, Z., Curtis Ellison, R., Eckfeldt, J. H., & Rozen, R. (2001). The 1298A-->C polymorphism in methylenetetrahydrofolate reductase (MTHFR): In vitro expression and association with homocysteine. Atherosclerosis, 156(2), 409–415.

https://doi.org/10.1016/s0021-9150(00)00671-7

TCN1

• Velkova, A., Diaz, J. E. L., Pangilinan, F., Molloy, A. M., Mills, J. L., Shane, B., Sanchez, E., Cunningham, C., McNulty, H., Cropp, C. D., Bailey-Wilson, J. E., Wilson, A. F., & Brody, L. C. (2017). The FUT2 secretor variant p.Trp154Ter influences serum vitamin B12 concentration via holo-haptocorrin, but not holo-transcobalamin, and is associated with haptocorrin glycosylation. Human Molecular Genetics, 26(24), 4975–4988. https://doi.org/10.1093/hmg/ddx369 • Tanaka, T., Scheet, P., Giusti, B., Bandinelli, S., Piras, M. G., Usala, G., Lai, S., Mulas, A., Corsi, A. M., Vestrini, A., Sofi, F., Gori, A. M., Abbate, R., Guralnik, J., Singleton, A., Abecasis, G. R., Schlessinger, D., Uda, M., & Ferrucci, L. (2009). Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. American Journal of Human Genetics, 84(4), 477–482. https://doi.org/10.1016/j.ajhg.2009.02.011 • Hall, C. A. (1975). Transcobalamins I and II as natural transport proteins of

vitamin B12. Journal of Clinical Investigation, 56(5), 1125–1131.

TCN2

• Castro, R., Barroso, M., Rocha, M., Esse, R., Ramos, R., Ravasco, P., Rivera, I., & de Almeida, I. T. (2010). The TCN2 776CNG polymorphism correlates with vitamin B(12) cellular delivery in healthy adult populations. Clinical Biochemistry, 43(7–8), 645–649. https://doi.org/10.1016/j.clinbiochem.2010.01.015 • von Castel-Dunwoody, K. M., Kauwell, G. P. A., Shelnutt, K. P., Vaughn, J. D., Griffin, E. R., Maneval, D. R., Theriaque, D. W., & Bailey, L. B. (2005). Transcobalamin 776C->G polymorphism negatively affects vitamin B-12 metabolism. The American Journal of Clinical Nutrition, 81(6), 1436–1441. https://doi.org/10.1093/ajcn/81.6.1436 • Oussalah, A., Levy, J., Filhine-Trésarrieu, P., Namour, F., & Guéant, J.-L. (2017). Association of TCN2 rs1801198 c.776G>C polymorphism with markers of one-carbon metabolism and related diseases: A systematic review and meta-analysis of genetic association studies. The American Journal of Clinical Nutrition, 106(4), 1142–1156. https://doi.org/10.3945/ajcn.117.156349 • Miller, J. W., Ramos, M. I., Garrod, M. G., Flynn, M. A., & Green, R. (2002). Transcobalamin II 775G>C polymorphism and indices of vitamin B12 status in healthy older adults. Blood, 100(2), 718–720. https://doi.org/10.1182/blood-2002-01-0209 • Lievers, K. J. A., Afman, L. A., Kluijtmans, L. A. J., Boers, G. H. J., Verhoef, P., den Heijer, M., Trijbels, F. J. M., & Blom, H. J. (2002). Polymorphisms in the transcobalamin gene: Association with plasma homocysteine in healthy individuals and vascular disease patients. Clinical Chemistry, 48(9), 1383–1389. • Guéant, J.-L., Chabi, N. W., Guéant-Rodriguez, R.-M., Mutchinick, O. M., Debard, R., Payet, C., Lu, X., Villaume, C., Bronowicki, J.-P., Quadros, E. V., Sanni, A., Amouzou, E., Xia, B., Chen, M., Anello, G., Bosco, P., Romano, C., Arrieta, H. R., Sánchez, B. E., … Namour, F. (2007). Environmental influence on the worldwide prevalence of a 776C->G variant in the transcobalamin gene (TCN2). Journal of Medical Genetics, 44(6), 363–367. https://doi.org/10.1136/jmg.2006.048041 • Afman, L. A., Lievers, K. J. A., van der Put, N. M. J., Trijbels, F. J. M., & Blom, H. J. (2002). Single nucleotide polymorphisms in the transcobalamin gene: Relationship with transcobalamin concentrations and risk for neural tube defects. European Journal of

Human Genetics: EJHG, 10(7), 433–438. https://doi.org/10.1038/sj.ejhg.5200830

MITOCHONDRIA SNP References

SLC19A1

• Stanis?awska-Sachadyn, A., Mitchell, L. E., Woodside, J. V., Buckley, P. T., Kealey, C., Young, I. S., Scott, J. M., Murray, L., Boreham, C. A., McNulty, H., Strain, J. J., & Whitehead, A. S. (2009). The reduced folate carrier (SLC19A1) c.80G>A polymorphism is associated with red cell folate concentrations among women. Annals of Human Genetics, 73(Pt 5), 484–491. https://doi.org/10.1111/j.1469-1809.2009.00529.x • Cai, C., Xiao, R., Van Halm-Lutterodt, N., Zhen, J., Huang, X., Xu, Y., Chen, S., & Yuan, L. (2016). Association of MTHFR, SLC19A1 Genetic Polymorphism, Serum Folate, Vitamin B12 and Hcy Status with Cognitive Functions in Chinese Adults. Nutrients, 8(10), 665. https://doi.org/10.3390/nu8100665 • Cao, L., Wang, Y., Zhang, R., Dong, L., Cui, H., Fang, Y., Zhao, L., Shi, O., & Cai, C. (2018). Association of neural tube defects with gene polymorphisms in one-carbon metabolic pathway. Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery, 34(2), 277–284. https://doi.org/10.1007/s00381-017-3558-z • Chango, A., Emery-Fillon, N., de Courcy, G. P., Lambert, D., Pfister, M., Rosenblatt, D. S., & Nicolas, J. P. (2000). A polymorphism (80G->A) in the reduced folate carrier gene and its associations with folate status and homocysteinemia. Molecular Genetics and Metabolism, 70(4), 310–315. https://doi.org/10.1006/mgme.2000.3034 • Cho, Y., Kim, J. O., Lee, J. H., Park, H. M., Jeon, Y. J., Oh, S. H., Bae, J., Park, Y. S., Kim, O. J., & Kim, N. K. (2015). Association of reduced folate carrier-1 (RFC-1) polymorphisms with ischemic stroke and silent brain infarction. PloS One, 10(2), e0115295. https://doi.org/10.1371/journal.pone.0115295 • Clinical Annotation for rs1051266 (SLC19A1); methotrexate; Arthritis, Rheumatoid (level 2A Efficacy). (n.d.). PharmGKB. Retrieved January 15, 2024, from https://www.pharmgkb.org/clinicalAnnotation/1451245360 • Devlin, A. M., Clarke, R., Birks, J., Evans, J. G., & Halsted, C. H. (2006). Interactions among polymorphisms in folate-metabolizing genes and serum total homocysteine concentrations in a healthy elderly population. The American Journal of Clinical Nutrition, 83(3), 708–713. https://doi.org/10.1093/ajcn.83.3.708 • Yee, S. W., Gong, L., Badagnani, I., Giacomini, K. M., Klein, T. E., & Altman, R. B. (2010).

SLC19A1 Pharmacogenomics Summary. Pharmacogenetics and Genomics, 20(11), 708–715. https://doi.org/10.1097/FPC.0b013e32833eca92

NEUROTRANSMITTERS SNP References

COMT rs4680

• Scanlon, P. D., Raymond, F. A., & Weinshilboum, R. M. (1979). Catechol-O-methyltransferase: Thermolabile enzyme in erythrocytes of subjects homozygous for allele for low activity. Science (New York, N.Y.), 203(4375), 63–65. https://doi.org/10.1126/science.758679 • Tunbridge, E. M., Harrison, P. J., Warden, D. R., Johnston, C., Refsum, H., & Smith, A. D. (2008). Polymorphisms in the catechol-O-methyltransferase (COMT) gene influence plasma total homocysteine levels. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics, 147B(6), 996–999. https://doi.org/10.1002/ajmg.b.30700 • Dawling, S., Roodi, N., Mernaugh, R. L., Wang, X., & Parl, F. F. (2001). Catechol-O-methyltransferase (COMT)-mediated metabolism of catechol estrogens: Comparison of wild-type and variant COMT isoforms. Cancer Research, 61(18), 6716–6722. • Eriksson, A.-L., Suuriniemi, M., Mahonen, A., Cheng, S., & Ohlsson, C. (2005). The COMT val158met polymorphism is associated with early pubertal development, height and cortical bone mass in girls. Pediatric Research, 58(1), 71–77. https://doi.org/10.1203/01.PDR.0000163383.49747.B5 • Kumar, P., & Rai, V. (2020). Catechol-O-methyltransferase gene Val158Met polymorphism and obsessive compulsive disorder susceptibility: A meta-analysis. Metabolic Brain Disease, 35(2), 241–251. https://doi.org/10.1007/s11011-019-00495-0 • Lachman, H. M., Papolos, D. F., Saito, T., Yu, Y. M., Szumlanski, C. L., & Weinshilboum, R. M. (1996). Human catechol-O-methyltransferase pharmacogenetics: Description of a functional polymorphism and its potential application to neuropsychiatric disorders. Pharmacogenetics, 6(3), 243–250. https://doi.org/10.1097/00008571-199606000-00007 • Sardahaee, F. S., Holmen, T. L., Micali, N., & Kvaløy, K. (2017). Effects of single genetic variants and polygenic obesity risk scores on disordered eating in adolescents—The HUNT study. Appetite, 118, 8–16. https://doi.org/10.1016/j.appet.2017.07.003 • Wichers, M., Aguilera, M., Kenis, G., Krabbendam, L., Myin-Germeys, I., Jacobs, N., Peeters, F., Derom, C., Vlietinck, R., Mengelers, R., Delespaul, P., & van Os, J. (2008). The catechol-O-methyl transferase Val158Met polymorphism and experience of reward in the flow of daily life. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 33(13), 3030–3036. https://doi.org/10.1038/sj.npp.1301520 • Tunbridge, E. M., Narajos, M., Harrison, C. H., Beresford, C., Cipriani, A., & Harrison, P. J. (2019). Which Dopamine Polymorphisms Are Functional? Systematic Review and Meta-analysis of COMT, DAT, DBH, DDC, DRD1-5, MAOA, MAOB, TH, VMAT1, and VMAT2. Biological Psychiatry, 86(8), 608–620. https://doi.org/10.1016/j.biopsych.2019.05.014 • Stein, M. B., Fallin, M. D., Schork, N. J., & Gelernter, J. (2005). COMT polymorphisms and anxiety-related personality traits. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 30(11), 2092–2102. https://doi.org/10.1038/sj.npp.1300787 • Stein, D. J., Newman, T. K., Savitz, J., & Ramesar, R. (2006). Warriors versus worriers: The role of COMT gene variants. CNS Spectrums, 11(10), 745–748. https://doi.org/10.1017/s1092852900014863