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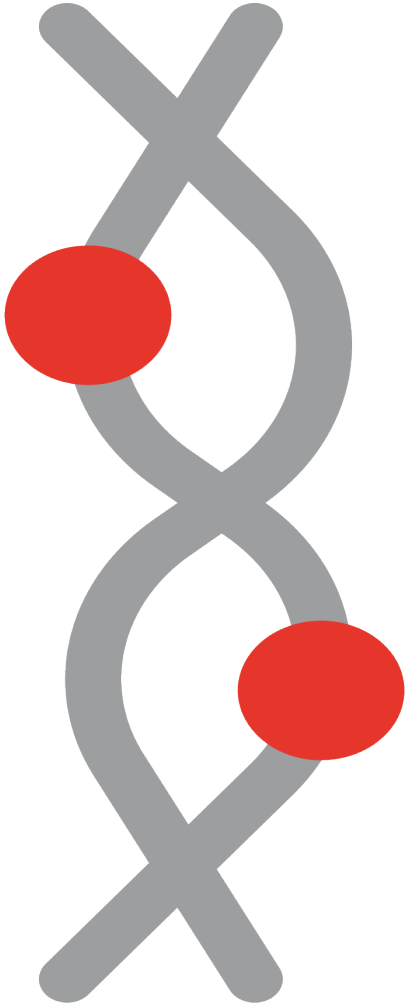
The Science of a Healthier Life™



Gene Comprehensive Nutrigenomic Report

Accession Number: ##########
Specimen Collected: ##/##/####
Specimen Received: ##/##/####
Report Generated: March 9, 2022
Specimen Type: Buccal Swab
Provider: ######## ########
Patient Name: ###### ######
Patient DOB: ##/##/####
Patient Gender: Male

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.

GX Sciences | 844-258-5564 | www.GXSciences.com
Lab | 4150 Freidrich Lane, Ste H | Austin, TX 78744
Laboratory Director: James W. Jacobson, Ph.D

– 57 – Male

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

rsID	Gene	Genetic Result	This column contains the targeted ingredients to support healthy gene activity of the specific genes listed.	Lifestyle Recommendations	Laboratory Recommendations
METHYLATION					
rs2071010	FOLR1	-/-	Methyltetrahydrofolate (5-MTHF)		
rs651933	FOLR2	+/+			
rs1643649	DHFR	-/-			
rs6495446	MTHFS	+/-			
rs1076991	MTHFD1	+/-			
rs1801133	MTHFR C677T	-/-			
rs1801131	MTHFR A1298C	-/-			
rs1051266	SLC19A1	+/-			
rs1802059	MTRR A664A	-/-	Methyl B12		Consider Checking Plasma B12 Level
rs1801394	MTRR A66G	+/-			
rs526934	TCN1	-/-	Methyl B12, Adenosyl B12		
rs1801198	TCN2	+/+			
rs558660	GIF	+/-			

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NEUROTRANSMITTER					
rs4680	COMT V158M	+/-	B2 (Riboflavin), Methyl Donors (Taurine, Choline, Trimethylglycine (TMG), Dimethylglycine (DMG), Inositol, L-Methionine	Higher Risk of Depression / Anxiety	Consider PGx Testing
rs6323	MAO-A	-/NA			
rs1799836	MAO-B	-/NA			
rs769407	GAD1	+/-	Prescription Amantadine, Ketamine, Glycine, N-Acetyl-Cysteine (NAC), Zinc, Magnesium, Oxaloacetate, Elderberry, L-Theanine, Melatonin	Be cautious with MSG (monosodium glutamate) exposure and glutamine supplementation	
rs3828275	GAD1	-/-			

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MITOCHONDRIA					
rs4147730	NDUFS3	-/-	CoQ 10, PQQ, L-Carnitine, Ornithine, Magnesium, NADH, Calcium		
rs809359	NDUFS7	-/-			
rs1051806	NDUFS8	-/-			
rs11648723	UQCRC2	-/-			
rs4850	UQCRC2	-/-			
rs8042694	COX5A	+/-			
rs4626565	COX6C	-/-			
rs1244414	ATP5C1	+/-			

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DETOXIFICATION					
rs1021737	CTH	+/+	N-Acetyl Cysteine (NAC), Glutathione	Herbicide and Pesticide Avoidance	
rs819147	AHCY	-/-			
rs1056806	GSTM1	-/-	Glutathione		
rs7483	GSTM3	+/-			
rs1695	GSTP1 I105V	+/-			
rs1208	NAT2	+/+	Silymarin, Alpha Lipoic Acid (ALA), P-5-P, Catechins	Avoid Industrial Carcinogens	
rs4880	SOD2	+/+	High Dose Antioxidants, Curcumin, Sulforaphane, Vitamin C	Consider high antioxidant diet (fruits and vegetables)	

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INFLAMMATORY					
rs2069812	IL5	+/+	Anti-Inflammatory Therapy: Curcumin, Omega 3s, Resveratrol, Quercetin, Low Dose Naltrexone (LDN), CBD Oil	Consider Low Inflammatory Diet	Consider Testing Pregnenolone, Cortisol, Progesterone, Testosterone
rs10402876	C3	+/-			
rs2569191	CD14	+/-			
rs1800925	IL13	+/-			
rs10181656	STAT4	+/+			
rs1800629	TNF	-/-			
rs231775	CTLA4	+/-			
rs2248814	NOS2	+/-	Anti-Infectives, Beta Glucans		

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ENVIRONMENTAL INFLAMMATORY					
rs10156191	AOC1	-/-	Poor Ability To Break Down External Histamine		
rs492602	FUT2	+/-	Prebiotics and Probiotics Needed		
rs2187668	HLA DQA1	-/-	High Risk of Gluten Based Issues		
rs2858331	HLA DQA2	-/-			
rs10210302	ATG16L1	+/-	Curcumin, Lithium Orotate, D-Chiro-Inositol, Catechins, Resveratrol, 12-15 Hour Fasting	12-15 Hour Fasting	Routine Blood Sugar, Insulin and Hb A1c
rs2241880	ATG16L1	+/-			
rs510432	ATG5	-/-			
rs26538	ATG12	-/-			
rs731236	VDR Taq	+/+	Vitamin D, Vitamin K		Consider Checking Vitamin D Level

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HEALTH PRECAUTIONS					
rs1867277	FOXE1	-/-	Iodine, Selenium, Increased Risk of Hypothyroidism		
rs4343	ACE	+/-	Increased risk of salt retention and hypertension		
rs1800440	CYP1B1	+/-	Increased Levels of 4-hydroxy Estrogen, Endometriosis and Osteoporosis		
rs6025	F5	-/-			
rs3211719	F10	+/-			

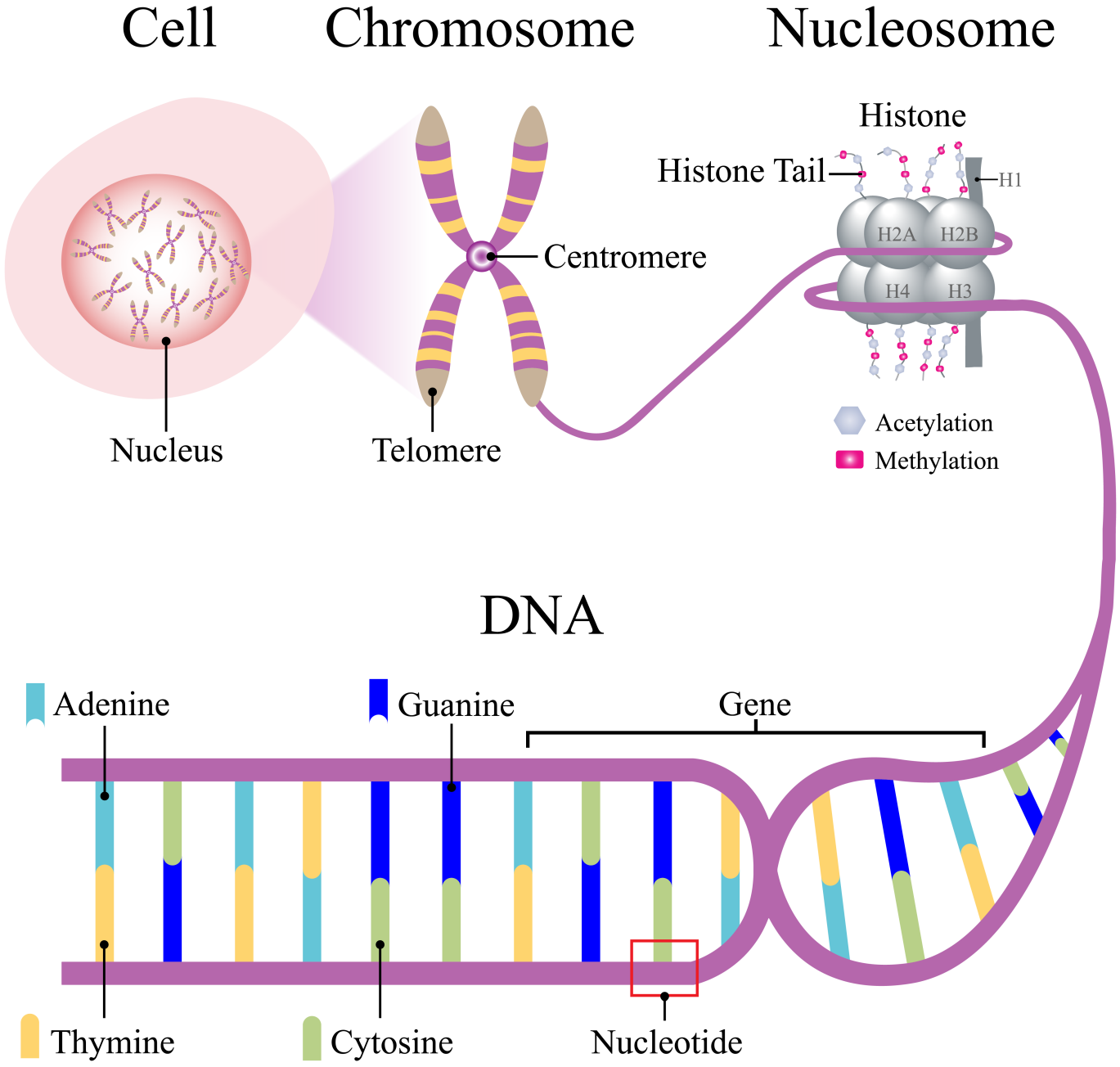
Summary for Pro7

Lifestyle Recommendations

- Higher Risk of Depression / Anxiety
- Be cautious with MSG (monosodium glutamate) exposure and glutamine supplementation
- Herbicide and Pesticide Avoidance
- Avoid Industrial Carcinogens
- Consider high antioxidant diet (fruits and vegetables)
- Consider Low Inflammatory Diet
- 12-15 Hour Fasting

Laboratory Recommendations

- Consider Checking Plasma B12 Level
- Consider PGx Testing
- Consider Testing Pregnenolone
- Cortisol
- Progesterone
- Testosterone
- Routine Blood Sugar
- Insulin and Hb A1c
- Consider Checking Vitamin D Level


Cell
Chromosome
Nucleosome
Histone
Histone Tail
H1
H2A
H2B
H4
H3
Centromere
Nucleus
Telomere
Acetylation
Methylation
DNA
Adenine
Guanine
Gene
Thymine
Cytosine
Nucleotide

Gene Information Key

rsID	Gene	"-" variant	"+" variant
rs4343	ACE	A	G
rs819147	AHCY	T	C
rs10156191	AOC1	C	T
rs26538	ATG12	T	C
rs2241880	ATG16L1	A	G
rs10210302	ATG16L1	C	T
rs510432	ATG5	C	T
rs1244414	ATP5C1	C	T
rs10402876	C3	G	C
rs2569191	CD14	T	C
rs4680	COMT V158M	G	A
rs8042694	COX5A	A	G
rs4626565	COX6C	T	C
rs1021737	CTH	G	T
rs231775	CTLA4	A	G
rs1800440	CYP1B1	T	C
rs1643649	DHFR	T	C
rs3211719	F10	A	G
rs6025	F5	C	T
rs2071010	FOLR1	G	A
rs651933	FOLR2	A	G
rs1867277	FOXE1	G	A
rs492602	FUT2	A	G
rs769407	GAD1	G	C
rs3828275	GAD1	C	T
rs558660	GIF	G	A
rs1056806	GSTM1	C	T
rs7483	GSTM3	C	T
rs1695	GSTP1:I105V	A	G

rsID	Gene	"-" variant	"+" variant
rs2187668	HLA-DQA1	C	T
rs2858331	HLA-DQA2	A	G
rs1800925	IL13	C	T
rs2069812	IL5	A	G
rs6323	MAO-A	T	G
rs1799836	MAO-B	T	C
rs1076991	MTHFD1	C	T
rs1801131	MTHFR:A1298C	T	G
rs1801133	MTHFR:C677T	G	A
rs6495446	MTHFS	C	T
rs1802059	MTRR:A664A	G	A
rs1801394	MTRR:A66G	A	G
rs1208	NAT2	A	G
rs4147730	NDUFS3	G	A
rs809359	NDUFS7	A	G
rs1051806	NDUFS8	C	T
rs2248814	NOS2	G	A
rs1051266	SLC19A1	T	C
rs4880	SOD2	A	G
rs10181656	STAT4	C	G
rs526934	TCN1	A	G
rs1801198	TCN2	C	G
rs1800629	TNF	G	A
rs4850	UQCRC2	G	A
rs11648723	UQCRC2	G	T
rs731236	VDR Taq	A	G

Definitions

CLOT RISK	The SNPs in this category define some areas of potential concern in the clotting mechanisms of the body. Polymorphisms in these proteins may need to be considered during pregnancy, surgery, trauma and/or certain forms of birth control
Factor V	A single nucleotide polymoprhism in the F5 gene (rs6025) leads to a mutant Factor V protein. This mutant protein is associated with increased clotting, especially in the veins.
Factor X	The F10 gene encodes a protein, Factor X, involved in coagulation and wound healing. Mutations in the F10 gene predict for clot risk and anticoagulant drug sensitivity.
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".
AHCY	Adenosylhomocysteinase (AHCY) is an enzyme that breaks down S-adenosylhomocysteine (SAH) to homocysteine and adenosine. Polymorphisms in this gene will lead to lower levels of homocysteine and glutathione.
CTH	Glutathione production is dependent on the function of the enzyme cystathionine gamma-lyase (CTH). CTH converts cystathionine to cysteine. Individuals with mutations in the CTH gene are predicted to have decreased glutathione-mediated detoxification.
GSTM1	Glutathione S-transferase M1 (GSTM1) is an important enzyme in the body's detoxification pathway. GSTM1 conjugates glutathione to molecules (drugs, environmental toxins, carcinogens etc.) bound for excretion. GSTM1 is mainly responsible for binding toxins in joints and for binding carcinogens.
GSTM3	Glutathione S-transferase mu 3 is an enzyme that detoxifies drugs, environmental toxins, and carcinogens by conjugating toxins to glutathione and subsequent excretion by the kidneys. Mutations in GSTM3 are associated with decreased clearance of toxins, anesthetics and drugs from the nervous system.
GSTP1	Glutathione S-transferases (GSTs) are a family of enzymes that play an important role in detoxification. The glutathione S-transferase pi gene (GSTP1) functions in chemical clearance and anti-inflammatory properities. High concentration of GST-p are found in the skin, lungs, sinuses, bladder and the intestinal tract. Polymorphisms of this enzyme allow for increased inflammatory activity in these areas that include eczema, asthma, chronic sinusitis, IBS, "leaky" gut and interstitial cystitis.
NAT2	N-Acetyl Transferase 2 (NAT2) is a liver enzyme that functions to both activate and deactivate drugs and carcinogens. Polymorphisms in this gene are divided into rapid, intermediate, and slow acetylator phenotypes. The slow polymorphism phenotype of NAT2 are also associated with higher incidences of cancer and drug toxicity.
SOD2	Mitochondrial Superoxide Dismutase 2 (SOD2)is a member of the iron/manganese mitochondrial superoxide dismutase family. This protein transforms toxic superoxide, a byproduct of the mitochondrial electron transport chain, into hydrogen peroxide and oxygen. This function allows SOD2 to clear mitochondrial reactive oxygen species (ROS) and, as a result, confer protection against mitochondrial damage and cell death.
DEVELOPMENTAL	The SNPs in this category have been identified as potential areas of weakness in the recovery of developmental disorders.
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.
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
CYP1B1	The CYP1B1 gene encodes a member of the cytochrome P450 family of enzymes. CYP1B1 is involved in metabolizing lipids, fats, cholesterol, and steroid hormones. SNPs in the CYP1B1 gene predict risk of hormone dependent diseases and efficacy of treatments of such diseases.
HYPERTENSION	The polymorphisms in this category will increase the risk of developing hypertension.
ACE	Angiotensin-converting enzyme (ACE) is an important target for therapeutic drugs treating hypertension and heart failure. The best studied single nucleotide polymorphism in the ACE gene (rs4343) has been linked to a wide variety of human phenotypes: nephropathy and renal disease, cancer, and even sports performance. Interestingly, rs4343 is a member of a large family of human mutations called Alu elements.
INFLAMMATORY	This Enzyme category has significant effects on the inflammatory state of a person's body. Polymorphisms in these specific enzymes will significantly increase the levels of inflammation in the body. By supplementing these enzyme deficiencies, the patient will effectively reduce inflammatory damage to the body.
AOC1	The SNP rs10156191 encodes a weaker form of the histamine degradation enzyme Amine Oxidase, Copper Containing 1 (AOC1). This mutation, Thr16Met, is predicted to produce an enzyme with less catalytic activity and associated higher levels of pro-inflammatory amines like histamine and putrescine.

ATG16L1 rs10210302	The ATG16L1 gene encodes a protein that is a vital component of a protein complex necessary for the cellular phenomena known as autophagy. Autophagy is the process of degrading and cleaning of inert debris of the cell. Weakness in autophagy leads to abnormal accumulation of cellular “garbage” that will eventually affect the cellular function and lead to autophagy-related disease states in including many neurological and immunological diseases, DM Type 2 and fatty liver disease.
ATG5	Autophagy-related 5 protein (ATG5) is an important intracellular mediator of the autophagy response. ATG5 is involved in a wide range of "quality control" features inside the cell: autophagy vesicle formation, innate immune system signaling, consumption of damaged mitochondria, and apoptosis. Mutations in the ATG5 gene are associated with numerous neurological, immunological and endocrine syndromes.
C3	Essential for the immune response, C3 is a protein involved in initiation of the complement system. C3 polymorphisms are associated with susceptibility to asthma and other inflammatory disorders.
CD14	The CD14 protein is a macrophage cell surface receptor that binds bacterial cell wall components. As one of the initiators of the innate immune response, fully functional CD14 is necessary for normal response to potential pathogens. Mutations in the CD14 gene are associated with susceptibility to asthma and other allergen-mediated inflammatory processes.
CTLA4	Cytotoxic T-lymphocyte Associated protein 4 (CTLA4) is an important inhibitor of T-cell activity: CTLA4 is part of the signaling cascade that turns off overactive T cells. Mutations in the gene that encodes CTLA4 are associated with a host of diseases characterized by a heightened immune state.
FUT2	Fucosyltransferase 2 (FUT2) is responsible for producing specific sugar groups that are secreted by the intestinal cells into the bowel to attract "good bacteria" . Polymorphisms in this gene produce "poor secreter" status. Lack of these sugars allows for gut dysbiosis and a higher risk of inflammatory bowel disease.
HLA-DQA1	Major histocompatibility complex, DQ alpha 1 (HLA-DQA1) is a human gene responsible for a cell surface receptor essential to the function of the immune system. Patients with a polymorphism in this gene are at higher risk for auto-immune based inflammatory disease including Celiac disease, Crohn's, Ulcerative Colitis, and gluten sensitivity.
HLA-DQA2	Major histocompatibility complex, DQ alpha 2 (HLA-DQA2) is a human gene responsible for a cell surface receptor essential to the function of the immune system. Patients with a polymorphism in this gene are at higher risk for auto-immune based inflammatory disease including Celiac disease, Crohn's, Ulcerative Colitis, and gluten sensitivity.
IL13	IL13 (Interleukin 13) is a member of the interleukin family of chemical messengers of the immune system. Polymorphisms in this gene are associated with changes in IL13 gene expression and increase the risk of more severe inflammatory responses to allergens.
IL5	The protein product of the Interleukin 5 gene (IL5) is important for normal development of B lymphocytes and eosinophils (a pro-inflammatory white blood cell). Inactivating mutations in the IL5 gene are associated with susceptibility to certain viral infections and increased aggression of inflammatory response. These polymorphisms are also associated with increased aggression of allergies, asthma and eosinophilia.
NOS2	Nitric Oxide Synthanse 2 (NOS2) is responsible for producing nitric oxide, a biologic mediator used by the nervous system, immune system and in blood vessel function. Polymorphisms in this enzyme can cause reduced immune system function, exercise intolerance and fatigue.
STAT4	The Signal Transducer and Activator of Transcription 4 (STAT4) gene encodes a transcription factor that responds to extracellular growth factors and cytokines. Mutations in the STAT4 gene are associated with inflammatory disorders like lupus and rheumatoid arthritis.
TNF	Tumor necrosis factor, TNF, is an important pro-inflammatory signaling molecule. Polymorphisms in the protein coding part of this gene are associated with more severe pro-inflammatory responses and require supplementation for inflammatory control.
VDR Taq1	The Vitamin D (calcitriol) Receptor is a member of the nuclear receptor family. Upon activation by vitamin D (a secosteroid), the VDR causes the activation or deactivation of protein production by the cell. Impaired vitamin D function can result in signigicant immune weakness and increased cancer risk, as well as, early bone loss, an increased risk of cognitive decline and mood disorders.
METABOLIC RISK FACTOR	The polymorphisms in this category relate to increase risk of developing metabolic syndromes including diabetes, fatty liver, hypothyroidism and insulin resistance.
FOXE1	FOXE1 (Forkhead Box Protein E1) is a gene that codes for a protein that is intimately involved in thyroid hormone synthesis. Polymorphisms in this gene most commonly lead to an increased risk of hypothyroidism due to a weakened ability to synthesize thyroid hormone.
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.
DHFR	Dihydrofolate reductase, or DHFR, is an enzyme that reduces dihydrofolic acid to tetrahydrofolic acid. This enzyme is the second enzyme in the folic acid conversion chain. Having a mutation in this enzyme can create a methylaiton deficiency with a MTHFR mutation.

FOLR1	Folate Receptor 1 (FOLR1) is a member of the folate receptor (FOLR) family. Members of this gene family have a high affinity for folate. Polymorphisms in this gene allow for poor delivery of folate 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.
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.
GIF	The glycoprotein product of the Gastric Intrinsic Factor (GIF) gene is secreted by the stomach lining. GIF protein is required for absorption of Vitamin B12. B12 is necessary for normal red blood cell maturation.
MTHFD1	Methylenetetrahydrofolate Dehydrogenase 1 enzyme handles 2 significant enzymes conversions in the production of L-MTHF. This common polymorphism causes a significant methylation deficiency due to the fact that it is utilized in two steps in methyl-folate production.
MTHFR A1298C	Methylenetetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the bioactive form of folic acid. Two significant polymorphism variants exist in this gene, the A1298C and the C677T. The 1298 confers a conversion weakness of 10% for one copy and approximately 20% for two copies. In contrast, the 677 variant is much more severe and conveys a 40% conversion weakness for one copy and 70% for two copies. A reduced level of MTHFolate produces significant biochemical effects including poor production of dopamine and serotonin, pregnancy complications, poor healing of the nervous system, weak mitochondrial function, reduced production of glutathione, poor cell turnover and poor function of T cell lymphocytes.
MTHFR C677T	Methylene tetrahydrofolate reductase (MTHFR) catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the bioactive form of folic acid. Two significant polymorphism variants exist in this gene, the A1298C and the C677T. The 1298 confers a conversion weakness of 10% for one copy and approximately 20% for two copies. In contrast, the 677 variant is much more severe and conveys a 40% conversion weakness for one copy and 70% for two copies. A reduced level of MTHFolate produces significant biochemical effects including poor production of dopamine and serotonin, pregnancy complications, poor healing of the nervous system, weak mitochondrial function, reduced production of glutathione, poor cell turnover and poor function of T cell lymphocytes.
MTHFS	MTHFS (methenyletetrahydrofolate synthase) is an enzyme that catalyzes the conversion of 5-formyltetrahydrofolate to 5,10-methenyltetrahydrofolate, a precursor of reduced folates. This polymorphism codes for a decreased function of the enzyme and results in poor utilization of Leucovorin (5-formyltetrahydrofolate)..
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.
SLC19A1	The SLC19A1 gene encodes the reduced folate carrier (RFC) protein. Mutations in the RFC are associated with reduced plasma folate.
TCN1	The protein product of the transcobalamin 1 (TCN1) gene binds Vitamin B12 and protects it from the low pH environment of the human stomach. Individuals homozygous for the G allele of the TCN1 SNP, rs526934, are predicted to have lower serum B12.
TCN2	The protein product of the Transcobalamin 2 gene, TCN2, binds the active form of vitamin B-12. Individuals with the G/G phenotype at rs1801198 have decreased serum B-12 and increased homocysteine when compared to individuals with the C/C phenotype.
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.
ATP5C1	ATPase 5c1 (ATP5C1) is an enzyme responsible for producing ATP (the energy component) in the mitochondria. This protein is known as Complex V (the 5th protein) in the mitochondrial respiratory chain. Polymorphisms in the gene confer a weakened energy production by the mitochondria.
COX5A	Cytochrome c oxidase subunit 5a (COX5A) is a protein in a subunit of the cytochrome c oxidase complex, also known as Complex IV of the mitochondrial electron transport chain. Polymorphisms in this enzyme produce a weakened energy production by the mitochondria.
COX6C	Cytochrome c oxidase subunit 6c (COX6C) is a protein in a subunit of the cytochrome c oxidase complex, also known as Complex IV of the mitochondrial electron transport chain. Polymorphisms in this enzyme produce a weakened energy production by the mitochondria.
NDUFS3	The NDUFS3 genes encodes a mitochondrial enzyme, NADH Dehydrogenase (Ubiquinone) Fe-S Protein 3. Like other NDUFS proteins, NDUFS3 is thought to require ubiquinone for full activity.
NDUFS7	NADH Dehydrogenase [ubiquinone] iron-sulfur protein 7 (NDUFS7) is a mitochondrial protein also know as Complex I of the mitochondrial respiratory chain. It is located in the mitochondrial inner membrane and is the largest of the five complexes of the electron transport chain. Polymorphisms in this enzyme produce a weakened energy production in the mitochondria.

NDUFS8	NADH Dehydrogenase (Ubiquinone) Fe-S Protein 8 (NDUFS8) encodes an enzyme in the mitochondrial respiratory chain. Mutations in the NDUFS8 gene are associated with Leigh Syndrome, osteoporosis, and mitochondrial complex I deficiency.
UQCRC2 Arg183Gln	Ubiquinol Cytochrome c Reductase (UQCR, Complex II) is a mitochondrial enzyme protein also known as Complex III of the electron transport chain. Polymorphisms in this enzyme produce a weakened energy production by the mitochondria.
NEUROTRANSMITTER	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 V158M	Catechol-O-methyltransferase (COMT) is one of several enzymes that degrade catecholamine neurotransmitters such as dopamine, epinephrine, and norepinephrine. COMT's main function is to inactivate neurotransmitters (dopamine, epinephrine, and norepinephrine) by the addition of a methyl group to the catecholamine. Normal COMT function allows people to rapidly reverse feelings of anxiety or depression. COMT (+/-) patients have sluggish ability to alter anxiety or depression episodes. COMT (+/+) patients are more prone to prolonged episodes of anxiety, depression and OCD.
GAD1 rs3828275	Glutamic Acid Decarboxylase (GAD 1) is the enzyme responsible for conversion of glutamic acid (a stimulant neurotransmitter) to GABA (a calming neurotransmitter). Deficiency of GABA from polymorphisms in this enzyme are associated with sleep disorders, "half glass empty" syndrome, dysphoria, and spasticity.
MAOA	Monoamine oxidase A (MAOA) is one of the classic neurotransmitter degradation enzymes. By degrading serotonin, dopamine, epinephrine, and norepinephrine, MAO-A ends neuronal signaling induced by those neurotransmitters. Mutations in the MAO-A gene leads to decreased degradation of these neurotransmitters and can be associated with increased aggression, mood disorders and drug addiction.
MAOB	Monoamine Oxidase B (MAO B) catalyzes the neuroactive amines, such as dopamine, epinephrine, norepinephrine, and plays a role in the stability of mood in the central nervous system,. MAO B's primary purpose is to degrade dopamine. Patients who possess polymorphisms of MAO B have a higher risk of clinical depression and mood disorders.

Disclaimers

METHODOLOGY AND LIMITATIONS:

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, 4150 Freidrich Lane, Ste H, Austin, TX. 78744. 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 GX Sciences' laboratory pursuant to Clinical Laboratory Improvement Amendments (CLIA) requirements.
CLIA #: 45D2144988 Laboratory Director: James Jacobson, PhD

DISCLAIMER:

This test was developed and its performance characteristics determined by GX Sciences. 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 purposes. It should not be regarded as investigational or for research. rsIDs for the alleles being tested were obtained from the dbSNP database (Build 142).

DISCLAIMER:

UND Result: If you have received the result Variant undetermined (UND) this indicates that we were not able to determine your carrier status based on your raw data. Please refer to the GX Sciences genetic knowledge database for more information: https://www.gxsciences.com/kb_results.asp

DISCLAIMER:

Report contents and report recommendations are created and approved by GX Sciences. Sole responsibility for the proper use of the information on the GX Sciences report rests with the user, or those professionals with whom the user may consult. Nutrigenomic Testing and Dietary Supplements are not "Designated Health Services" covered by Medicare or Medicaid and may not be reimbursed under any state or Federal health care program.

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GX Sciences SNP References

DETOXIFICATION SNP References

AHCY

• Vugrek, O., Beluži?, R. & Naki?, N. S-adenosylhomocysteine hydrolase (AHCY) deficiency: Two novel mutations with lethal outcome. Hum. Mutat. 30, (2009). • Motzek, A. et al. Abnormal hypermethylation at imprinting control regions in patients with S-adenosylhomocysteine hydrolase (AHCY) deficiency. PLoS One 11, (2016). • Schrock, M. How Metabolic Detoxification Can Help You Live a Healthier Life. Non Toxic Revolution (2019). Available at: https://www.nontoxicrevolution.org/blog/metabolic-detoxification. • Pizzorno, J. Glutathione! Integrative Medicine (Boulder) (2014). doi:10.5005/jp/books/13002_11 • Allocati, N., Masulli, M., Di Ilio, C. & Federici, L. Glutathione transferases: Substrates, inihibitors and pro-drugs in cancer and neurodegenerative diseases. Oncogenesis (2018). doi:10.1038/s41389-017-0025-3 • Whalen, R. & Boyer, T. D. Human glutathione S-transferases. Seminars in Liver Disease (1998). doi:10.1055/s-2007-1007169 • Hodges, R. E. & Minich, D. M. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. Journal of Nutrition and Metabolism (2015). doi:10.1155/2015/760689

CTH

• Huezo-Diaz, P. et al. Association of Cth genetic variant with veno-occlusive disease in children receiving intravenous busulfan before hematopoietic stem cell transplantation. Blood 120, (2012). • Pizzorno, J. Glutathione! Integrative Medicine (Boulder) (2014). doi:10.5005/jp/books/13002_11 • Allocati, N., Masulli, M., Di Ilio, C. & Federici, L. Glutathione transferases: Substrates, inihibitors and pro-drugs in cancer and neurodegenerative diseases. Oncogenesis (2018). doi:10.1038/s41389-017-0025-3 • Hodges, R. E. & Minich, D. M. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. Journal of Nutrition and Metabolism (2015). doi:10.1155/2015/760689 • Wang, J. & Hegele, R. a. Genomic basis of cystathioninuria (MIM 219500) revealed by multiple mutations in cystathionine gamma-lyase (CTH). Hum. Genet. 112, 404–408 (2003). • Schrock, M. How Metabolic Detoxification Can Help You Live a Healthier Life. Non Toxic Revolution (2019). Available at: https://www.nontoxicrevolution.org/blog/metabolic-detoxification. • Whalen, R. & Boyer, T. D. Human glutathione S-transferases. Seminars in Liver Disease (1998). doi:10.1055/s-2007-1007169

GSTM1

• Ghatak, S. et al. Xenobiotic Pathway Gene Polymorphisms Associated with Gastric Cancer in High Risk Mizo-Mongoloid Population, Northeast India. Helicobacter (2016). doi:10.1111/hel.12308 • Whalen, R. & Boyer, T. D. Human glutathione S-transferases. Seminars in Liver Disease (1998). doi:10.1055/s-2007-1007169 • Hodges, R. E. & Minich, D. M. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. Journal of Nutrition and Metabolism (2015). doi:10.1155/2015/760689 • Pizzorno, J. Glutathione! Integrative Medicine (Boulder) (2014). doi:10.5005/jp/books/13002_11 • Schrock, M. How Metabolic Detoxification Can Help You Live a Healthier Life. Non Toxic Revolution (2019). Available at: https://www.nontoxicrevolution.org/blog/metabolic-detoxification. • Brackett, J. et al. Antioxidant enzyme polymorphisms and neuropsychological outcomes in medulloblastoma survivors: A report from the Childhood Cancer Survivor Study. Neuro. Oncol. (2012). doi:10.1093/neuonc/nos123 • Gori?ar, K. et al. Genetic variability of DNA repair mechanisms and glutathione-S-transferase genes influences treatment outcome in osteosarcoma. Cancer Epidemiol. (2015). doi:10.1016/j.canep.2014.12.009 • Klen, J., Gori?ar, K., Janež, A. & Dolžan, V. Common polymorphisms in antioxidant genes are associated with diabetic nephropathy in Type 2 diabetes patients. Per. Med. (2015). doi:10.2217/pme.14.86 • Allocati, N., Masulli, M., Di Ilio, C. & Federici, L. Glutathione transferases: Substrates, inihibitors and pro-drugs in cancer and neurodegenerative diseases. Oncogenesis (2018). doi:10.1038/s41389-017-0025-3

GSTM3

• Patskovsky, Y. V, Huang, M. Q., Takayama, T., Listowsky, I. & Pearson, W. R. Distinctive structure of the human GSTM3 gene-inverted orientation relative to the mu class glutathione transferase gene cluster. Arch. Biochem. Biophys. (1999). doi:10.1006/abbi.1998.0964 • Maes, O. C., Schipper, H. M., Chong, G., Chertkow, H. M. & Wang, E. A GSTM3 polymorphism associated with an etiopathogenetic mechanism in Alzheimer disease. Neurobiol. Aging (2010). doi:10.1016/j.neurobiolaging.2008.03.007

GSTP1

• Sekine, I., Minna, J. D., Nishio, K., Tamura, T. & Saijo, N. A literature review of molecular markers predictive of clinical response to cytotoxic chemotherapy in patients with lung cancer. J Thorac Oncol (2006). doi:01243894-200601000-00008 [pii] • Buch, S. C., Notani, P. N. & Bhisey, R. A. Polymorphism at GSTM1, GSTM3 and GSTT1 gene loci and susceptibility to oral cancer in an Indian population. Carcinogenesis (2002). doi:10.1093/carcin/23.5.803 • Whalen, R. & Boyer, T. D. Human glutathione S-transferases. Seminars in Liver Disease (1998). doi:10.1055/s-2007-1007169 • Allocati, N., Masulli, M., Di Ilio, C. & Federici, L. Glutathione transferases: Substrates, inihibitors and pro-drugs in cancer and neurodegenerative diseases. Oncogenesis (2018). doi:10.1038/s41389-017-0025-3 • Pizzorno, J. Glutathione! Integrative Medicine (Boulder) (2014). doi:10.5005/jp/books/13002_11 • Schrock, M. How Metabolic Detoxification Can Help You Live a Healthier Life. Non Toxic Revolution (2019). Available at: https://www.nontoxicrevolution.org/blog/metabolic-detoxification. • Strange, R. C. & Fryer, A. A. The glutathione S-transferases: influence of polymorphism on cancer susceptibility. IARC Sci. Publ. (1999). • Hodges, R. E. & Minich, D. M. Modulation of Metabolic Detoxification Pathways Using Foods and Food-Derived Components: A Scientific Review with Clinical Application. Journal of Nutrition and Metabolism (2015). doi:10.1155/2015/760689 • Kellen, E. et al. Pooled analysis and meta-analysis of the glutathione S-transferase P1 Ile 105Val polymorphism and bladder cancer: A HuGE-GSEC review. American Journal of Epidemiology (2007). doi:10.1093/aje/kwm003 • Gerhard, D. S. et al. The status, quality, and expansion of the NIH full-length cDNA project: The Mammalian Gene Collection (MGC). Genome Res. (2004). doi:10.1101/gr.2596504

NAT2

• Agundez, J. A. Polymorphisms of human N-acetyltransferases and cancer risk. Curr Drug Metab (2008). doi:10.2174/138920008784892083 • NAT2 N-acetyltransferase 2 [Homo sapiens (human)] - Gene - NCBI. National Center for Biotechnology Information (2018). Available at: https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=10 • NAT2PRED: a computational predictor of the human N-AcetylTransferase-2 (NAT2) acetylator phenotype. NAT2PRED: a computational predictor of the human N-AcetylTransferase-2 (NAT2) acetylator phenotype (2009). Available at: http://nat2pred.rit.albany.edu/. • Ochs-Balcom, H. M., Wiesner, G. & Elston, R. C. A meta-analysis of the association of N-acetyltransferase 2 gene (NAT2) variants with breast cancer. American Journal of Epidemiology (2007). doi:10.1093/aje/kwm066 • Windmill, K. F. et al. The role of xenobiotic metabolizing enzymes in arylamine toxicity and carcinogenesis: Functional and localization studies. Mutat. Res. - Fundam. Mol. Mech. Mutagen. (1997). doi:10.1016/S0027-5107(97)00038-9 • Vatsis, K. P. et al. Nomenclature for N-acetyltransferases. Pharmacogenetics (1995). doi:10.1097/00008571-199502000-00001

SOD2

• Reilly, C. T. Top 20 Foods High In Antioxidants - St. Johns Health. Available at: https://www.stjohns.health/documents/content/top-20-foods-high-in-antioxidants.pdf. • Wilson, D. W. et al. The role of food antioxidants, benefits of functional foods, and influence of feeding habits on the health of the older person: An overview. Antioxidants (2017). doi:10.3390/antiox6040081 • Danial, N. N. & Korsmeyer, S. J. Cell Death: Critical Control Points. Cell (2004). doi:10.1016/S0092-8674(04)00046-7 • Perry, J. J. P. et al. Contribution of human manganese superoxide dismutase tyrosine 34 to structure and catalysis. Biochemistry (2009). doi:10.1021/bi8023288 • Becuwe, P., Ennen, M., Klotz, R., Barbieux, C. & Grandemange, S. Manganese superoxide dismutase in breast cancer: From molecular mechanisms of gene regulation to biological and clinical significance. Free Radical Biology and Medicine (2014). doi:10.1016/j.freeradbiomed.2014.08.026 • Van Remmen, H. et al. Life-long reduction in MnSOD activity results in increased DNA damage and higher incidence of cancer but does not accelerate aging. Physiol. Genomics (2003). doi:10.1152/physiolgenomics.00122.2003 • SOD2 superoxide dismutase 2 [Homo sapiens (human)] - Gene - NCBI. National Center for Biotechnology Information (2018). Available at: https://www.ncbi.nlm.nih.gov/gene/6648. • Muller, F. L., Lustgarten, M. S., Jang, Y., Richardson, A. & Van Remmen, H. Trends in oxidative aging theories. Free Radical Biology and Medicine (2007). doi:10.1016/j.freeradbiomed.2007.03.034 • Murray, C. J. L. & Lopez, A. D. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet (1997). doi:10.1016/S0140-6736(96)07492-2 • Kerr, J. F. R., Wyllie, A. H. & Currie, A. R. Apoptosis : a Basic Biological Phenomenon With Wide-Ranging Implications in tissue kinetics. Br. J. Cancer (1972). doi:10.1111/j.1365-2796.2005.01570.x • Birben, E., Sahiner, U. M., Sackesen, C., Erzurum, S. & Kalayci, O. Oxidative stress and antioxidant defense. World Allergy Organization Journal (2012). doi:10.1097/WOX.0b013e3182439613 • Harvard T.H. Chan School of Public Health. Antioxidants. The Nutrition Source (2019). Available at: https://www.hsph.harvard.edu/nutritionsource/antioxidants/. • Raman, R. 12 Healthy Foods High in Antioxidants. Healthline (2018). Available at: https://www.healthline.com/nutrition/foods-high-in-antioxidants.

DEVELOPMENTAL SNP References

ATG12

• 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 • Yuan, J. et al. Polymorphisms in autophagy related genes and the coal workers' pneumoconiosis in a Chinese

population. Gene 632, 36–42 (2017). • Anton, R. F. et al. Pharmacogenomics. Nat. Genet. 16, 268–278 (2008). • Mizushima, N. Autophagy: Process and function. Genes and Development (2007). doi:10.1101/gad.1599207 • 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 • Lindberg, S. Autophagy: Definition, Diet, Fasting, Cancer, Benefits, and More. Healthline (2014). Available at: https://www.healthline.com/health/autophagy#bottom-line.

HEALTH PRECAUTIONS SNP References

ACE

• The ACE gene and human performance: 12 years on. Puthucheary Z1, Skipworth JR, Rawal J, Loosemore M, Van Someren K, Montgomery HE. Sports Med. 2011 Jun 1;41(6):433-48. doi: 10.2165/11588720-0. • Structural details on the binding of antihypertensive drugs captopril and enalaprilat to human testicular angiotensin I-converting enzyme. (PMID: 15236580) Natesh R. … Acharya K.R.(Biochemistry 2004) • Angiotensin-converting enzyme inhibition by perindopril in the treatment of cardiovascular disease. (PMID: 19379059) Brugts J.J. … Simoons M.L.(Expert Rev Cardiovasc Ther 2009) • Meta-analysis of genetic studies in ischemic stroke: thirty-two genes involving approximately 18,000 cases and 58,000 controls. (PMID: 15534175) Casas J.P. … Sharma P.(Arch. Neurol. 2004) • Triple pharmacological blockade of the renin-angiotensin-aldosterone system in nondiabetic CKD: an open-label crossover randomized controlled trial. (PMID: 18423812) Tylicki L. … Rutkowski B.(Am. J. Kidney Dis. 2008)

CYP1B1

• Zahid, M. et al. Unbalanced estrogen metabolism in ovarian cancer. Int. J. Cancer (2014). doi:10.1002/ijc.28565 • Taioli, E. et al. Comparison of estrogens and estrogen metabolites in human breast tissue and urine. Reprod. Biol. Endocrinol. (2010). doi:10.1186/1477-7827-8-93 • Banerjee, A., Chakraborty, S., Chakraborty, A., Chakrabarti, S. & Ray, K. Functional and structural analyses of CYP1B1 variants linked to congenital and adult-Onset glaucoma to investigate the molecular basis of these diseases. PLoS One (2016). doi:10.1371/journal.pone.0156252 • Nishida, C. R., Everett, S. & Ortiz de Montellano, P. R. Specificity Determinants of CYP1B1 Estradiol Hydroxylation. Mol. Pharmacol. (2013). doi:10.1124/mol.113.087700 • Wiggs, J. L., Langgurth, A. M. & Allen, K. F. Carrier frequency of CYP1B1 mutations in the United States (an American Ophthalmological Society thesis). Trans. Am. Ophthalmol. Soc. (2014). • Bansal, S. et al. Mitochondrial targeting of cytochrome P450 (CYP) 1B1 and its role in polycyclic aromatic hydrocarbon-induced mitochondrial dysfunction. J. Biol. Chem. (2014). doi:10.1074/jbc.M113.525659 • Li, F. et al. Lipidomics reveals a link between CYP1B1 and SCD1 in promoting obesity. J. Proteome Res. (2014). doi:10.1021/pr500145n • Dumas, I. & Diorio, C. Polymorphisms in genes involved in the estrogen pathway and mammographic density. BMC Cancer (2010). doi:10.1186/1471-2407-10-636 • Samavat, H. & Kurzer, M. S. Estrogen metabolism and breast cancer. Cancer Lett. (2014). doi:10.1016/j.canlet.2014.04.018 • Alves Dos Santos, R. et al. Variability in estrogen-metabolizing genes and their association with genomic instability in untreated breast cancer patients and healthy women. J. Biomed. Biotechnol. (2011). doi:10.1155/2011/571784 • Crooke, P. S. et al. Estrogen metabolism and exposure in a genotypic-phenotypic model for breast cancer risk prediction. Cancer Epidemiol. Biomarkers Prev. (2011). doi:10.1158/1055-9965.EPI-11-0060 • Napoli, N. et al. The Val432Leu polymorphism of the CYP1B1 gene is associated with differences in estrogen metabolism and bone density. Bone (2009). doi:10.1016/j.bone.2008.09.018

F10

• Eichholz, K., Mennechet, F. J. D. & Kremer, E. J. Human Coagulation Factor X-Adenovirus Type 5 Complexes Poorly Stimulate an Innate Immune Response in Human Mononuclear Phagocytes. J. Virol. (2015). doi:10.1128/JVI.03576-14 • Lu, Q., Yang, L., Manithody, C., Wang, X. & Rezaie, A. R. Molecular basis of the clotting defect in a bleeding patient missing the Asp-185 codon in the factor X gene. Thromb. Res. (2014). doi:10.1016/j.thromres.2014.08.004 • Fair, D. S., Plow, E. F. & Edgington, T. S. Combined Functional and Immunochemical Analysis of Normal and Abnormal Human Factor X. Journal of Clinical Investigation 64, 884–894 (1979). • Yang, L., Manithody, C. & Rezaie, A. R. Functional role of O-linked and N-linked glycosylation sites present on the activation peptide of factor X. J. Thromb. Haemost. (2009). doi:10.1111/j.1538-7836.2009.03578.x • Ding, Q., Shen, Y., Yang, L., Wang, X. & Rezaie, A. R. The missense Thr211Pro mutation in the factor X activation peptide of a bleeding patient causes molecular defect in the clotting cascade. Thromb. Haemost. (2013). doi:10.1160/TH13-03-0184 • PANTELEEV, M. A., SAENKO, E. L., ANANYEVA, N. M. & ATAULLAKHANOV, F. I. Kinetics of Factor X activation by the membrane-bound complex of Factor IXa and Factor VIIIa. Biochem. J. (2004). doi:10.1042/BJ20031748 • Baumann Kreuziger, L. M. et al. Monitoring anticoagulation in patients with an unreliable prothrombin time/international normalized ratio: Factor II versus chromogenic factor X testing. Blood Coagul. Fibrinolysis (2014). doi:10.1097/MBC.0000000000000030 • Manithody, C., Yang, L. & Rezaie, A. R. Identification of a basic region on tissue factor that interacts with the first epidermal growth factor-like domain of factor X. Biochemistry (2007). doi:10.1021/bi6025193 • Corjon, S. et al. Cell entry and trafficking of human adenovirus bound to blood factor X is determined by the fiber serotype and not hexon:heparan sulfate interaction. PLoS One (2011). doi:10.1371/journal.pone.0018205 • Greig, J. A. et al. Influence of coagulation factor X on in vitro and in vivo gene delivery by adenovirus (Ad) 5, Ad35, and chimeric Ad5/Ad35 vectors. Mol. Ther. (2009). doi:10.1038/mt.2009.152

F5

• Soria, J. M. et al. Multilocus genetic risk scores for venous thromboembolism risk assessment. J. Am. Heart Assoc. (2014). doi:10.1161/JAHA.114.001060 • Nahar, R., Saxena, R., Deb, R. & Verma, I. C. Pharmacogenetic typing for oral anti-coagulant response among factor V Leiden mutation carriers. Indian J. Hum. Genet. (2012). doi:10.4103/0971-6866.107987 • Ruigrok, Y. M., Slooter, A. J. C., Rinkel, G. J. E., Wijmenga, C. & Rosendaal, F. R. Genes influencing coagulation and the risk of aneurysmal subarachnoid hemorrhage, and subsequent complications of secondary cerebral ischemia and rebleeding. Acta Neurochir. (Wien). (2010). doi:10.1007/s00701-009-0505-0 • Simone, B. et al. Risk of venous thromboembolism associated with single and combined effects of Factor v Leiden, Prothrombin 20210A and Methylenetethraydrofolate reductase C677T: A meta-analysis involving over 11,000 cases and 21,000 controls. Eur. J. Epidemiol. (2013). doi:10.1007/s10654-013-9825-8 • Mäkelburg, A. B. U. et al. Different risk of deep vein thrombosis and pulmonary embolism in carriers with factor V Leiden compared with non-carriers, but not in other thrombophilic defects. results from a large retrospective family cohort study. Haematologica (2010). doi:10.3324/haematol.2009.017061 • Sedano-Balbás, S. et al. APCR, factor V gene known and novel SNPs and adverse pregnancy outcomes in an Irish cohort of pregnant women. BMC Pregnancy Childbirth (2010). doi:10.1186/1471-2393-10-11 • Allon, M., Zhang, L., Maya, I. D., Bray, M. S. & Fernandez, J. R. Association of factor V gene polymorphism with arteriovenous graft failure. Am. J. Kidney Dis. (2012). doi:10.1053/j.ajkd.2011.11.036 • Himabindu, G. et al. Factor V Leiden mutation is not a predisposing factor for acute coronary syndromes. Indian Heart J. (2012). doi:10.1016/j.ihj.2012.07.006 • Wang, X., Bai, T., Liu, S., Pan, H. & Wang, B. Association between thrombophilia gene polymorphisms and preeclampsia: A meta-analysis. PLoS One (2014). doi:10.1371/journal.pone.0100789 • Peck, G. et al. The genetics of primary haemorrhagic stroke, subarachnoid haemorrhage and ruptured intracranial aneurysms in adults. PLoS One (2008). doi:10.1371/journal.pone.0003691 • Arsov, T., Miladinova, D. & Spiroski, M. Factor V Leiden is associated with higher risk of deep venous thrombosis of large blood vessels. Croat. Med. J. (2006). • Kaiser, R. et al. Factor V Leiden and thrombosis in patients with systemic lupus erythematosus: a meta-analysis. Genes Immun. (2009). doi:10.1038/gene.2009.32 • Sode, B. F., Allin, K. H., Dahl, M., Gyntelberg, F. & Nordestgaard, B. G. Risk of venous thromboembolism and myocardial infarction associated with factor V Leiden and prothrombin mutations and blood type. CMAJ (2013). doi:10.1503/cmaj.121636 • Cai, C. et al. Association of MTHFR, SLC19A1 Genetic Polymorphism, Serum Folate, Vitamin B12 and Hcy Status with Cognitive Functions in Chinese Adults. Nutrients (2016). doi:10.3390/nu8100665 • Bentley, P., Peck, G., Smeeth, L., Whittaker, J. & Sharma, P. Causal relationship of susceptibility genes to ischemic stroke: Comparison to ischemic heart disease and biochemical determinants. PLoS One (2010). doi:10.1371/journal.pone.0009136 • Yang, B. et al. Associations of MTHFR gene polymorphisms with hypertension and hypertension in pregnancy: A meta-analysis from 114 studies with 15411 cases and 21970 controls. PLoS One (2014). doi:10.1371/journal.pone.0087497

FOXE1

• Genetic Predisposition to Papillary Thyroid Carcinoma: Involvement of FOXE1, TSHR, and a Novel lincRNA Gene, PTCSC2 Huiling He, Wei Li, Sandya Liyanarachchi, Jaroslaw Jendrzejewski, Mukund Srinivas, Ramana V. Davuluri, Rebecca Nagy, Albert de la Chapelle J Clin Endocrinol Metab. 2015 Jan; 100(1): E164–E172. Published online 2014 Oct 10. doi: 10.1210/jc.2014-2147 • Variants Near FOXE1 Are Associated with Hypothyroidism and Other Thyroid Conditions: Using Electronic Medical Records for Genome- and Phenome-wide Studies Joshua C. Denny, Dana C. Crawford, Marylyn D. Ritchie, Suzette J. Bielinski, Melissa A. Basford, Yuki Bradford, High Seng Chai, Lisa Bastarache, Rebecca Zuvich, Peggy Peissig, David Carrell, Andrea H. Ramirez, Jyotishman Pathak, Russell A. Wilke, Luke Rasmussen, Xiaoming Wang, Jennifer A. Pacheco, Abel N. Kho, M. Geoffrey Hayes, Noah Weston, Martha Matsumoto, Peter A. Kopp, Katherine M. Newton, Gail P. Jarvik, Rongling Li, Teri A. Manolio, Iftikhar J. Kullo, Christopher G. Chute, Rex L. Chisholm, Eric B. Larson, Catherine A. McCarty, Daniel R. Masys, Dan M. Roden, Mariza de Andrade Am J Hum Genet. 2011 Oct 7; 89(4): 529–542. doi: 10.1016/j.ajhg.2011.09.008 • Multiple functional variants in long-range enhancer elements contribute to the risk of SNP rs965513 in thyroid cancer Huiling He, Wei Li, Sandya Liyanarachchi, Mukund Srinivas, Yanqiang Wang, Keiko Akagi, Yao Wang, Dayong Wu, Qianben Wang, Victor Jin, David E. Symer, Rulong Shen, John Phay, Rebecca Nagy, Albert de la Chapelle Proc Natl Acad Sci U S A. 2015 May 12; 112(19): 6128–6133. Published online 2015 Apr 27. doi: 10.1073/pnas.1506255112 • Genetic associations with neonatal thyroid stimulating hormone levels Farah Y. Alul, Oleg A. Shchelochkov, Stanton L. Berberich, Jeffrey C. Murray, Kelli K. Ryckman Pediatr Res. 2013 Apr; 73(4 0 1): 484–491. Published online 2013 Jan 23.doi: 10.1038/pr.2013.18 • Novel Genetic Loci Identified for the Pathophysiology of Childhood Obesity in the Hispanic Population Anthony G. Comuzzie, Shelley A. Cole, Sandra L. Laston, V. Saroja Voruganti, Karin Haack, Richard A. Gibbs, Nancy F. Butte PLoS One. 2012; 7(12): e51954. Published online 2012 Dec 14. doi: 10.1371/journal.pone.0051954 • The Variant rs1867277 in FOXE1 Gene Confers Thyroid Cancer Susceptibility through the Recruitment of USF1/USF2 Transcription Factors Iñigo Landa, Sergio Ruiz-Llorente, Cristina Montero-Conde, Lucía Inglada-Pérez, Francesca Schiavi, Susanna Leskelä, Guillermo Pita, Roger Milne, Javier Maravall, Ignacio Ramos, Víctor Andía, Paloma Rodríguez-Poyo, Antonino Jara-Albarrán, Amparo Meoro, Cristina del Peso, Luis Arribas, Pedro Iglesias, Javier Caballero, Joaquín Serrano, Antonio Picó, Francisco Pomares, Gabriel Giménez, Pedro López-Mondéjar, Roberto Castello, Isabella Merante-Boschin, Maria-Rosa Pelizzo, Didac Mauricio, Giuseppe Opocher, Cristina Rodríguez-Antona, Anna González-Neira, Xavier Matías-Guiu, Pilar Santisteban, Mercedes Robledo PLoS Genet. 2009 Sep; 5(9): e1000637. Published online 2009 Sep 4. doi: 10.1371/journal.pgen.1000637 • Quantitative Assessment of Common Genetic Variants on FOXE1 and Differentiated Thyroid Cancer Risk Hongling Zhu, Qian Xi, Lianyong Liu, Jingnan Wang, Mingjun Gu PLoS One. 2014; 9(1): e87332. Published online 2014 Jan 29. doi: 10.1371/journal.pone.0087332 • Patterns of FOXE1 Expression in Papillary Thyroid Carcinoma by Immunohistochemistry Andrey Bychkov, Vladimir Saenko, Masahiro Nakashima, Norisato Mitsutake, Tatiana Rogounovitch, Alyaksandr Nikitski, Florence Orim, Shunichi Yamashita Thyroid. 2013 Jul; 23(7): 817–828. doi: 10.1089/thy.2012.0466 • The investigation of foxe1 variations in papillary thyroid carcinoma Erkan Somuncu, Adem Karatas, Sina Ferahman, Neslihan Saygili, Eren Yilmaz, Oguz Ozturk, Metin Kapan Int J Clin Exp Pathol. 2015; 8(10): 13458–13464. Published online 2015 Oct 1. • FOXE1 Association with Differentiated Thyroid Cancer and Its Progression Marissa Penna-Martinez, Friederike Epp, Heinrich Kahles, Elizabeth Ramos-Lopez, Nora Hinsch, Martin-Leo Hansmann, Ivan Selkinski, Frank Grünwald, Katharina Holzer, Wolf O. Bechstein, Stefan Zeuzem, Christian Vorländer, Klaus Badenhoop Thyroid. 2014 May 1; 24(5): 845–851. doi: 10.1089/thy.2013.0274

INFLAMMATORY SNP References

AOC1

• McGrath, A. P. et al. Structure and Inhibition of Human Diamine Oxidase - Biochemistry (ACS Publications). Biochemistry 48, 9810–22 (2009). • Maintz, L. & Novak, N. Histamine and histamine intolerance. Am. J. Clin. Nutr. (2007). doi:10.1093/ajcn/85.5.1185 • McGrath, A. P. et al. Structure and inhibition of human diamine oxidase. Biochemistry 48, 9810–9822 (2009). • Schwelberger, H. G. The origin of mammalian plasma amine oxidases. in Journal of Neural Transmission 114, 757–762 (2007). • Solismaa, A. et al. Histaminergic gene polymorphisms associated with sedation in clozapine-treated patients. Eur. Neuropsychopharmacol. 27, 442–449 (2017).

ATG16L1

• Mizushima, N. Autophagy: Process and function. Genes and Development (2007). doi:10.1101/gad.1599207 • Salem, M., Nielsen, O. H., Nys, K., Yazdanyar, S. & Seidelin, J. B. Impact of T300A Variant of ATG16L1 on antibacterial response, risk of culture positive infections, and clinical course of Crohn's disease. Clin. Transl. Gastroenterol. (2015). doi:10.1038/ctg.2015.47 • Begun, J. et al. Integrated Genomics of Crohn's Disease Risk Variant Identifies a Role for CLEC12A in Antibacterial Autophagy. Cell Rep. (2015). doi:10.1016/j.celrep.2015.05.045 • Cheng, J. F., Ning, Y. J., Zhang, W., Lu, Z. H. & Lin, L. T300A polymorphism of ATG16L1 and susceptibility to inflammatory bowel diseases: A meta-analysis. World J. Gastroenterol. (2010). doi:10.3748/wjg.v16.i10.1258 • Kabat, A. M. et al. The autophagy gene Atg16l1 differentially regulates Treg and TH2 cells to control intestinal inflammation. Elife (2016). doi:10.7554/eLife.12444 • Lassen, K. G. et al. Atg16L1 T300A variant decreases selective autophagy resulting in altered cytokine signaling and decreased antibacterial defense. Proc. Natl. Acad. Sci. (2014). doi:10.1073/pnas.1407001111 • 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 • Levine, B. & Kroemer, G. Autophagy in the Pathogenesis of Disease. Cell (2008). doi:10.1016/j.cell.2007.12.018 • Lindberg, S. Autophagy: Definition, Diet, Fasting, Cancer, Benefits, and More. Healthline (2014). Available at: https://www.healthline.com/health/autophagy#bottom-line. • 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 • Gazouli, M. et al. NOD2/CARD15, ATG16L1 and IL23R gene polymorphisms and childhood-onset of Crohn's disease. World J. Gastroenterol. (2010). doi:10.3748/wjg.v16.i14.1753 • Kuballa, P., Huett, A., Rioux, J. D., Daly, M. J. & Xavier, R. J. Impaired autophagy of an intracellular pathogen induced by a Crohn's disease associated ATG16L1 variant. PLoS One (2008). doi:10.1371/journal.pone.0003391 • Rosentul, D. C. et al. Role of autophagy genetic variants for the risk of Candida infections. Med. Mycol. (2014). doi:10.1093/mmy/myt035 • Raju, D., Hussey, S. & Jones, N. L. Crohn disease ATG16L1 polymorphism increases susceptibility to infection with Helicobacter pylori in humans. Autophagy (2012). doi:10.4161/auto.21007 • Stappenbeck, T. S. et al. Crohn disease: A current perspective on genetics, autophagy and immunity. Autophagy (2011). doi:10.4161/auto.7.4.13074 • Csöngei, V. et al. Interaction of the major inflammatory bowel disease susceptibility alleles in Crohn's disease patients. World J. Gastroenterol. (2010). doi:10.3748/wjg.v16.i2.176 • Boada-Romero, E. et al. The T300A Crohn's disease risk polymorphism impairs function of the WD40 domain of ATG16L1. Nat. Commun. (2016). doi:10.1038/ncomms11821 • Glubb, D. M. et al. NOD2 and ATG16L1 polymorphisms affect monocyte responses in crohn's disease. World J. Gastroenterol. (2011). doi:10.3748/wjg.v17.i23.2829 • Salem, M., Ammitzboell, M., Nys, K., Seidelin, J. B. & Nielsen, O. H. ATG16L1: A multifunctional susceptibility factor in crohn disease. Autophagy (2015). doi:10.1080/15548627.2015.1017187 • Usategui-Martín, R. et al. Polymorphisms in autophagy genes are associated with paget disease of bone. PLoS One (2015). doi:10.1371/journal.pone.0128984 • Messer, J. S. et al. The Crohn's disease: Associated ATG16L1 variant and Salmonella invasion. BMJ Open (2013). doi:10.1136/bmjopen-2013-002790

ATG5

• Lindberg, S. Autophagy: Definition, Diet, Fasting, Cancer, Benefits, and More. Healthline (2014). Available at: https://www.healthline.com/health/autophagy#bottom-line. • 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 • Antunes, F. et al. Autophagy and intermittent fasting: the connection for cancer therapy? Clinics (Sao Paulo, Brazil) (2018). doi:10.6061/clinics/2018/e814s • Levine, B. & Kroemer, G. Autophagy in the Pathogenesis of Disease. Cell (2008). doi:10.1016/j.cell.2007.12.018 • 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). • White, K. A. M. et al. Variants in autophagy-related genes and clinical characteristics in melanoma: a population-based study. Cancer Med. 5, 3336–3345 (2016). • Yuan, J. et al. Polymorphisms in autophagy related genes and the coal workers' pneumoconiosis in a Chinese population. Gene 632, 36–42 (2017). • Martin, L. J. et al. Functional Variant in the Autophagy-Related 5 Gene Promotor is Associated with Childhood Asthma. PLoS One 7, e33454 (2012).

C3

• Liu, Y. Z., Wang, Y. X. & Jiang, C. L. Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience (2017). doi:10.3389/fnhum.2017.00316 • Harvard Health Publishing. Take steps to prevent or reverse stress-related health problems. Harvard Health (2017). Available at: https://www.health.harvard.edu/stress/take-steps-to-prevent-or-reverse-stress-related-health-problems. • Chen, L. et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget (2018). doi:10.18632/oncotarget.23208 • Harvard Health Publishing. Foods that fight inflammation. Harvard Health (2018). Available at: https://www.health.harvard.edu/staying-healthy/foods-that-fight-inflammation. • Oke, S. L. & Tracey, K. J. The inflammatory reflex and the role of complementary and alternative medical therapies. in Annals of the New York Academy of Sciences (2009). doi:10.1196/annals.1393.013 • Maydych, V. The interplay between stress, inflammation, and emotional attention: Relevance for depression. Frontiers in Neuroscience (2019). doi:10.3389/fnins.2019.00384 • Wei, M. Yoga could slow the harmful effects of stress and inflammation. Harvard Health Blog (2020). Available at: https://www.health.harvard.edu/blog/yoga-could-slow-the-harmful-effects-of-stress-and-inflammation-2017101912588. • Ferreira, S. T., Clarke, J. R., Bomfim, T. R. & De Felice, F. G. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimer's and Dementia (2014). doi:10.1016/j.jalz.2013.12.010 • Tanaka, T. & Kishimoto, T. Targeting interleukin-6: All the way to treat autoimmune and inflammatory diseases. International Journal of Biological Sciences (2012). doi:10.7150/ijbs.4666 • Oh, J. Y. & Sin, D. D. Lung inflammation in COPD: why does it matter? F1000 Medicine Reports 4, (2012). • Loos B, et al. Polymorphisms in an interferon-? receptor-1 gene marker and susceptibility to periodontitis. Acta Odontol. Scand. (2003). doi:10.1080/00016350310006168 • Disabato, D. J., Quan, N. & Godbout, J. P. Neuroinflammation: the devil is in the details. Journal of Neurochemistry 139, 136–153 (2016). • Simpson, N. & Dinges, D. F. Sleep and Inflammation. Nutr. Rev. (2007). doi:10.1111/j.1753-4887.2007.tb00371.x • Kalogeropoulos, A. P., Georgiopoulou, V. V. & Butler, J. From Risk Factors to Structural Heart Disease: The Role of Inflammation. Heart Failure Clinics (2012). doi:10.1016/j.hfc.2011.08.002 • Lurie, D. I. An integrative approach to neuroinflammation in psychiatric disorders and neuropathic pain. J. Exp. Neurosci. (2018). doi:10.1177/1179069518793639 • Research Area. Neuroinflammation - Creative Diagnostics (2020). Available at: https://www.creative-diagnostics.com/neuroinflammation.htm. • Rasheed, H. et al. Replication of association of the apolipoprotein A1-C3-A4 gene cluster with the risk of gout. Rheumatol. (United Kingdom) (2016). doi:10.1093/rheumatology/kew057 • Nsaiba, M. J. et al. C3 Polymorphism Influences Circulating Levels of C3, ASP and Lipids in Schizophrenic Patients. Neurochem. Res. (2015). doi:10.1007/s11064-015-1543-z • Prechl, J. et al. Serological and genetic evidence for altered complement system functionality in systemic lupus erythematosus: Findings of the GAPAID consortium. PLoS One (2016). doi:10.1371/journal.pone.0150685 • Wu, Y. et al. Interactions of environmental factors and APOA1-APOC3-APOA4-APOA5 gene cluster gene polymorphisms with metabolic syndrome. PLoS One (2016). doi:10.1371/journal.pone.0147946 • Saksens, N. T. M. et al. Rare Genetic Variants Associated With Development of Age-Related Macular Degeneration. JAMA Ophthalmol. (2016). doi:10.1001/jamaophthalmol.2015.5592 • Bonyadi, M. et al. Association of polymorphisms in complement component 3 with age-related macular degeneration in an Iranian population. Ophthalmic Genet. (2016). doi:10.3109/13816810.2015.1126612 • Nakayama, Y. et al. C3 Promotes Expansion of CD8 + and CD4 + T Cells in a Listeria monocytogenes Infection . J. Immunol. (2009). doi:10.4049/jimmunol.0801191 • Western, K. A. Overview of the Immune System | National Institute of Allergy and Infectious Diseases (NIAID): An Overview. National Institute of Allergy and Infectious Diseases, NIH 3–8 (2008). doi:10.1007/978-1-59745-569-5_1 • Johns Hopkins Medicine Pathology. Definition of Autoimmunity & Autoimmune Disease. Definition of Autoimmunity & Autoimmune Disease - Autoimmune Disease | Johns Hopkins Pathology (2020). Available at: https://pathology.jhu.edu/autoimmune/definitions. • Orbai, A.-M. Autoimmune Disease: Why Is My Immune System Attacking Itself? Autoimmune Disease: Why Is My Immune System Attacking Itself? | Johns Hopkins Medicine Available at: https://www.hopkinsmedicine.org/health/wellness-and-prevention/autoimmune-disease-why-is-my-immune-system-attacking-itself. • Watson, S. Autoimmune Diseases: Types, Symptoms, Causes, Diagnosis & More. Healthline (2002). Available at: https://www.healthline.com/health/autoimmune-disorders#treatment. • Wu, W. et al. Polymorphisms in complement genes and risk of preeclampsia in Taiyuan, China. Inflamm. Res. (2016). doi:10.1007/s00011-016-0968-4 • Li, Y., Li, C. & Gao, J. Apolipoprotein C3 gene variants and the risk of coronary heart disease: A meta-analysis. Meta Gene (2016). doi:10.1016/j.mgene.2016.04.004

CD14

• Loo, W. T. Y. et al. Clinical application of human ?-defensin and CD14 gene polymorphism in evaluating the status of chronic inflammation. J. Transl. Med. (2012). doi:10.1186/1479-5876-10-S1-S9 • Harvard Health Publishing. Foods that fight inflammation. Harvard Health (2018). Available at: https://www.health.harvard.edu/staying-healthy/foods-that-fight-inflammation. • Chen, L. et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget (2018). doi:10.18632/oncotarget.23208 • Harvard Health Publishing. Take steps to prevent or reverse stress-related health problems. Harvard Health (2017). Available at: https://www.health.harvard.edu/stress/take-steps-to-prevent-or-reverse-stress-related-health-problems. • Liu, Y. Z., Wang, Y. X. & Jiang, C. L. Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience (2017). doi:10.3389/fnhum.2017.00316 • Oke, S. L. & Tracey, K. J. The inflammatory reflex and the role of complementary and alternative medical therapies. in Annals of the New York Academy of Sciences (2009). doi:10.1196/annals.1393.013 • Maydych, V. The interplay between stress, inflammation, and emotional attention: Relevance for depression. Frontiers in Neuroscience (2019). doi:10.3389/fnins.2019.00384 • Wei, M. Yoga could slow the harmful effects of stress and inflammation. Harvard Health Blog (2020). Available at: https://www.health.harvard.edu/blog/yoga-could-slow-the-harmful-effects-of-stress-and-inflammation-2017101912588. • Ferreira, S. T., Clarke, J. R., Bomfim, T. R. & De Felice, F. G. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimer's and Dementia (2014). doi:10.1016/j.jalz.2013.12.010 • Tanaka, T. & Kishimoto, T. Targeting interleukin-6: All the way to treat autoimmune and inflammatory diseases. International Journal of Biological Sciences (2012). doi:10.7150/ijbs.4666 • Loos B, et al. Polymorphisms in an interferon-? receptor-1 gene marker and susceptibility to periodontitis. Acta Odontol. Scand. (2003). doi:10.1080/00016350310006168 • Simpson, N. & Dinges, D. F. Sleep and Inflammation. Nutr. Rev. (2007). doi:10.1111/j.1753-4887.2007.tb00371.x • Kalogeropoulos, A. P., Georgiopoulou, V. V. & Butler, J. From Risk Factors to Structural Heart Disease: The Role of Inflammation. Heart Failure Clinics (2012). doi:10.1016/j.hfc.2011.08.002 • Western, K. A. Overview of the Immune System | National Institute of Allergy and Infectious Diseases (NIAID): An Overview. National Institute of Allergy and Infectious Diseases, NIH 3–8 (2008). doi:10.1007/978-1-59745-569-5_1 • Johns Hopkins Medicine Pathology. Definition of Autoimmunity & Autoimmune Disease. Definition of Autoimmunity & Autoimmune Disease - Autoimmune Disease | Johns Hopkins Pathology (2020). Available at: https://pathology.jhu.edu/autoimmune/definitions. • Orbai, A.-M. Autoimmune Disease: Why Is My Immune System Attacking Itself? Autoimmune Disease: Why Is My Immune System Attacking Itself? | Johns Hopkins Medicine Available at: https://www.hopkinsmedicine.org/health/wellness-and-prevention/autoimmune-disease-why-is-my-immune-system-attacking-itself. • Watson, S. Autoimmune Diseases: Types, Symptoms, Causes, Diagnosis & More. Healthline (2002). Available at: https://www.healthline.com/health/autoimmune-disorders#treatment. • Turner, D. et al. Overexpression of a Novel Lymphocyte Population, Positive for an Intracellular CD14-Like Antigen, in Patients Positive for Human Immunodeficiency Virus Type 1. Clinical Diagnostic Laboratory Immunology 11, 1040–1044 (2004). • Zhang, A. Q. et al. Association between CD14 promoter -159C/T polymorphism and the risk of sepsis and mortality: a systematic review and meta-analysis. PloS one (2013). doi:10.1371/journal.pone.0071237 • Misra, S. et al. Genetic association between inflammatory genes (IL-1?, CD14, LGALS2, PSMA6) and risk of ischemic stroke: A meta-analysis. Meta Gene (2016). doi:10.1016/j.mgene.2016.01.003 • Areeshi, M. Y., Mandal, R. K., Panda, A. K., Bisht, S. C. & Haque, S. CD14 -159 C>T Gene Polymorphism with Increased Risk of Tuberculosis: Evidence from a Meta-Analysis. PLoS One (2013). doi:10.1371/journal.pone.0064747 • Kim, E. J. et al. Helicobacter pylori infection enhances gastric mucosal inflammation in individuals carrying the 260-T allele of the CD14 gene. Gut Liver (2013). doi:10.5009/gnl.2013.7.3.317 • Wang, J. et al. Association between CD14 gene polymorphisms and cancer risk: A meta-analysis. PLoS One (2014). doi:10.1371/journal.pone.0100122 • Wang, S. et al. Racial differences in the association of CD14 polymorphisms with serum total IgE levels and allergen skin test reactivity. J. Asthma Allergy (2013). doi:10.2147/JAA.S42695 • Wang, Z., Hu, J., Fan, R., Zhou, J. & Zhong, J. Association between CD14 Gene C-260T Polymorphism and Inflammatory Bowel Disease: A Meta-Analysis. PLoS One (2012). doi:10.1371/journal.pone.0045144 • Liu, B. et al. CD14 ++ CD16 + Monocytes Are Enriched by Glucocorticoid Treatment and Are Functionally Attenuated in Driving Effector T Cell Responses. J. Immunol. (2015). doi:10.4049/jimmunol.1402409 • Cheah, M. T. et al. CD14-expressing cancer cells establish the inflammatory and proliferative tumor microenvironment in bladder cancer. Proc. Natl. Acad. Sci. (2015). doi:10.1073/pnas.1424795112 • Research Area. Neuroinflammation - Creative Diagnostics (2020). Available at: https://www.creative-diagnostics.com/neuroinflammation.htm. • Lurie, D. I. An integrative approach to neuroinflammation in psychiatric disorders and neuropathic pain. J. Exp. Neurosci. (2018). doi:10.1177/1179069518793639 • Disabato, D. J., Quan, N. & Godbout, J. P. Neuroinflammation: the devil is in the details. Journal of Neurochemistry 139, 136–153 (2016).

CTLA4

• Jeffery, L. E. et al. Vitamin D antagonises the suppressive effect of inflammatory cytokines on CTLA-4 expression and regulatory function. PLoS One (2015). doi:10.1371/journal.pone.0131539 • Tai, X. et al. Basis of CTLA-4 function in regulatory and conventional CD4 T cells. Blood 119, 5155–5163 (2012). • Wei, M. Yoga could slow the harmful effects of stress and inflammation. Harvard Health Blog (2020). Available at: https://www.health.harvard.edu/blog/yoga-could-slow-the-harmful-effects-of-stress-and-inflammation-2017101912588. • Nie, W., Chen, J. & Xiu, Q. Cytotoxic T-lymphocyte associated antigen 4 polymorphisms and asthma risk: A meta-analysis. PLoS One (2012). doi:10.1371/journal.pone.0042062 • Patel, H. et al. Association of Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) and Thyroglobulin (TG) genetic variants with autoimmune hypothyroidism. PLoS One (2016). doi:10.1371/journal.pone.0149441 • Wang, J. et al. Common variants on cytotoxic T lymphocyte antigen-4 polymorphisms contributes to type 1 diabetes susceptibility: Evidence based on 58 studies. PLoS One (2014). doi:10.1371/journal.pone.0085982 • Yan, Q., Chen, P., Lu, A., Zhao, P. & Gu, A. Association between CTLA-4 60G/A and -1661A/G polymorphisms and the risk of cancers: A meta-analysis. PLoS One (2013). doi:10.1371/journal.pone.0083710 • Maydych, V. The interplay between stress, inflammation, and emotional attention: Relevance for depression. Frontiers in Neuroscience (2019). doi:10.3389/fnins.2019.00384 • Liu, Y. Z., Wang, Y. X. & Jiang, C. L. Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience (2017). doi:10.3389/fnhum.2017.00316 • Oke, S. L. & Tracey, K. J. The inflammatory reflex and the role of complementary and alternative medical therapies. in Annals of the New York Academy of Sciences (2009). doi:10.1196/annals.1393.013 • Disabato, D. J., Quan, N. & Godbout, J. P. Neuroinflammation: the devil is in the details. Journal of Neurochemistry 139, 136–153 (2016). • Orrù, S. et al. Recipient CTLA-4*CT60-AA genotype is a prognostic factor for acute graft-versus-host disease in hematopoietic stem cell transplantation for thalassemia. Hum. Immunol. (2012). doi:10.1016/j.humimm.2011.12.014 • Wang, D. C., Tan, B. Y., Wang, F. & Yuan, Z. N. Association between CTLA-4 gene polymorphism and ankylosing spondylitis: A case-control study. Int. J. Clin. Exp. Pathol. (2015). • Western, K. A. Overview of the Immune System | National Institute of Allergy and Infectious Diseases (NIAID): An Overview. National Institute of Allergy and Infectious Diseases, NIH 3–8 (2008). doi:10.1007/978-1-59745-569-5_1 • Bour-Jordan, H. et al. Intrinsic and extrinsic control of peripheral T-cell tolerance by costimulatory molecules of the CD28/ B7 family. Immunol. Rev. (2011). doi:10.1111/j.1600-065X.2011.01011.x • Tector, M., Khatri, B. O., Kozinski, K., Dennert, K. & Oaks, M. K. Biochemical analysis of CTLA-4 immunoreactive material from human blood. BMC Immunol. (2009). doi:10.1186/1471-2172-10-51 • Karabon, L. et al. The CTLA-4 gene polymorphisms are associated with CTLA-4 protein expression levels in multiple sclerosis patients and with susceptibility to disease. Immunology (2009). doi:10.1111/j.1365-2567.2009.03083.x • AlFadhli, S. Overexpression and Secretion of the Soluble CTLA-4 Splice Variant in Various Autoimmune Diseases and in Cases with Overlapping Autoimmunity. Genet. Test. Mol. Biomarkers (2013). doi:10.1089/gtmb.2012.0391 • Wolff, A. S. B. et al. CTLA-4 as a genetic determinant in autoimmune Addison's

disease. Genes Immun. (2015). doi:10.1038/gene.2015.27 • Zaletel, K. et al. Association of CT60 cytotoxic T lymphocyte antigen-4 gene polymorphism with thyroid autoantibody production in patients with Hashimoto's and postpartum thyroiditis. Clin. Exp. Immunol. (2010). doi:10.1111/j.1365-2249.2010.04113.x • Abdel Galil, S. M. & Hagrass, H. A. The role of CTLA-4 exon-1 49 A/G polymorphism and soluble CTLA-4 protein level in Egyptian patients with Behçet's disease. Biomed Res. Int. (2014). doi:10.1155/2014/513915 • Kalogeropoulos, A. P., Georgiopoulou, V. V. & Butler, J. From Risk Factors to Structural Heart Disease: The Role of Inflammation. Heart Failure Clinics (2012). doi:10.1016/j.hfc.2011.08.002 • Simpson, N. & Dinges, D. F. Sleep and Inflammation. Nutr. Rev. (2007). doi:10.1111/j.1753-4887.2007.tb00371.x • Liu, J. & Zhang, H.-X. CTLA-4 polymorphisms and systemic lupus erythematosus: a comprehensive meta-analysis. Genet. Test. Mol. Biomarkers (2013). doi:10.1089/gtmb.2012.0302 • Du, L. et al. The associations between the polymorphisms in the CTLA-4 gene and the risk of Graves' disease in the Chinese population. BMC Med. Genet. (2013). doi:10.1186/1471-2350-14-46 • Esposito, L. et al. Investigation of Soluble and Transmembrane CTLA-4 Isoforms in Serum and Microvesicles. J. Immunol. (2014). doi:10.4049/jimmunol.1303389 • Walker, L. S. K. Treg and CTLA-4: Two intertwining pathways to immune tolerance. Journal of Autoimmunity (2013). doi:10.1016/j.jaut.2013.06.006 • Zhao, J. J., Wang, D., Yao, H., Sun, D. W. & Li, H. Y. CTLA-4 and MDR1 polymorphisms increase the risk for ulcerative colitis: A meta-analysis. World J. Gastroenterol. (2015). doi:10.3748/wjg.v21.i34.10025 • Harvard Health Publishing. Foods that fight inflammation. Harvard Health (2018). Available at: https://www.health.harvard.edu/staying-healthy/foods-that-fight-inflammation. • Chen, L. et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget (2018). doi:10.18632/oncotarget.23208 • Harvard Health Publishing. Take steps to prevent or reverse stress-related health problems. Harvard Health (2017). Available at: https://www.health.harvard.edu/stress/take-steps-to-prevent-or-reverse-stress-related-health-problems. • Loos B, et al. Polymorphisms in an interferon-? receptor-1 gene marker and susceptibility to periodontitis. Acta Odontol. Scand. (2003). doi:10.1080/00016350310006168 • Oh, J. Y. & Sin, D. D. Lung inflammation in COPD: why does it matter? F1000 Medicine Reports 4, (2012). • Tanaka, T. & Kishimoto, T. Targeting interleukin-6: All the way to treat autoimmune and inflammatory diseases. International Journal of Biological Sciences (2012). doi:10.7150/ijbs.4666 • Ferreira, S. T., Clarke, J. R., Bomfim, T. R. & De Felice, F. G. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimer's and Dementia (2014). doi:10.1016/j.jalz.2013.12.010 • Western, K. A. Overview of the Immune System | National Institute of Allergy and Infectious Diseases (NIAID): An Overview. National Institute of Allergy and Infectious Diseases, NIH 3–8 (2008). doi:10.1007/978-1-59745-569-5_1 • Johns Hopkins Medicine Pathology. Definition of Autoimmunity & Autoimmune Disease. Definition of Autoimmunity & Autoimmune Disease - Autoimmune Disease | Johns Hopkins Pathology (2020). Available at: https://pathology.jhu.edu/autoimmune/definitions. • Orbai, A.-M. Autoimmune Disease: Why Is My Immune System Attacking Itself? Autoimmune Disease: Why Is My Immune System Attacking Itself? | Johns Hopkins Medicine Available at: https://www.hopkinsmedicine.org/health/wellness-and-prevention/autoimmune-disease-why-is-my-immune-system-attacking-itself. • Watson, S. Autoimmune Diseases: Types, Symptoms, Causes, Diagnosis & More. Healthline (2002). Available at: https://www.healthline.com/health/autoimmune-disorders#treatment. • Orbai, A.-M. Autoimmune Disease: Why Is My Immune System Attacking Itself? Autoimmune Disease: Why Is My Immune System Attacking Itself? | Johns Hopkins Medicine Available at: https://www.hopkinsmedicine.org/health/wellness-and-prevention/autoimmune-disease-why-is-my-immune-system-attacking-itself. • Johns Hopkins Medicine Pathology. Definition of Autoimmunity & Autoimmune Disease. Definition of Autoimmunity & Autoimmune Disease - Autoimmune Disease | Johns Hopkins Pathology (2020). Available at:

https://pathology.jhu.edu/autoimmune/definitions.

FUT2

• FUT2 fucosyltransferase 2 (secretor status included) [Bos taurus (cattle)] - Gene - NCBI. Current neurology and neuroscience reports. Available at: https://www.ncbi.nlm.nih.gov/gene/281175. • Kimura, K. et al. Diversification of transcriptional modulation: Large-scale identification and characterization of putative alternative promoters of human genes. Genome Res. (2006). doi:10.1101/gr.4039406 • 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 • Koda, Y., Soejima, M., Wang, B. & Kimura, H. Structure and expression of the gene encoding secretor-type galactoside 2-alpha-L-fucosyltransferase (FUT2). Eur. J. Biochem. (1997). doi:10.1111/j.1432-1033.1997.t01-1-00750.x • Reguigne-Arnould, I. et al. Relative positions of two clusters of human ?-L-fucosyltransferases in 19q (FUT1–FUT2) and 19p (FUT6–FUT3–FUT5) within the

microsatellite genetic map of chromosome 19. Cytogenet. Genome Res. (1995). doi:10.1159/000134098 • BALL, S. P. et al. The human chromosome 19 linkage group FUT1 (H), FUT2 (SE), LE, LU, PEPD, C3, APOC2, D19S7 and D19S9. Ann. Hum. Genet. (1991). doi:10.1111/j.1469-1809.1991.tb00417.x

HLA-DQA1

• Kao, H. T. et al. Molecular analysis of the HLA class II genes in two DRw6-related haplotypes, DRw13 DQw1 and DRw14 DQw3. J. Immunol. (1989). • Todd, J. a, Fukui, Y., Kitagawa, T. & Sasazuki, T. The A3 allele of the HLA-DQA1 locus is associated with susceptibility to type 1 diabetes in Japanese. Proc. Natl. Acad. Sci. U. S. A. (1990). • Marsh, S. G. & Bodmer, J. G. HLA class II nucleotide sequences, 1992. Immunogenetics (1993). • Liu, C. P., Bach, F. H. & Wu, S. K. Molecular studies of a rare DR2/LD-5a/DQw3 HLA class II haplotype. Multiple genetic mechanisms in the generation of polymorphic HLA class II genes. J Immunol (1988). • Histocompatibility complex - Genetics Home Reference - NIH. U.S. National Library of Medicine (2020). Available at: https://ghr.nlm.nih.gov/primer/genefamily/hla. • Schmidt, H., Williamson, D. & Ashley-Koch, A. HLA-DR15 haplotype and multiple sclerosis: A HuGE review. American Journal of Epidemiology (2007). doi:10.1093/aje/kwk118 • Horn, G. T., Bugawan, T. L., Long, C. M., Manos, M. M. & Erlich, H. A. Sequence analysis of HLA class II genes from insulin-dependent diabetic individuals. Hum. Immunol. (1988). doi:10.1016/0198-8859(88)90034-1 • Schiffenbauer, J. et al. Complete sequence of the HLA DQ alpha and DQ beta cDNA from a DR5/DQw3 cell line. J. Immunol. (1987). • Jonsson, A.-K. et al. Class II genes of the human major histocompatibility complex. Comparisons of the DQ and DX ? and ? genes. J. Biol. Chem. (1987). • Blum, A. & Miller, H. The major histocompatibility complex and inflammation. Southern Medical Journal (2000). doi:10.1097/00007611-200002000-00002 • Mangalam, A.

K., Taneja, V. & David, C. S. HLA Class II Molecules Influence Susceptibility versus Protection in Inflammatory Diseases by Determining the Cytokine Profile. J. Immunol. (2013). doi:10.4049/jimmunol.1201891

HLA-DQA2

• Khalil, I. et al. Trans-encoded DQ alpha beta heterodimers confer susceptibility to myasthenia gravis disease. C.R.Acad.Sci.III (1993). • Kwok, W. W. et al. Polymorphic DQ alpha and DQ beta interactions dictate HLA class II determinants of allo-recognition. Journal Of Experimental Medicine (1990). doi:10.1084/jem.171.1.85 • Hall, M. A., Lanchbury, J. S. S., Bolsover, W. J., Welsh, K. I. & Ciclitira, P. J. Celiac disease is associated with an extended HLA-DR3 haplotype which includes HLA-DPw1. Hum. Immunol. (1990). doi:10.1016/0198-8859(90)90052-Q • Sollid, L. M. Evidence for a primary association of celiac disease to a particular HLA-DQ alpha/beta heterodimer. J. Exp. Med. (1989). doi:10.1084/jem.169.1.345 • Wang, H. & He, R. HLA-DQA and DQB alleles contribute to susceptibility to insulin-dependent diabetes mellitus. Chinese Med. Sci. J. = Chung-kuo i hsueh k'o hsueh tsa chih (1993). • Bolsover, W. J., Hall, M. A., Vaughan, R. W., Welsh, K. I. & J. Ciclitira, P. A family study confirms that the HLA-DP associations with celiac disease are the result of an extended HLA-DR3 haplotype. Hum. Immunol. (1991). doi:10.1016/0198-8859(91)90012-X • Yu, L. & Sheehy, M. The cryptic HLA-DQA2 ('DX alpha') gene is expressed in human B cell lines. J Immunol. (1991). • Olerup, O. & Hillert, J. HLA class II-associated genetic susceptibility in multiple sclerosis: a critical evaluation. Tissue Antigens (1991). doi:10.1111/j.1399-0039.1991.tb02029.x • HLA-DQA2 major histocompatibility complex, class II, DQ alpha 2 [Homo sapiens (human)] - Gene - NCBI. Current neurology and neuroscience reports. Available at: https://www.ncbi.nlm.nih.gov/gene/3118. • Histocompatibility complex - Genetics Home Reference - NIH. U.S. National Library of Medicine (2020). Available at: https://ghr.nlm.nih.gov/primer/genefamily/hla. • Blum, A. & Miller, H. The major histocompatibility complex and inflammation. Southern Medical Journal (2000). doi:10.1097/00007611-200002000-00002 • Mangalam, A. K., Taneja, V. & David, C. S. HLA Class II Molecules Influence Susceptibility versus Protection in Inflammatory Diseases by Determining the Cytokine Profile. J. Immunol. (2013). doi:10.4049/jimmunol.1201891 • Khalil, I. et al. A combination of HLA-DQ beta Asp57-negative

and HLA DQ alpha Arg52 confers susceptibility to insulin-dependent diabetes mellitus. J. Clin. Invest. (1990). doi:10.1172/JCI114569

IL-13

• Gervas-Arruga, J. et al. The influence of genetic variability and proinflammatory status on the development of bone disease in patients with Gaucher disease. PLoS One (2015). doi:10.1371/journal.pone.0126153 • Harvard Health Publishing. Foods that fight inflammation. Harvard Health (2018). Available at: https://www.health.harvard.edu/staying-healthy/foods-that-fight-inflammation. • Chen, L. et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget (2018). doi:10.18632/oncotarget.23208 • Harvard Health Publishing. Take steps to prevent or reverse stress-related health problems. Harvard Health (2017). Available at: https://www.health.harvard.edu/stress/take-steps-to-prevent-or-reverse-stress-related-health-problems. • Liu, Y. Z., Wang, Y. X. & Jiang, C. L. Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience (2017). doi:10.3389/fnhum.2017.00316 • Oke, S. L. & Tracey, K. J. The inflammatory reflex and the role of complementary and alternative medical therapies. in Annals of the New York Academy of Sciences (2009). doi:10.1196/annals.1393.013 • Maydych, V. The interplay between stress, inflammation, and emotional attention: Relevance for depression. Frontiers in Neuroscience (2019). doi:10.3389/fnins.2019.00384 • Wei, M. Yoga could slow the harmful effects of stress and inflammation. Harvard Health Blog (2020). Available at: https://www.health.harvard.edu/blog/yoga-could-slow-the-harmful-effects-of-stress-and-inflammation-2017101912588. • Ferreira, S. T., Clarke, J. R., Bomfim, T. R. & De Felice, F. G. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimer's and Dementia (2014). doi:10.1016/j.jalz.2013.12.010 • Tanaka, T. & Kishimoto, T. Targeting interleukin-6: All the way to treat autoimmune and inflammatory diseases. International Journal of Biological Sciences (2012). doi:10.7150/ijbs.4666 • Oh, J. Y. & Sin, D. D. Lung inflammation in COPD: why does it matter? F1000 Medicine Reports 4, (2012). • Loos B, et al. Polymorphisms in an interferon-? receptor-1 gene marker and susceptibility to periodontitis. Acta Odontol. Scand. (2003). doi:10.1080/00016350310006168 • Simpson, N. & Dinges, D. F. Sleep and Inflammation. Nutr. Rev. (2007). doi:10.1111/j.1753-4887.2007.tb00371.x • Kalogeropoulos, A. P., Georgiopoulou, V. V. & Butler, J. From Risk Factors to Structural Heart Disease: The Role of Inflammation. Heart Failure Clinics (2012). doi:10.1016/j.hfc.2011.08.002 • Accordini, S. et al. An Interleukin 13 polymorphism is associated with symptom severity in adult subjects with ever asthma. PLoS One (2016). doi:10.1371/journal.pone.0151292 • Chen, P., Chen, C., Chen, K., Xu, T. & Luo, C. Polymorphisms in IL-4/IL-13 pathway genes and glioma risk: an updated meta-analysis. Tumor Biology (2014). doi:10.1007/s13277-014-2895-8 • Liu, Z. et al. A meta-analysis of IL-13 polymorphisms and pediatric asthma risk. Medical science monitor : international medical journal of experimental and clinical research. (2014). Available at: https://www.ncbi.nlm.nih.gov/pubmed/25502839. • Egli, A. et al. IL-28B is a Key Regulator of B- and T-Cell Vaccine Responses against Influenza. PLoS Pathog. (2014). doi:10.1371/journal.ppat.1004556 • Seyfizadeh, N. et al. Association of IL-13 single nucleotide polymorphisms in Iranian patients to multiple sclerosis. Am. J. Clin. Exp. Immunol. (2014). • Blanchard, C. Molecular pathogenesis of eosinophilic esophagitis. Curr. Opin. Gastroenterol. (2015). doi:10.1097/MOG.0000000000000186 • Sonntag, K. et al. Chronic graft-versus-host-disease in CD34+-humanized NSG mice is associated with human susceptibility HLA haplotypes for autoimmune disease. J. Autoimmun. (2015). doi:10.1016/j.jaut.2015.06.006 • McCormick, S. M. & Heller, N. M. Commentary: IL-4 and IL-13 receptors and signaling. Cytokine (2015). doi:10.1016/j.cyto.2015.05.023 • Cianferoni, A. & Spergel, J. M. From genetics to treatment of eosinophilic esophagitis. Current Opinion in Allergy and Clinical Immunology (2015). doi:10.1097/ACI.0000000000000200 • Narozna, B. et al. Polymorphisms in the interleukin 4, interleukin 4 receptor and interleukin 13 genes and allergic phenotype: A case control study. Adv. Med. Sci. (2016). doi:10.1016/j.advms.2015.07.003 • Shamran, H. A. et al. Single nucleotide polymorphisms in IL-10, IL-12p40, and IL-13 genes and susceptibility to glioma. Int. J. Med. Sci. (2015). doi:10.7150/ijms.12609 • Mitchel, J. A. et al. IL-13 Augments Compressive Stress–Induced Tissue Factor Expression in Human Airway Epithelial Cells. Am. J. Respir. Cell Mol. Biol. (2016). doi:10.1165/rcmb.2015-0252OC • Nicodemus-Johnson, J. et al. Genome-wide methylation study identifies an IL-13-induced epigenetic signature in asthmatic airways. Am. J. Respir. Crit. Care Med. (2016). doi:10.1164/rccm.201506-1243OC • Research Area. Neuroinflammation - Creative Diagnostics (2020). Available at: https://www.creative-diagnostics.com/neuroinflammation.htm. • Becher, B., Spath, S. & Goverman, J. Cytokine networks in neuroinflammation. Nature Reviews Immunology (2017).

doi:10.1038/nri.2016.123 • Lurie, D. I. An integrative approach to neuroinflammation in psychiatric disorders and neuropathic pain. J. Exp. Neurosci. (2018). doi:10.1177/1179069518793639 • Disabato, D. J., Quan, N. & Godbout, J. P. Neuroinflammation: the devil is in the details. Journal of Neurochemistry 139, 136–153 (2016).

IL5

• Wei, M. Yoga could slow the harmful effects of stress and inflammation. Harvard Health Blog (2020). Available at: https://www.health.harvard.edu/blog/yoga-could-slow-the-harmful-effects-of-stress-and-inflammation-2017101912588. • Maydych, V. The interplay between stress, inflammation, and emotional attention: Relevance for depression. Frontiers in Neuroscience (2019). doi:10.3389/fnins.2019.00384 • Lurie, D. I. An integrative approach to neuroinflammation in psychiatric disorders and neuropathic pain. J. Exp. Neurosci. (2018). doi:10.1177/1179069518793639 • Simpson, N. & Dinges, D. F. Sleep and Inflammation. Nutr. Rev. (2007). doi:10.1111/j.1753-4887.2007.tb00371.x • Oke, S. L. & Tracey, K. J. The inflammatory reflex and the role of complementary and alternative medical therapies. in Annals of the New York Academy of Sciences (2009). doi:10.1196/annals.1393.013 • Becher, B., Spath, S. & Goverman, J. Cytokine networks in neuroinflammation. Nature Reviews Immunology (2017). doi:10.1038/nri.2016.123 • Research Area. Neuroinflammation - Creative Diagnostics (2020). Available at: https://www.creative-diagnostics.com/neuroinflammation.htm. • Liu, Y. Z., Wang, Y. X. & Jiang, C. L. Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience (2017). doi:10.3389/fnhum.2017.00316 • Kalogeropoulos, A. P., Georgiopoulou, V. V. & Butler, J. From Risk Factors to Structural Heart Disease: The Role of Inflammation. Heart Failure Clinics (2012). doi:10.1016/j.hfc.2011.08.002 • Harvard Health Publishing. Take steps to prevent or reverse stress-related health problems. Harvard Health (2017). Available at: https://www.health.harvard.edu/stress/take-steps-to-prevent-or-reverse-stress-related-health-problems. • Chen, L. et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget (2018). doi:10.18632/oncotarget.23208 • Harvard Health Publishing. Foods that fight inflammation. Harvard Health (2018). Available at: https://www.health.harvard.edu/staying-healthy/foods-that-fight-inflammation. • Disabato, D. J., Quan, N. & Godbout, J. P. Neuroinflammation: the devil is in the details. Journal of Neurochemistry 139, 136–153 (2016). • Loos B, et al. Polymorphisms in an interferon-? receptor-1 gene marker and susceptibility to periodontitis. Acta Odontol. Scand. (2003). doi:10.1080/00016350310006168 • Oh, J. Y. & Sin, D. D. Lung inflammation in COPD: why does it matter? F1000 Medicine Reports 4, (2012). • Tanaka, T. & Kishimoto, T. Targeting interleukin-6: All the way to treat autoimmune and inflammatory diseases. International

Journal of Biological Sciences (2012). doi:10.7150/ijbs.4666 • Ferreira, S. T., Clarke, J. R., Bomfim, T. R. & De Felice, F. G. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimer's and Dementia (2014). doi:10.1016/j.jalz.2013.12.010

NOS2

• Cuny, E. et al. Association of elevated glial expression of interleukin-1beta with improved survival in patients with glioblastomas multiforme. J Neurosurg (2002). doi:10.3171/jns.2002.96.2.0294 • De Meyer, G. R. Y. et al. Platelet phagocytosis and processing of ?-amyloid precursor protein as a mechanism of macrophage activation in atherosclerosis. Circ. Res. (2002). doi:10.1161/01.RES.0000020017.84398.61 • Mollace, V. Modulation of Prostaglandin Biosynthesis by Nitric Oxide and Nitric Oxide Donors. Pharmacol. Rev. (2005). doi:10.1124/pr.57.2.1 • Liu, J., Zhao, M. L., Brosnan, C. F. & Lee, S. C. Expression of type II nitric oxide synthase in primary human astrocytes and microglia: role of IL-1beta and IL-1 receptor antagonist. J. Immunol. (1996). • Barcellos, L. F. et al. Linkage and association with the NOS2A locus on chromosome 17q11 in multiple sclerosis. Ann. Neurol. (2004). doi:10.1002/ana.20092 • Gonzalez-Gay, M. A. et al. Association of a functional inducible nitric oxide synthase promoter variant with susceptibility to biopsy-proven giant cell arteritis. J. Rheumatol. (2005). doi:0315162X-32-2178 [pii] • Singleton, A. B. et al. Nitric oxide synthase gene polymorphisms in Alzheimer's disease and dementia with Lewy bodies. Neurosci. Lett. (2001). doi:10.1016/S0304-3940(01)01694-9 • MacMicking, J., Xie, Q. & Nathan, C. NITRIC OXIDE AND MACROPHAGE FUNCTION. Annu. Rev. Immunol. (1997). doi:10.1146/annurev.immunol.15.1.323 • Ricciardolo, F. L. M., Sterk, P. J., Gaston, B. & Folkerts, G. Nitric oxide in health and disease of the respiratory system. Physiol. Rev. (2004). doi:10.1152/physrev.00034.2003 • Dröge, W. Free Radicals in the Physiological Control of Cell Function. Physiol. Rev. (2002). doi:10.1152/physrev.00018.2001 • Brandi, M. L. et al. Bidirectional regulation of osteoclast function by nitric oxide synthase isoforms. Proc. Natl. Acad. Sci. (1995). doi:10.1073/pnas.92.7.2954 • Konttinen, Y. T. et al. Role of nitric oxide in Sjögren's syndrome. Arthritis and rheumatism. (1997). Available at: https://www.ncbi.nlm.nih.gov/pubmed/9153549. • Hoffjan, S. et al. Genetic variation in immunoregulatory pathways and atopic phenotypes in infancy. J. Allergy Clin. Immunol. (2004). doi:10.1016/j.jaci.2003.10.044 • Rosenkranz-Weiss, P. et al. Regulation of nitric oxide synthesis by proinflammatory cytokines in human umbilical vein endothelial cells. Elevations in tetrahydrobiopterin levels enhance endothelial nitric oxide synthase specific activity. J. Clin. Invest. (1994). doi:10.1172/JCI117221 • Tetsuka, T. et al. Cross-talk between cyclooxygenase and nitric oxide pathways: prostaglandin E2 negatively modulates induction of nitric oxide synthase by interleukin 1. Proc. Natl. Acad. Sci. (1994). doi:10.1073/pnas.91.25.12168 • Geller, D. A. et al. Molecular cloning and expression of inducible nitric oxide synthase from human hepatocytes. Proc.Natl.Acad.Sci.U.S.A (1993). doi:10.1002/cbic.200600054 • Martin, E., Nathan, C. & Xie, Q. W. Role of Interferon Regulatory Factor 1 in Induction of Nitric Oxide Synthase. J Exp Med (1994). doi:10.1084/jem.180.3.977 • Ignarro, L. J. Physiology and pathophysiology of nitric oxide. Kidney international. Supplement. (1996). Available at: https://www.ncbi.nlm.nih.gov/pubmed/8743501. • Massion, P. B., Pelat, M.,

Belge, C. & Balligand, J. L. Regulation of the mammalian heart function by nitric oxide. in Comparative Biochemistry and Physiology - A Molecular and Integrative Physiology (2005). doi:10.1016/j.cbpb.2005.05.048

STAT4

• Harvard Health Publishing. Foods that fight inflammation. Harvard Health (2018). Available at: https://www.health.harvard.edu/staying-healthy/foods-that-fight-inflammation. • Chen, L. et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget (2018). doi:10.18632/oncotarget.23208 • Harvard Health Publishing. Take steps to prevent or reverse stress-related health problems. Harvard Health (2017). Available at: https://www.health.harvard.edu/stress/take-steps-to-prevent-or-reverse-stress-related-health-problems. • Liu, Y. Z., Wang, Y. X. & Jiang, C. L. Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience (2017). doi:10.3389/fnhum.2017.00316 • Oke, S. L. & Tracey, K. J. The inflammatory reflex and the role of complementary and alternative medical therapies. in Annals of the New York Academy of Sciences (2009). doi:10.1196/annals.1393.013 • Maydych, V. The interplay between stress, inflammation, and emotional attention: Relevance for depression. Frontiers in Neuroscience (2019). doi:10.3389/fnins.2019.00384 • Oke, S. L. & Tracey, K. J. The inflammatory reflex and the role of complementary and alternative medical therapies. in Annals of the New York Academy of Sciences (2009). doi:10.1196/annals.1393.013 • Disabato, D. J., Quan, N. & Godbout, J. P. Neuroinflammation: the devil is in the details. Journal of Neurochemistry 139, 136–153 (2016). • Sigurdsson, S. et al. A risk haplotype of STAT4 for systemic lupus erythematosus is over-expressed, correlates with anti-dsDNA and shows additive effects with two risk alleles of IRF5. Hum. Mol. Genet. (2008). doi:10.1093/hmg/ddn184 • Liu, Y. Z., Wang, Y. X. & Jiang, C. L. Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience (2017). doi:10.3389/fnhum.2017.00316 • Harvard Health Publishing. Take steps to prevent or reverse stress-related health problems. Harvard Health (2017). Available at: https://www.health.harvard.edu/stress/take-steps-to-prevent-or-reverse-stress-related-health-problems. • O'Shea, J. J., Lahesmaa, R., Vahedi, G., Laurence, A. & Kanno, Y. Genomic views of STAT function in CD4 + T helper cell differentiation. Nature Reviews Immunology (2011). doi:10.1038/nri2958 • Orbai, A.-M. Autoimmune Disease: Why Is My Immune System Attacking Itself? Autoimmune Disease: Why Is My Immune System Attacking Itself? | Johns Hopkins Medicine Available at: https://www.hopkinsmedicine.org/health/wellness-and-prevention/autoimmune-disease-why-is-my-immune-system-attacking-itself. • Watson, S. Autoimmune Diseases: Types, Symptoms, Causes, Diagnosis & More. Healthline (2002). Available at: https://www.healthline.com/health/autoimmune-disorders#treatment. • Chen, L. et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget (2018). doi:10.18632/oncotarget.23208 • Harvard Health Publishing. Foods that fight inflammation. Harvard Health (2018). Available at: https://www.health.harvard.edu/staying-healthy/foods-that-fight-inflammation. • Research Area. Neuroinflammation - Creative Diagnostics (2020). Available at: https://www.creative-diagnostics.com/neuroinflammation.htm. • Lurie, D. I. An integrative approach to neuroinflammation in psychiatric disorders and neuropathic pain. J. Exp. Neurosci. (2018). doi:10.1177/1179069518793639 • Western, K. A. Overview of the Immune System | National Institute of Allergy and Infectious Diseases (NIAID): An Overview. National Institute of Allergy and Infectious Diseases, NIH 3–8 (2008). doi:10.1007/978-1-59745-569-5_1 • Johns Hopkins Medicine Pathology. Definition of Autoimmunity & Autoimmune Disease. Definition of Autoimmunity & Autoimmune Disease - Autoimmune Disease | Johns Hopkins Pathology (2020). Available at: https://pathology.jhu.edu/autoimmune/definitions. • Lamana, A. et al. The minor allele of rs7574865 in the STAT4 gene is associated with increased mRNA and protein expression. PLoS One (2015). doi:10.1371/journal.pone.0142683 • Wang, Y., Qu, A. & Qu, A. Signal transducer and activator of transcription 4 in liver diseases. International Journal of Biological Sciences (2015). doi:10.7150/ijbs.11164 • Yan, N. et al. Association between STAT4 Gene Polymorphisms and Autoimmune Thyroid Diseases in a Chinese Population. Int. J. Mol. Sci. (2014). doi:10.3390/ijms150712280 • McWilliams, I. L., Rajbhandari, R., Nozell, S., Benveniste, E. & Harrington, L. E. STAT4 controls GM-CSF production by both Th1 and Th17 cells during EAE. J. Neuroinflammation (2015). doi:10.1186/s12974-015-0351-3 • Jabeen, R. et al. Altered STAT4 Isoform Expression in Patients with Inflammatory Bowel Disease. Inflamm. Bowel Dis. (2015). doi:10.1097/MIB.0000000000000495 • Namjou, B. et al. High-density genotyping of STAT4 reveals multiple haplotypic associations with Systemic lupus erythematosus in different racial groups. Arthritis Rheum. (2009). doi:10.1002/art.24387 • Glas, J. et al. Evidence for STAT4 as a common autoimmune gene: Rs7574865 is associated with colonic Crohn's disease and early disease onset. PLoS One (2010). doi:10.1371/journal.pone.0010373 • Lamana, A. et al. The TT genotype of the STAT4 rs7574865 polymorphism is associated with high disease activity and disability in patients with early arthritis. PLoS One (2012). doi:10.1371/journal.pone.0043661 • Gourh, P. et al. Polymorphisms in TBX21 and STAT4 increase the risk of systemic sclerosis: Evidence of possible gene-gene interaction and alterations in Th1/Th2 cytokines. Arthritis Rheum. (2009). doi:10.1002/art.24958 • Sugiura, T. et al. Association between a C8orf13-BLK polymorphism and polymyositis/ dermatomyositis in the Japanese population: An additive effect with STAT4 on disease susceptibility. PLoS One (2014). doi:10.1371/journal.pone.0090019 •

Svensson, A. et al. STAT4 Regulates Antiviral Gamma Interferon Responses and Recurrent Disease during Herpes Simplex Virus 2 Infection. J. Virol. (2012). doi:10.1128/JVI.00947-12

TNF

• Watson, S. Autoimmune Diseases: Types, Symptoms, Causes, Diagnosis & More. Healthline (2002). Available at: https://www.healthline.com/health/autoimmune-disorders#treatment. • Idriss, H. T. & Naismith, J. H. TNF? and the TNF receptor superfamily: Structure-function relationship(s). Microsc. Res. Tech. (2000). doi:10.1002/1097-0029(20000801)50:33.0.CO;2-H • Kalogeropoulos, A. P., Georgiopoulou, V. V. & Butler, J. From Risk Factors to Structural Heart Disease: The Role of Inflammation. Heart Failure Clinics (2012). doi:10.1016/j.hfc.2011.08.002 • Tanaka, T. & Kishimoto, T. Targeting interleukin-6: All the way to treat autoimmune and inflammatory diseases. International Journal of Biological Sciences (2012). doi:10.7150/ijbs.4666 • Ferreira, S. T., Clarke, J. R., Bomfim, T. R. & De Felice, F. G. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimer's and Dementia (2014). doi:10.1016/j.jalz.2013.12.010 • Wei, M. Yoga could slow the harmful effects of stress and inflammation. Harvard Health Blog (2020). Available at: https://www.health.harvard.edu/blog/yoga-could-slow-the-harmful-effects-of-stress-and-inflammation-2017101912588. • Maydych, V. The interplay between stress, inflammation, and emotional attention: Relevance for depression. Frontiers in Neuroscience (2019). doi:10.3389/fnins.2019.00384 • Oke, S. L. & Tracey, K. J. The inflammatory reflex and the role of complementary and alternative medical therapies. in Annals of the New York Academy of Sciences (2009). doi:10.1196/annals.1393.013 • Liu, Y. Z., Wang, Y. X. & Jiang, C. L. Inflammation: The common pathway of stress-related diseases. Frontiers in Human Neuroscience (2017). doi:10.3389/fnhum.2017.00316 • Harvard Health Publishing. Take steps to prevent or reverse stress-related health problems. Harvard Health (2017). Available at: https://www.health.harvard.edu/stress/take-steps-to-prevent-or-reverse-stress-related-health-problems. • Chen, L. et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget (2018). doi:10.18632/oncotarget.23208 • Harvard Health Publishing. Foods that fight inflammation. Harvard Health (2018). Available at: https://www.health.harvard.edu/staying-healthy/foods-that-fight-inflammation. • Disabato, D. J., Quan, N. & Godbout, J. P. Neuroinflammation: the devil is in the details. Journal of Neurochemistry 139, 136–153 (2016). • Simpson, N. & Dinges, D. F. Sleep and Inflammation. Nutr. Rev. (2007). doi:10.1111/j.1753-4887.2007.tb00371.x • Chen, S. et al. Associations between TNF-?-308A/G Polymorphism and Susceptibility with Dermatomyositis: A Meta-Analysis. PLoS ONE 9, (2014). • Oh, J. Y. & Sin, D. D. Lung inflammation in COPD: why does it matter? F1000 Medicine Reports 4, (2012). • Chen, M. et al. Tumor Mecrosis Factor (TNF) -308G>A, Nitric Oxide Synthase 3 (NOS3) +894G>T polymorphisms and migraine risk: A meta-analysis. PLoS One (2015). doi:10.1371/journal.pone.0129372 • Lee, J. J. et al. Genetic polymorphism at codon 10 of the transforming growth factor-?1 gene in patients with alcoholic liver cirrhosis. Korean J. Hepatol. (2011). doi:10.3350/kjhep.2011.17.1.37 • Zeng, X., Zhang, L., Gu, H. & Gu, Y. Association between TNF-? -308 G/A polymorphism and COPD susceptibility: a meta-analysis update. International Journal of Chronic Obstructive Pulmonary Disease 1367 (2016). doi:10.2147/copd.s105394 • Li, M., Han, Y., Wu, T. T., Feng, Y. & Wang, H. B. Tumor Necrosis Factor Alpha rs1800629 Polymorphism and Risk of Cervical Lesions: A Meta-Analysis. PLoS One (2013). doi:10.1371/journal.pone.0069201 • Guo, X. F. et al. TNF-?-308 polymorphism and risk of digestive system cancers: A meta-analysis. World J. Gastroenterol. (2013). doi:10.3748/wjg.v19.i48.9461 • Ma, Zhang & Baloch. Pathogenetic and Therapeutic Applications of Tumor Necrosis Factor-? (TNF-?) in Major Depressive Disorder: A Systematic Review. Int. J. Mol. Sci. (2016). doi:10.1016/j.cherd.2012.09.019 • Khan, S. et al. TNF-? -308 G?>?A (rs1800629) Polymorphism is Associated with Celiac Disease: A Meta-analysis of 11 Case-Control Studies. Scientific Reports 6, (2016). • Li, H. H. et al. Tumour Necrosis Factor-? Gene Polymorphism Is Associated with Metastasis in Patients with Triple Negative Breast Cancer. Sci. Rep. (2015). doi:10.1038/srep10244 • Ayhan, G. et al. Relation between inflammatory cytokine levels in serum and bronchoalveolar lavage fluid and gene polymorphism in young adult patients with bronchiectasis. J. Thorac. Dis. (2014). doi:10.3978/j.issn.2072-1439.2014.04.14 • Loos B, et al. Polymorphisms in an interferon-? receptor-1 gene marker and susceptibility to periodontitis. Acta Odontol. Scand. (2003). doi:10.1080/00016350310006168 • Laddha, N. C., Dwivedi, M., Gani, A. R., Mansuri, M. S. & Begum, R. Tumor Necrosis Factor B (TNFB) genetic variants and its increased expression are associated with vitiligo susceptibility. PLoS One (2013). doi:10.1371/journal.pone.0081736 • Yang, J.-K., Wu, W.-J., Qi, J., He, L. & Zhang, Y.-P. TNF -308 G/A Polymorphism and Risk of Acne Vulgaris: A Meta-Analysis. PLoS ONE 9, (2014). • Feng, R. N., Zhao, C., Sun, C. H. & Li, Y. Meta-analysis of TNF 308 G/A polymorphism and type 2 diabetes mellitus. PLoS One (2011). doi:10.1371/journal.pone.0018480 • Delongui, F. et al. Association of tumor necrosis factor ß genetic polymorphism and sepsis susceptibility. Exp. Ther. Med. (2011). doi:10.3892/etm.2011.213 • Western, K. A. Overview of the Immune System | National Institute of Allergy and Infectious Diseases (NIAID): An Overview. National Institute of Allergy and Infectious Diseases, NIH 3–8 (2008). doi:10.1007/978-1-59745-569-5_1 • Johns Hopkins Medicine Pathology. Definition of Autoimmunity & Autoimmune Disease. Definition of Autoimmunity & Autoimmune Disease - Autoimmune Disease | Johns Hopkins Pathology (2020). Available at: https://pathology.jhu.edu/autoimmune/definitions. • Orbai, A.-M. Autoimmune Disease: Why Is My Immune System Attacking Itself? Autoimmune Disease: Why Is My Immune System Attacking Itself? | Johns Hopkins Medicine Available at:

https://www.hopkinsmedicine.org/health/wellness-and-prevention/autoimmune-disease-why-is-my-immune-system-attacking-itself.

VDRTaq

• Adorini, L., Daniel, K. & Penna, G. Vitamin D Receptor Agonists, Cancer and the Immune System: An Intricate Relationship. Curr. Top. Med. Chem. (2006). doi:10.2174/156802606777864890 • McKenna, M. J. & Murray, B. Vitamin D deficiency. in Endocrinology and Diabetes: A Problem-Oriented Approach (2014). doi:10.1007/978-1-4614-8684-8_23 • Fischer, K. Vitamin D. in Principles of Nutrigenetics and Nutrigenomics: Fundamentals of Individualized Nutrition (2019). doi:10.1016/B978-0-12-804572-5.00032-X • Bikle, D. D. Vitamin D metabolism, mechanism of action, and clinical applications. Chemistry and Biology (2014). doi:10.1016/j.chembiol.2013.12.016 • Ciésli?ska, A. et al. Vitamin D receptor gene polymorphisms associated with childhood autism. Brain Sci. (2017). doi:10.3390/brainsci7090115 • Kamel, M. M., Fouad, S. A., Salaheldin, O., El-Razek, A. E. R. A. A. & El-Fatah, A. I. A. Impact of vitamin D receptor gene polymorphisms in pathogenesis of Type-1 diabetes mellitus. Int. J. Clin. Exp. Med. (2014). • El-Shal, A. S., Shalaby, S. M., Aly, N. M., Rashad, N. M. & Abdelaziz, A. M. Genetic variation in the vitamin D receptor gene and vitamin D serum levels in Egyptian women with polycystic ovary syndrome. Mol. Biol. Rep. (2013). doi:10.1007/s11033-013-2716-y • Keen, R. W., Hart, D. J., Lanchbury, J. S. & Spector, T. D. Association of early, osteoarthritis of the knee with a Taq I polymorphism of the vitamin D receptor gene. Arthritis Rheum. (1997). doi:10.1002/art.1780400812 • Kyung, S. P., Jung, H. N. & Choi, J. The short vitamin D receptor is associated with increased risk for generalized aggressive periodontitis. J. Clin. Periodontol. (2006). doi:10.1111/j.1600-051X.2006.00944.x • Wang, Y. et al. Variants in Vitamin D binding protein gene are associated with gestational diabetes mellitus. Med. (United States) (2015). doi:10.1097/MD.0000000000001693 • Hill, A. How to Get Vitamin D: 7 Effective Ways. Healthline (2019). Available at: https://www.healthline.com/nutrition/how-to-increase-vitamin-d. • Baudino, T. A. et al. Isolation and characterization of a novel coactivator protein, NCoA-62, involved in vitamin D-mediated transcription. J. Biol. Chem. (1998). doi:10.1074/jbc.273.26.16434 • Lisse, T. S., Chun, R. F., Rieger, S., Adams, J. S. & Hewison, M. Vitamin D activation of functionally distinct regulatory miRNAs in primary human osteoblasts. J. Bone Miner. Res. (2013). doi:10.1002/jbmr.1882 • Fleet, J. C. & Schoch, R. D. Molecular mechanisms for regulation of intestinal calcium and phosphate absorption by vitamin D. in Vitamin D (2011). doi:10.1016/B978-0-12-381978-9.10019-8 • Germain, P., Staels, B., Dacquet, C., Spedding, M. & Laudet, V. Overview of Nomenclature of Nuclear Receptors. Pharmacol. Rev. (2006). doi:10.1124/pr.58.4.2 • Tagami, T., Lutz, W. H., Kumar, R. & Jameson, J. L. The interaction of the vitamin D receptor with nuclear receptor corepressors and coactivators. Biochem. Biophys. Res. Commun. (1998). doi:10.1006/bbrc.1998.9799 • Herdick, M., Steinmeyer, A. & Carlberg, C. Antagonistic action of a 25-carboxylic ester analogue of 1??,25- dihydroxyvitamin D3 is mediated by a lack of ligand-induced vitamin D receptor interaction with coactivators. J. Biol. Chem. (2000). doi:10.1074/jbc.M910000199 • Luderer, H. F. & Demay, M. B. The vitamin D receptor, the skin and stem cells. J. Steroid Biochem. Mol. Biol. (2010). doi:10.1016/j.jsbmb.2010.01.015 • Vdr vitamin D (1,25-dihydroxyvitamin D3) receptor [Mus musculus (house mouse)] - Gene - NCBI. National Center for Biotechnology Information

(2018). Available at: https://www.ncbi.nlm.nih.gov/gene/22337.

METHYLATION SNP References

DHFR

• Beierlein, J. M., Karri, N. G. & Anderson, A. C. Targeted mutations of bacillus anthracis dihydrofolate reductase condense complex structure-activity relationships. J. Med. Chem. (2010). doi:10.1021/jm100727t • Osborne, M. J., Schnell, J., Benkovic, S. J., Dyson, H. J. & Wright, P. E. Backbone dynamics in dihydrofolate reductase complexes: Role of loop flexibility in the catalytic mechanism. Biochemistry (2001). doi:10.1021/bi010621k • Chen, M. J. et al. The functional human dihydrofolate reductase gene. J. Biol. Chem. (1984). • Funanage, V. L., Myoda, T. T., Moses, P. a & Cowell, H. R. Assignment of the human dihydrofolate reductase gene to the q11----q22 region of chromosome 5. Mol. Cell. Biol. (1984). doi:10.1128/mcb.4.10.2010 • Schnell, J. R., Dyson, H. J. & Wright, P. E. Structure, Dynamics, and Catalytic Function of Dihydrofolate Reductase. Annu. Rev. Biophys. Biomol. Struct. (2004). doi:10.1146/annurev.biophys.33.110502.133613 • Crabtree, M. J., Tatham, A. L., Hale, A. B., Alp, N. J. & Channon, K. M. Critical role for tetrahydrobiopterin recycling by dihydrofolate reductase in regulation of endothelial nitric-oxide synthase coupling: Relative importance of the de novo biopterin synthesis versus salvage pathways. J. Biol. Chem. (2009). doi:10.1074/jbc.M109.041483 • Benkovic, S. J., Fierke, C. A. & Naylor, A. M. Insights into enzyme function from studies on mutants of dihydrofolate reductase. Science (80-.). (1988). doi:10.1126/science.3125607 • Huennekens, F. M. In search of dihydrofolate reductase. Protein Sci. (1996). doi:10.1002/pro.5560050626 • Bailey, S. W. & Ayling, J. E. The extremely slow and variable activity of dihydrofolate reductase in human liver and its implications for high folic acid intake. Proc. Natl. Acad. Sci. (2009). doi:10.1073/pnas.0902072106 • 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/ • 5-Methyl-tetrahydrofolate. National Center for Biotechnology Information. PubChem Compound Database (2004). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/135483998. • Scaglione, F. & Panzavolta, G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica (2014). doi:10.3109/00498254.2013.845705 • 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

FOLR1

• 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 • Sadasivan E, Rothenberg SP (1989). "Molecular cloning of the complementary DNA for a human folate binding protein • 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 • Ducker, G. S. & Rabinowitz, J. D. One-Carbon Metabolism in Health and Disease. Cell Metabolism (2017). doi:10.1016/j.cmet.2016.08.009 • 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 • 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 • Moore, L. D., Le, T. & Fan, G. DNA methylation and its basic function. Neuropsychopharmacology (2013). doi:10.1038/npp.2012.112 • Scaglione, F. & Panzavolta, G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica (2014). doi:10.3109/00498254.2013.845705 • 5-Methyl-tetrahydrofolate. National Center for Biotechnology Information. PubChem Compound Database (2004). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/135483998. • Office of Dietary Supplements - Folate. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ • 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. • Henderson, G. B. Folate-binding proteins. Annu. Rev. Nutr. (1990). doi:10.1146/annurev.nutr.10.1.319 • Kelemen, L. E. The role of folate receptor ?? in cancer development, progression and treatment: Cause, consequence or innocent bystander? International Journal of Cancer (2006). doi:10.1002/ijc.21712 • 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 • Elwood, P. C. Molecular cloning and characterization of the human folate-binding protein cDNA from placenta and malignant tissue culture (KB) cells. J. Biol. Chem. (1989). • Yan, W. & Ratnam, M. Preferred Sites of Glycosylphosphatidylinositol Modification in Folate Receptors and Constraints in the Primary Structure of the Hydrophobic Portion of the Signal. Biochemistry (1995).

doi:10.1021/bi00044a039

FOLR2

• Scaglione, F. & Panzavolta, G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica (2014). doi:10.3109/00498254.2013.845705 • 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 • 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 • 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 • 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)42:83.0.CO;2-L • 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 • 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). • 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 • 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). • 5-Methyl-tetrahydrofolate. National Center for Biotechnology Information. PubChem Compound Database (2004). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/135483998. • Office of Dietary Supplements - Folate. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ • 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. • 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 • Ducker, G. S. & Rabinowitz, J. D. One-Carbon Metabolism in Health and Disease. Cell Metabolism (2017). doi:10.1016/j.cmet.2016.08.009 • Henderson, G. B. Folate-binding proteins. Annu. Rev. Nutr. (1990). doi:10.1146/annurev.nutr.10.1.319 • 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 • 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 • Moore, L. D., Le, T. & Fan, G. DNA methylation and its basic function. Neuropsychopharmacology (2013). doi:10.1038/npp.2012.112

GIF

• Ferrand, A. et al. Biochemical and Hematologic Manifestations of Gastric Intrinsic Factor (GIF) Deficiency: A Treatable Cause of B12 Deficiency in the Old Order Mennonite Population of Southwestern Ontario. JIMD Rep. (2015). doi:10.1007/8904_2014_351 • Sturm, A. C. et al. Hereditary intrinsic factor deficiency in chaldeans. JIMD Rep. (2013). doi:10.1007/8904_2012_133 • Tanner, S. M., Sturm, A. C., Baack, E. C., Liyanarachchi, S. & De La Chapelle, A. Inherited cobalamin malabsorption. Mutations in three genes reveal functional and ethnic patterns. Orphanet J. Rare Dis. (2012). doi:10.1186/1750-1172-7-56 • Quadros, E. V. Advances in the understanding of cobalamin assimilation and metabolism. British Journal of Haematology (2010). doi:10.1111/j.1365-2141.2009.07937.x • Tanner, S. M. et al. Hereditary juvenile cobalamin deficiency caused by mutations in the intrinsic factor gene. Proc.Natl.Acad.Sci.U.S.A (2005). • Agréus, L. et al. Rationale in diagnosis and screening of atrophic gastritis with stomach-specific plasma biomarkers. Scand. J. Gastroenterol. (2012). doi:10.3109/00365521.2011.645501 • Semeco, A. Top 12 Foods That Are High in Vitamin B12. Healthline (2020). Available at: https://www.healthline.com/nutrition/vitamin-b12-foods#10.-Fortified-nondairy-milk. • Office of Dietary Supplements - Vitamin B12. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/#:~:text=Vitamin%20B12%20is%20naturally%20found,5%2C13%2D15%5D. • Miller, A. L. The methionine-homocysteine cycle and its effects on cognitive diseases. Alternative Medicine Review (2003). • 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

MTHFD1

• Jiang, J., Zhang, Y., Wei, L., Sun, Z. & Liu, Z. Association between MTHFD1 G1958A polymorphism and neural tube defects susceptibility: A meta-analysis. PLoS One (2014). doi:10.1371/journal.pone.0101169 • Field, M. S., Kamynina, E., Watkins, D., Rosenblatt, D. S. & Stover, P. J. Human mutations in methylenetetrahydrofolate dehydrogenase 1 impair nuclear de novo thymidylate biosynthesis. Proc. Natl. Acad. Sci. U. S. A. (2014). doi:10.1073/pnas.1414555112 • 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/ • 5-Methyl-tetrahydrofolate. National Center for Biotechnology Information. PubChem Compound Database (2004). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/135483998. • Scaglione, F. & Panzavolta, G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica (2014). doi:10.3109/00498254.2013.845705 • 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 • Wu, J. et al. Polymorphisms in MTHFD1 Gene and Susceptibility to Neural Tube Defects: A Case-Control Study in a Chinese Han Population with Relatively Low Folate Levels. Med. Sci. Monit. (2015). doi:10.12659/MSM.895155 • Carroll, N. et al. Analysis of the MTHFD1 promoter and risk of neural tube defects. Hum. Genet. (2009). doi:10.1007/s00439-008-0616-3 • Neagos, D., Cretu, R., Tutulan-Cunita, A., Stoian, V. & Bohiltea, L. C. Methylenetetrahydrofolate dehydrogenase (MTHFD) enzyme polymorphism as a maternal risk factor for trisomy 21: a clinical study. J. Med. Life (2010). • Silva, L. M. R. D. da et al. Head and neck carcinogenesis : impact of MTHFD1 G1958A polymorphism. Head Neck Carcinog. (2011). • Sutherland, H. G. et al. Association study of MTHFD1 coding polymorphisms R134K and R653Q with migraine susceptibility. Headache (2014). doi:10.1111/head.12428 • Saha, T., Dutta, S., Rajamma, U., Sinha, S. & Mukhopadhyay, K. A pilot study on the contribution of folate gene variants in the cognitive function of ADHD probands. Neurochem. Res. (2014). doi:10.1007/s11064-014-1393-0 • Zheng, J. et al. MTHFD1 polymorphism as maternal risk for neural tube defects: a meta-analysis. Neurol. Sci (2015). • Lorenc, A., Seremak-Mrozikiewicz, A., Barlik, M., Wolski, H. & Drews, K. The role of 401a>G polymorphism of methylenetetrahydrofolate dehydrogenase gene (MTHFD1) in fetal hypotrophy. Ginekol. Pol. (2014). doi:10.17772/gp/1759 • Cri?an, T. O. et al.

The MTHFD1 c.1958 G>A polymorphism and recurrent spontaneous abortions. J. Matern. Fetal. Neonatal Med. (2011). doi:10.3109/14767051003702794

MTHFR

• Mischoulon, D. & Raab, M. F. The role of folate in depression and dementia. Journal of Clinical Psychiatry (2007). • Goyette, P. et al. Human methylenetetrahydrofolate reductase: Isolation of cDNA, mapping and mutation identification. Nat. Genet. (1994). doi:10.1038/ng0694-195 • Hua, Y., Zhao, H., Kong, Y. & Lu, X. Association between Alzheimer's disease and the NOS3 gene Glu298Asp polymorphism. Int. J. Neurosci. (2014). doi:10.3109/00207454.2013.834336 • Tran, P. et al. Multiple transcription start sites and alternative splicing in the methylenetetrahydrofolate reductase gene result in two enzyme isoforms. Mamm. Genome (2002). doi:10.1007/s00335-002-2167-6 • Födinger, M., Hörl, W. H. & Sunder-Plassmann, G. Molecular biology of 5,10-methylenetetrahydrofolate reductase. Journal of Nephrology (2000). doi:10.5860/CHOICE.39-4838 • E. Trimmer, E. Methylenetetrahydrofolate Reductase: Biochemical Characterization and Medical Significance. Curr. Pharm. Des. (2013). doi:10.2174/1381612811319140008 • Wu, X. et al. Association Between the MTHFR C677T Polymorphism and Recurrent Pregnancy Loss: A Meta-Analysis. Genet. Test. Mol. Biomarkers (2012). doi:10.1089/gtmb.2011.0318 • 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 • Ducker, G. S. & Rabinowitz, J. D. One-Carbon Metabolism in Health and Disease. Cell Metabolism (2017). doi:10.1016/j.cmet.2016.08.009 • Papakostas, G. I. et al. Effect of adjunctive L-methylfolate 15 mg among inadequate responders to SSRIs in depressed patients who were stratified by Biomarker levels and genotype: Results from a randomized clinical trial. in Journal of Clinical Psychiatry (2014). doi:10.4088/JCP.13m08947 • Schneider, J. A., Rees, D. C., Liu, Y.-T. & Clegg, J. B. Worldwide Distribution of a Common Methylenetetrahydrofolate Reductase Mutation. The American Journal of Human Genetics 62, 1258–1260 (1998). • Moore, L. D., Le, T. & Fan, G. DNA methylation and its basic function. Neuropsychopharmacology (2013). doi:10.1038/npp.2012.112 • Scaglione, F. & Panzavolta, G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica (2014). doi:10.3109/00498254.2013.845705 • 5-Methyl-tetrahydrofolate. National Center for Biotechnology Information. PubChem Compound Database (2004). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/135483998. • Office of Dietary Supplements - Folate. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ • Sibani, S. et al. Characterization of six novel mutations in the methylenetetrahydrofolate reductase (MTHFR) gene in patients with homocystinuria. Hum. Mutat. (2000). doi:10.1002/(SICI)1098-1004(200003)15:33.0.CO;2-I • Goyette, P. et al. Human methylenetetrahydrofolate reductase: Isolation of cDNA, mapping and mutation identification. Nat. Genet. (1994). doi:10.1038/ng0694-195 • 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 • 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. • Matthews, R. G. & Daubner, S. C. Modulation of methylenetetrahydrofolate reductase activity by S-adenosylmethionine and by dihydrofolate and its polyglutamate analogues. Adv. Enzyme Regul. (1982). doi:10.1016/0065-2571(82)90012-7 • Yamada, K., Strahler, J. R., Andrews, P. C. & Matthews, R. G. Regulation of human methylenetetrahydrofolate reductase by phosphorylation. Proc. Natl. Acad. Sci. (2005). doi:10.1073/pnas.0504786102 • 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 • Schwahn, B. & Rozen, R. Polymorphisms in the methylenetetrahydrofolate reductase gene: Clinical consequences. American journal of pharmacogenomics : genomics-related research in drug development and clinical practice (2001). doi:10.2165/00129785-200101030-00004 • Yamada, K., Chen, Z., Rozen, R. & Matthews, R. G. Effects of common polymorphisms on the properties of recombinant human methylenetetrahydrofolate reductase. Proc. Natl. Acad. Sci. (2001). doi:10.1073/pnas.261469998 • 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 • Bailey, L. B. Folate, Methyl-Related Nutrients, Alcohol, and the MTHFR 677C?T Polymorphism Affect Cancer Risk: Intake Recommendations. J. Nutr. (2003). doi:10.1093/jn/133.11.3748S • Nishiyama, M., Kato, Y., Hashimoto, M., Yukawa, S. & Omori, K. Apolipoprotein E, Methylenetetrahydrofolate Reductase(MTHFR) Mutation and the Risk of Senile Dementia. An Epidemiological Study Using the Polymerase Chain Reaction(PCR) Method. J. Epidemiol. (2000). doi:10.2188/jea.10.163 • Reilly, R., McNulty, H., Pentieva, K., Strain, J. J. & Ward, M. MTHFR 677TT genotype and disease risk: Is there a modulating role for B-vitamins'. Proc. Nutr. Soc. (2014). doi:10.1017/S0029665113003613

MTHFS

• Office of Dietary Supplements - Folate. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ • Anguera, M. C., & Stover, P. J. (2006). Methenyltetrahydrofolate synthetase is a high-affinity catecholamine-binding protein. Archives of Biochemistry and Biophysics. https://doi.org/10.1016/j.abb.2006.09.008 • Field, M. S., Anderson, D. D., & Stover, P. J. (2011). Mthfs is an essential gene in mice and a component of the purinosome. Frontiers in Genetics. https://doi.org/10.3389/fgene.2011.00036 • Lee, K. M., Lan, Q., Kricker, A., Purdue, M. P., Grulich, A. E., Vajdic, C. M., … Armstrong, B. K. (2007). One-carbon metabolism gene polymorphisms and risk of non-Hodgkin lymphoma in Australia. Human Genetics. https://doi.org/10.1007/s00439-007-0431-2 • Matakidou, A., El Galta, R., Rudd, M. F., Webb, E. L., Bridle, H., Eisen, T., & Houlston, R. S. (2007). Prognostic significance of folate metabolism polymorphisms for lung cancer. British Journal of Cancer. https://doi.org/10.1038/sj.bjc.6603830 • Rodan, L. H., Qi, W., Ducker, G. S., Demirbas, D., Laine, R., Yang, E., … Berry, G. T. (2018). 5,10-methenyltetrahydrofolate synthetase deficiency causes a neurometabolic disorder associated with microcephaly, epilepsy, and cerebral hypomyelination. Molecular Genetics and Metabolism. https://doi.org/10.1016/j.ymgme.2018.06.006 • Zhao, R., Chen, Y., Tan, W., Waly, M., Sharma, A., Stover, P., … Deth, R. C. (2001). Relationship between dopamine-stimulated phospholipid methylation and the single-carbon folate pathway. Journal of Neurochemistry. https://doi.org/10.1046/j.1471-4159.2001.00471.x • 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. • 5-Methyl-tetrahydrofolate. National Center for Biotechnology Information. PubChem Compound Database (2004). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/135483998. • Scaglione, F. & Panzavolta, G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica (2014). doi:10.3109/00498254.2013.845705 • 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

MTRR

• Vaughn, J. D. et al. Methionine synthase reductase 66A->G polymorphism is associated with increased plasma homocysteine concentration when combined with the homozygous methylenetetrahydrofolate reductase 677C->T variant. J. Nutr. (2004). doi:134/11/2985 [pii] • Brilakis, E. S., Berger, P. B., Ballman, K. V. & Rozen, R. Methylenetetrahydrofolate reductase (MTHFR) 677C>T and methionine synthase reductase (MTRR) 66A>G polymorphisms: Association with serum homocysteine and angiographic coronary artery disease in the era of flour products fortified with folic acid. Atherosclerosis (2003). doi:10.1016/S0021-9150(03)00098-4 • Beyer, K. et al. Methionine synthase polymorphism is a risk factor for Alzheimer disease. Neuroreport (2003). doi:10.1097/00001756-200307180-00022 • Office of Dietary Supplements - Vitamin B12. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/#:~:text=Vitamin%20B12%20is%20naturally%20found,5%2C13%2D15%5D. • Office of Dietary Supplements - Vitamin B12. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/#:~:text=Vitamin%20B12%20is%20naturally%20found,5%2C13%2D15%5D. • Miller, A. L. The methionine-homocysteine cycle and its effects on cognitive diseases. Alternative Medicine Review (2003). • 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 • Semeco, A. Top 12 Foods That Are High in Vitamin B12. Healthline (2020). Available at: https://www.healthline.com/nutrition/vitamin-b12-foods#10.-Fortified-nondairy-milk. • Miller, A. L. The methionine-homocysteine cycle and its effects on cognitive diseases. Alternative Medicine Review (2003). • 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 • MTRR 5-methyltetrahydrofolate-homocysteine methyltransferase reductase [Homo sapiens (human)] - Gene - NCBI. National Center for Biotechnology Information Available at: https://www.ncbi.nlm.nih.gov/gene/4552. • Leclerc, D. et al. Cloning and mapping of a cDNA for methionine synthase reductase, a flavoprotein defective in patients with homocystinuria. Proc. Natl Acad. Sci. USA (1998). doi:10.1073/pnas.95.6.3059 • Leclerc, D. et al. Cloning and mapping of a cDNA for methionine synthase reductase, a flavoprotein defective in patients with homocystinuria. Proc. Natl Acad. Sci. USA (1998). doi:10.1073/pnas.95.6.3059 • Wilson, A. et al. A common variant in methionine synthase reductase combined with low cobalamin (Vitamin B12) increases risk for spina bifida. Mol. Genet. Metab. (1999). doi:10.1006/mgme.1999.2879 • James, S. J. et al. Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. Am. J. Clin. Nutr. (1999). doi:10.1093/ajcn/70.4.495 • Leclerc, D. et al. Molecular cloning, expression and physical mapping of the human methionine synthase reductase gene. Gene (1999). doi:10.1016/S0378-1119(99)00431-X • Doolin, M.-T. et al. Maternal Genetic Effects, Exerted by Genes Involved in Homocysteine Remethylation, Influence the Risk of Spina Bifida. Am. J. Hum. Genet. (2002). doi:10.1086/344209 • Pietrzyk, J. J., Bik-Multanowski, M., Sanak, M. & Twardowska, M. Polymorphisms of the 5,10-methylenetetrahydrofolate and the methionine synthase reductase genes as independent risk factors for spina bifida. J. Appl. Genet. (2003). • Zhu, H. et al. Homocysteine remethylation enzyme polymorphisms and increased risks for neural tube defects. Mol. Genet. Metab. (2003). doi:10.1016/S1096-7192(03)00008-8 • Moore, L. D., Le, T. & Fan, G. DNA methylation and its basic function. Neuropsychopharmacology (2013). doi:10.1038/npp.2012.112 • Bosco, P. et al. Methionine synthase (MTR) 2756 (A?G) polymorphism, double heterozygosity methionine synthase 2756 AG/methionine synthase reductase (MTRR) 66 AG, and elevated monocysteinemia are three risk factors for having a child with down syndrome. Am. J. Med. Genet. (2003). doi:10.1002/ajmg.a.20234 • Olteanu, H., Wolthers, K. R., Munro, A. W., Scrutton, N. S. & Banerjee, R. Kinetic and Thermodynamic Characterization of the Common Polymorphic Variants of Human Methionine Synthase Reductase†. Biochemistry 43, 1988–1997 (2004). • Semeco, A. Top 12 Foods That Are High in Vitamin B12. Healthline (2020). Available at: https://www.healthline.com/nutrition/vitamin-b12-foods#10.-Fortified-nondairy-milk.

TCN1

• Semeco, A. Top 12 Foods That Are High in Vitamin B12. Healthline (2020). Available at: https://www.healthline.com/nutrition/vitamin-b12-foods#10.-Fortified-nondairy-milk. • Office of Dietary Supplements - Vitamin B12. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/#:~:text=Vitamin%20B12%20is%20naturally%20found,5%2C13%2D15%5D. • Miller, A. L. The methionine-homocysteine cycle and its effects on cognitive diseases. Alternative Medicine Review (2003). • 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 • Remacha, A. F. et al. Role of serum holotranscobalamin (holoTC) in the diagnosis of patients with low serum cobalamin. Comparison with methylmalonic acid and homocysteine. Ann. Hematol. (2014). doi:10.1007/s00277-013-1905-z • Irizar, H. et al. Transcriptomic profile reveals gender-specific molecular mechanisms driving multiple sclerosis progression. PLoS One (2014). doi:10.1371/journal.pone.0090482 • Johnston, J., Yang-Feng, T. & Berliner, N. Genomic structure and mapping of the chromosomal gene for transcobalamin I (TCN1): Comparison to human intrinsic factor. Genomics 12, 459–464 (1992). • Anello, G. et al. Homocysteine and methylenetetrahydrofolate reductase polymorphism in Alzheimer's disease. Neuroreport (2004). doi:10.1097/00001756-200404090-00025 • Johnston, J., Bollekens, J., Allen, R. H. & Berliner, N. Structure of the cDNA encoding transcobalamin I, a neutrophil granule protein. J. Biol. Chem. (1989). doi:10.1016/j.tetlet.2007.03.117 • Carmel, R., Parker, J. & Kelman, Z. Genomic mutations associated with mild and severe deficiencies of transcobalamin i (haptocorrin) that cause mildly and severely low serum cobalamin levels. Br. J. Haematol. (2009). doi:10.1111/j.1365-2141.2009.07855.x • Matteini, A. M. et al. Transcobalamin-II variants, decreased vitamin B12 availability and increased risk of frailty. J. Nutr. Heal. Aging (2010). doi:10.1007/s12603-010-0013-1 • Carmel, R. Haptocorrin (transcobalamin I) and cobalamin deficiencies [10]. Clinical Chemistry (2007). doi:10.1373/clinchem.2006.078808 • Carmel, R., Parker, J. & Kelman, Z. Genomic mutations associated with mild and severe deficiencies of transcobalamin i (haptocorrin) that cause mildly and severely low serum cobalamin levels. Br. J. Haematol. (2009). doi:10.1111/j.1365-2141.2009.07855.x • Bowen, R. A. R. et al. Elevated vitamin B12levels in autoimmune lymphoproliferative syndrome attributable to elevated haptocorrin in lymphocytes. Clin. Biochem. (2012). doi:10.1016/j.clinbiochem.2012.01.016 • Furger, E., Frei, D. C., Schibli, R., Fischer, E. & Prota, A. E. Structural basis for universal corrinoid recognition by the cobalamin transport protein haptocorrin. J. Biol. Chem. (2013). doi:10.1074/jbc.M113.483271

TCN2

• Regec, A., Quadros, E. V, Platica, O. & Rothenberg, S. P. The cloning and characterization of the human transcobalamin II gene. Blood (1995). • Linnebank, M. et al. Association of transcobalamin c. 776C>G with overall survival in patients with primary central nervous system lymphoma. Br. J. Cancer (2012). doi:10.1038/bjc.2012.476 • Martinelli, M. et al. A candidate gene study of one-carbon metabolism pathway genes and colorectal cancer risk. Br. J. Nutr. (2013). doi:10.1017/S0007114512002796 • 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 • Koushik, A. et al. Nonsynonymous polymorphisms in genes in the one-carbon metabolism pathway and associations with colorectal cancer. Cancer Epidemiol. Biomarkers Prev. (2006). doi:10.1158/1055-9965.EPI-06-0624 • Semeco, A. Top 12 Foods That Are High in Vitamin B12. Healthline (2020). Available at: https://www.healthline.com/nutrition/vitamin-b12-foods#10.-Fortified-nondairy-milk. • Mills, J. L. et al. Folate-related genes and omphalocele. Am. J. Med. Genet. (2005). doi:10.1002/ajmg.a.30772 • Martinelli, M. et al. Idiopathic pulmonary fibrosis and polymorphisms of the folate pathway genes. Clin. Biochem. (2013). doi:10.1016/j.clinbiochem.2012.10.009 • Office of Dietary Supplements - Vitamin B12. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional/#:~:text=Vitamin%20B12%20is%20naturally%20found,5%2C13%2D15%5D. • Miller, A. L. The methionine-homocysteine cycle and its effects on cognitive diseases. Alternative Medicine Review (2003). • Teplitsky, V. et al. Hereditary partial transcobalamin II deficiency with neurologic, mental and hematologic abnormalities in children and adults. Isr. Med. Assoc. J. (2003). • Refsum, H., Johnston, C., Guttormsen, A. B. & Nexo, E. Holotranscobalamin and total transcobalamin in human plasma: Determination, determinants, and reference values in healthy adults. Clin. Chem. (2006). doi:10.1373/clinchem.2005.054619 • Seetharam, B., Bose, S. & Li, N. Cellular Import of Cobalamin (Vitamin B-12) 1,2. J. Nutr (1999). • Winkelmayer, W. C., Skoupy, S., Eberle, C., Födinger, M. & Sunder-Plassmann, G. Effects of TCN2 776C>G on vitamin B, folate, and total homocysteine levels in kidney transplant patients. Kidney international. (2004). Available at: https://www.ncbi.nlm.nih.gov/pubmed/15086930 • Hoffbrand, A. V., Tripp, E., Jackson, B. F., Luck, W. E. & Frater-Schroder, M. N. Hereditary Abnormal Transcobalamin II Previously Diagnosed as Congenital Dihydrofolate Reductase Deficiency. New England Journal of Medicine 310, 789–790 (1984). • Garg, G. et al. Polymorphisms in transcobalamin II gene is associated with coronary artery disease in Indian population. Biomarkers (2012). doi:10.3109/1354750X.2011.642408 • Cascalheira, J. F. et al. Association of the transcobalamin II gene 776C?G polymorphism with Alzheimer's type dementia: dependence on the 5, 10-methylenetetrahydrofolate reductase 1298A?C polymorphism genotype. Ann. Clin. Biochem. (2015). doi:10.1177/0004563214561770

MITOCHONDRIA SNP References

ATP5C1

• Yoshida, M., Muneyuki, E. & Hisabori, T. ATP synthase - A marvellous rotary engine of the cell. Nature Reviews Molecular Cell Biology (2001). doi:10.1038/35089509 • Gerhard, D. S. et al. The status, quality, and expansion of the NIH full-length cDNA project: The Mammalian Gene Collection (MGC). Genome Res. (2004). doi:10.1101/gr.2596504 • Hillier, L. W. et al. Generation and annotation of the DNA sequences of human chromosomes 2 and 4. Nature (2005). doi:10.1038/nature03466 • Cross, R. L. Turning the ATP motor. Nature (2004). doi:10.1038/427407b • Deloukas, P. et al. The DNA sequence and comparative analysis of human chromosome 10. Nature (2004). doi:10.1038/nature02462 • Friedman, J. R. & Nunnari, J. Mitochondrial form and function. Nature (2014). doi:10.1038/nature12985 • West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. Nature Reviews Immunology (2011). doi:10.1038/nri2975 • Kann, O. & Kovács, R.

Mitochondria and neuronal activity. American Journal of Physiology - Cell Physiology (2007). doi:10.1152/ajpcell.00222.2006 • Pizzorno, J. Mitochondria-fundamental to life and health. Integrative Medicine (Boulder) (2014). • MitoQ. Which Foods Help Your Mitochondria? MitoQ (2019). Available at: https://www.mitoq.com/blog/which-foods-help-your-mitochondria#:~:text=Simple carbohydrates like white flour,efficient, long-lasting way. • Yan, W. L., Lerner, T. J., Haines, J. L. & Gusella, J. F. Sequence analysis and mapping of a novel human mitochondrial ATP synthase subunit 9 cDNA (ATP5G3). Genomics (1994). doi:10.1006/geno.1994.1631

COX5A

• Friedman, J. R. & Nunnari, J. Mitochondrial form and function. Nature (2014). doi:10.1038/nature12985 • West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. Nature Reviews Immunology (2011). doi:10.1038/nri2975 • MitoQ. Which Foods Help Your Mitochondria? MitoQ (2019). Available at: https://www.mitoq.com/blog/which-foods-help-your-mitochondria#:~:text=Simple carbohydrates like white flour,efficient, long-lasting way. • Pizzorno, J. Mitochondria-fundamental to life and health. Integrative Medicine (Boulder) (2014). • Kann, O. & Kovács, R. Mitochondria and neuronal activity. American Journal of Physiology - Cell Physiology (2007). doi:10.1152/ajpcell.00222.2006 • Garavito, R. M. & Mulichak, A. M. The Structure of Mammalian Cyclooxygenases. Annu. Rev. Biophys. Biomol. Struct. (2003). doi:10.1146/annurev.biophys.32.110601.141906 • Clark, K. M. et al. An mtDNA mutation in the initiation codon of the cytochrome C oxidase subunit II gene results in lower levels of the protein and a mitochondrial encephalomyopathy. Am. J. Hum. Genet. (1999). doi:10.1086/302361 • Zee, J. M. & Glerum, D. M. Defects in cytochrome oxidase assembly in humans: lessons from yeast. Biochem. Cell Biol. (2006). doi:10.1139/O06-201 • Kraytsberg, Y. et al. Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. Nat. Genet. (2006). doi:10.1038/ng1778 • Jaksch, M. et al. A systematic mutation screen of 10 nuclear and 25 mitochondrial candidate genes in 21 patients with cytochrome c oxidase (COX) deficiency shows tRNA(Ser)(UCN) mutations in a subgroup with syndromal encephalopathy. Journal of Medical Genetics 35, 895–900 (1998).

COX6C

• Lenka, N., Vijayasarathy, C., Mullick, J. & Avadhani, N. G. Structural organization and transcription regulation of nuclear genes encoding the mammalian cytochrome c oxidase complex. Prog Nucleic Acid Res Mol Biol (1998). doi:10.1016/S0079-6603(08)60830-2 • Ewing, R. M. et al. Large-scale mapping of human protein-protein interactions by mass spectrometry. Mol. Syst. Biol. (2007). doi:10.1038/msb4100134 • Gerhard, D. S. et al. The status, quality, and expansion of the NIH full-length cDNA project: The Mammalian Gene Collection (MGC). Genome Res. (2004). doi:10.1101/gr.2596504 • MitoQ. Which Foods Help Your Mitochondria? MitoQ (2019). Available at: https://www.mitoq.com/blog/which-foods-help-your-mitochondria#:~:text=Simple carbohydrates like white flour,efficient, long-lasting way. • 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 • Otsuka, M., Mizuno, Y., Yoshida, M., Kagawa, Y. & Ohta, S. Nucleotide sequence of cDNA encoding human cytochrome c oxidase subunit Vic. Nucleic Acids Research 16, 10916–10916 (1988). • Kish, S. J. et al. Decreased brain protein levels of cytochrome oxidase subunits in Alzheimer's disease and in hereditary spinocerebellar ataxia disorders: A nonspecific change? J. Neurochem. (1999). doi:10.1046/j.1471-4159.1999.0720700.x • Friedman, J. R. & Nunnari, J. Mitochondrial form and function. Nature (2014). doi:10.1038/nature12985 • West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. Nature Reviews Immunology (2011). doi:10.1038/nri2975 • Kann, O. & Kovács, R. Mitochondria and neuronal activity. American Journal of Physiology - Cell Physiology (2007). doi:10.1152/ajpcell.00222.2006 • Pizzorno, J. Mitochondria-fundamental to life and health. Integrative Medicine (Boulder) (2014).

NDUFS3

• Pizzorno, J. Mitochondria-fundamental to life and health. Integrative Medicine (Boulder) (2014). • Friedman, J. R. & Nunnari, J. Mitochondrial form and function. Nature (2014). doi:10.1038/nature12985 • West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. Nature Reviews Immunology (2011). doi:10.1038/nri2975 • Kann, O. & Kovács, R. Mitochondria and neuronal activity. American Journal of Physiology - Cell Physiology (2007). doi:10.1152/ajpcell.00222.2006 • MitoQ. Which Foods Help Your Mitochondria? MitoQ (2019). Available at: https://www.mitoq.com/blog/which-foods-help-your-mitochondria#:~:text=Simple carbohydrates like white flour,efficient, long-lasting way. • Benit, P. Mutant NDUFS3 subunit of mitochondrial complex I causes Leigh syndrome. J. Med. Genet. (2004). doi:10.1136/jmg.2003.014316 • Suhane, S., Kanzaki, H., Arumugaswami, V., Murali, R. & Ramanujan, V. K. Mitochondrial NDUFS3 regulates the ROS-mediated onset of metabolic switch in transformed cells. Biol. Open (2013). doi:10.1242/bio.20133244 • Procaccio, V. et al. Human NDUFS3 gene coding for the 30-kDa subunit of mitochondrial complex I: Genomic organization and expression. Mamm. Genome (2000). doi:10.1007/s003350010160

NDUFS7

• Kann, O. & Kovács, R. Mitochondria and neuronal activity. American Journal of Physiology - Cell Physiology (2007). doi:10.1152/ajpcell.00222.2006 • West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. Nature Reviews Immunology (2011). doi:10.1038/nri2975 • Murray, J. et al. The subunit composition of the human NADH dehydrogenase obtained by rapid one-step immunopurification. J. Biol. Chem. (2003). doi:10.1074/jbc.C300064200 • Ugalde, C., Janssen, R. J. R. J., van den Heuvel, L. P., Smeitink, J. A. M. & Nijtmans, L. G. J. Differences in assembly or stability of complex I and other mitochondrial OXPHOS complexes in inherited complex I deficiency. Hum. Mol. Genet. (2004). doi:10.1093/hmg/ddh071 • Ota, T. et al. Complete sequencing and characterization of 21,243 full-length human cDNAs. Nat. Genet. (2004). doi:10.1038/ng1285 • Friedman, J. R. & Nunnari, J. Mitochondrial form and function. Nature (2014). doi:10.1038/nature12985 • Smeitink, J. & van, L. Human mitochondrial complex I in health and disease. American journal of human genetics. (1999). Available at: https://www.ncbi.nlm.nih.gov/pubmed/10330338. • Loeffen, J. L. C. M. et al. cDNA of eight nuclear encoded subunits of NADH:ubiquinone oxidoreductase: Human complex I cDNA characterization completed. Biochem. Biophys. Res. Commun. (1998). doi:10.1006/bbrc.1998.9786 • MitoQ. Which Foods Help Your Mitochondria? MitoQ (2019). Available at: https://www.mitoq.com/blog/which-foods-help-your-mitochondria#:~:text=Simple carbohydrates like white flour,efficient, long-lasting way. • Pizzorno, J. Mitochondria-fundamental to life and health. Integrative Medicine (Boulder) (2014).

NDUFS8

• West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. Nature Reviews Immunology (2011). doi:10.1038/nri2975 • MitoQ. Which Foods Help Your Mitochondria? MitoQ (2019). Available at: https://www.mitoq.com/blog/which-foods-help-your-mitochondria#:~:text=Simple carbohydrates like white flour,efficient, long-lasting way. • Pizzorno, J. Mitochondria-fundamental to life and health. Integrative Medicine (Boulder) (2014). • Kann, O. & Kovács, R. Mitochondria and neuronal activity. American Journal of Physiology - Cell Physiology (2007). doi:10.1152/ajpcell.00222.2006 • Friedman, J. R. & Nunnari, J. Mitochondrial form and function. Nature (2014). doi:10.1038/nature12985 • De Sury, R., Martinez, P., Procaccio, V., Lunardi, J. & Issartel, J. P. Genomic structure of the human NDUFS8 gene coding for the iron-sulfur TYKY subunit of the mitochondrial NADH:ubiquinone oxidoreductase. Gene (1998). doi:10.1016/S0378-1119(98)00275-3 • Su, C. Y., Chang, Y. C., Yang, C. J., Huang, M. S. & Hsiao, M. The opposite prognostic effect of NDUFS1 and NDUFS8 in lung cancer reflects the oncojanus role of mitochondrial complex i. Sci. Rep. (2016). doi:10.1038/srep31357 • Procaccio, V. et al. cDNA sequence and chromosomal localization of the NDUFS8 human gene coding for the 23 kDa subunit of the mitochondrial complex I. Biochimica et Biophysica Acta - Gene Structure and Expression (1997). doi:10.1016/S0167-4781(97)00020-1

SLC19A1

• 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. • 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 • Ducker, G. S. & Rabinowitz, J. D. One-Carbon Metabolism in Health and Disease. Cell Metabolism (2017). doi:10.1016/j.cmet.2016.08.009 • 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 • 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 • Moore, L. D., Le, T. & Fan, G. DNA methylation and its basic function. Neuropsychopharmacology (2013). doi:10.1038/npp.2012.112 • Scaglione, F. & Panzavolta, G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica (2014). doi:10.3109/00498254.2013.845705 • 5-Methyl-tetrahydrofolate. National Center for Biotechnology Information. PubChem Compound Database (2004). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/135483998. • Office of Dietary Supplements - Folate. NIH Office of Dietary Supplements (2020). Available at: https://ods.od.nih.gov/factsheets/Folate-HealthProfessional/ • Stanis?awska-Sachadyn, A. et al. The reduced folate carrier (SLC19A1) c.80G > a polymorphism is associated with red cell folate concentrations among women. Ann. Hum. Genet. (2009). doi:10.1111/j.1469-1809.2009.00529.x • Ananth, C. V. et al. Reduced folate carrier 80A?G polymorphism, plasma folate, and risk of placental abruption. Hum. Genet. (2008). doi:10.1007/s00439-008-0531-7 • Blanton, S. H. et al. Folate pathway and nonsyndromic cleft lip and palate. Birth Defects Res. Part A - Clin. Mol. Teratol. (2011). doi:10.1002/bdra.20740 • Mazumdar, M. et al. Polymorphisms in maternal folate pathway genes interact with arsenic in drinking water to influence risk of myelomeningocele. Birth Defects Res. Part A - Clin. Mol. Teratol. (2015). doi:10.1002/bdra.23399 • James, S. J. et al. A functional polymorphism in the reduced folate carrier gene and DNA hypomethylation in mothers of children with autism. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. (2010). doi:10.1002/ajmg.b.31094 • Clifford, A. J. et al. Single nucleotide polymorphisms in CETP, SLC46A1, SLC19A1, CD36, BCMO1, APOA5, and ABCA1 are significant predictors of plasma HDL in healthy adults. Lipids Health Dis. (2013). doi:10.1186/1476-511X-12-66 • Yee, S. W. et al. SLC19A1 pharmacogenomics summary. Pharmacogenetics and Genomics 20, 708–715 (2010). • Figueiredo, J. C. et al. Genes involved with folate uptake and distribution and their association with colorectal cancer risk. Cancer Causes Control (2010). doi:10.1007/s10552-009-9489-6 • Cho, Y. et al. Association of reduced folate carrier-1 (RFC-1) polymorphisms with ischemic stroke and silent brain infarction. PLoS One (2015). doi:10.1371/journal.pone.0115295 • Matherly, L. H., Wilson, M. R. & Hou, Z. The major facilitative folate transporters solute carrier 19A1 and solute carrier 46A1: Biology and role in antifolate chemotherapy of cancer. Drug Metabolism and Disposition (2014). doi:10.1124/dmd.113.055723 • Coppedè, F., Lorenzoni, V. & Migliore, L. The reduced folate carrier (RFC-1) 80A>G polymorphism and maternal risk of having a child with down syndrome: A meta-analysis. Nutrients (2013). doi:10.3390/nu5072551 • O'Byrne, M. R. et al. Association of folate receptor (FOLR1, FOLR2, FOLR3) and reduced folate carrier (SLC19A1) genes with meningomyelocele. Birth Defects Res. A. Clin. Mol. Teratol. (2010). doi:10.1002/bdra.20706 • Coppedè, F. et al. A pilot study evaluating the contribution of SLC19A1 (RFC-1) 80G>A polymorphism to Alzheimer's disease in Italian caucasians. Biomed Res. Int. (2014). doi:10.1155/2014/608104

UQCRC2

• Ota, T. et al. Complete sequencing and characterization of 21,243 full-length human cDNAs. Nat. Genet. (2004). doi:10.1038/ng1285 • Strausberg, R. L. et al. Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. Proceedings of the National Academy of Sciences of the United States of America. (2002). Available at: https://www.ncbi.nlm.nih.gov/pubmed/12477932. • Hosokawa, Y., Suzuki, H., Toda, H., Nishikimi, M. & Ozawa, T. The primary structure of the precursor to core protein II, a putative member of mitochondrial processing protease family, of rat mitochondrial cytochrome bc1 complex deduced from cDNA sequence analysis. Biochemistry international. (1990). Available at: https://www.ncbi.nlm.nih.gov/pubmed/2162168. • Ewing, R. M. et al. Large-scale mapping of human protein-protein interactions by mass spectrometry. Mol. Syst. Biol. (2007). doi:10.1038/msb4100134 • Rual, J. F. et al. Towards a proteome-scale map of the human protein-protein interaction network. Nature (2005). doi:10.1038/nature04209 • Gerhard, D. S. et al. The status, quality, and expansion of the NIH full-length cDNA project: The Mammalian Gene Collection (MGC). Genome Res. (2004). doi:10.1101/gr.2596504 • Kann, O. & Kovács, R. Mitochondria and neuronal activity. American Journal of Physiology - Cell Physiology (2007). doi:10.1152/ajpcell.00222.2006 • Hu, W. H. et al. Identification and characterization of a novel Nogo-interacting mitochondrial protein (NIMP). J. Neurochem. (2002). doi:10.1046/j.1471-4159.2002.00788.x • Hosokawa, Y., Suzuki, H., Toda, H., Nishikimi, M. & Ozawa, T. Complementary DNA encoding core protein II of human mitochondrial cytochrome bc1 complex. Substantial diversity in deduced primary structure from its yeast counterpart. J. Biol. Chem. (1989). • Friedman, J. R. & Nunnari, J. Mitochondrial form and function. Nature (2014). doi:10.1038/nature12985 • West, A. P., Shadel, G. S. & Ghosh, S. Mitochondria in innate immune responses. Nature Reviews Immunology (2011). doi:10.1038/nri2975 • MitoQ. Which Foods Help Your Mitochondria? MitoQ (2019). Available at: https://www.mitoq.com/blog/which-foods-help-your-mitochondria#:~:text=Simple carbohydrates like white flour,efficient, long-lasting way. • Pizzorno, J.

Mitochondria-fundamental to life and health. Integrative Medicine (Boulder) (2014).

NEUROTRANSMITTER SNP References

COMT

• Lotta, T. et al. Kinetics of Human Soluble and Membrane-Bound Catechol O-Methyltransferase: A Revised Mechanism and Description of the Thermolabile Variant of the Enzyme. Biochemistry (1995). doi:10.1021/bi00013a008 • Stein, M. B., Fallin, M. D., Schork, N. J. & Gelernter, J. COMT polymorphisms and anxiety-related personality traits. Neuropsychopharmacology (2005). doi:10.1038/sj.npp.1300787 • Lee, L. O. & Prescott, C. A. Association of the catechol-O-methyltransferase val158met polymorphism and anxiety-related traits: A meta-analysis. Psychiatr. Genet. (2014). doi:10.1097/YPG.0000000000000018 • Ulmanen, I. et al. Expression and intracellular localization of catechol O-methyltransferase in transfected mammalian cells. Eur. J. Biochem. (1997). doi:10.1111/j.1432-1033.1997.0452a.x • Axelrod, J. O-methylation of epinephrine and other catechols in vitro and in vivo. Science (80-.). (1957). doi:10.1126/science.126.3270.400 • Tai, C. H. & Wu, R. M. Catechol-O-methyltransferase and Parkinson's disease. Acta Medica Okayama (2002). • Grossman, M. H., Emanuel, B. S. & Budarf, M. L. Chromosomal mapping of the human catechol-O-methyltransferase gene to 22q11.1?q11.2. Genomics (1992). doi:10.1016/0888-7543(92)90316-K • Golan, D. E., Armstrong, E. J. & Armstrong, A. W. Principles of pharmacology: the pathophysiologic basis of drug therapy. (Wolters Kluwer Health, 2017). • Bonifácio, M. J., Palma, P. N., Almeida, L. & Soares-Da-Silva, P. Catechol-O-methyltransferase and its inhibitors in Parkinson's disease. CNS Drug Reviews (2007). doi:10.1111/j.1527-3458.2007.00020.x • Wichers, M. et al. The catechol-O-methyl transferase Val158Met polymorphism and experience of reward in the flow of daily life. Neuropsychopharmacology (2008). doi:10.1038/sj.npp.1301520 • Diamond, A., Briand, L., Fossella, J. & Gehlbach, L. Genetic and Neurochemical Modulation of Prefrontal Cognitive Functions in Children. Am. J. Psychiatry (2004). doi:10.1176/appi.ajp.161.1.125 • Robinson, S., Goddard, L., Dritschel, B., Wisley, M. & Howlin, P. Executive functions in children with Autism Spectrum Disorders. Brain Cogn. (2009). doi:10.1016/j.bandc.2009.06.007 • Bruder, G. E. et al. Catechol-O-methyltransferase (COMT) genotypes and working memory: Associations with differing cognitive operations. Biol. Psychiatry (2005). doi:10.1016/j.biopsych.2005.05.010 • Chen, J. et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. Am. J. Hum. Genet. (2004). doi:10.1086/425589

GAD1

• GAD1 glutamate decarboxylase 1 [Homo sapiens (human)] - Gene - NCBI. National Center for Biotechnology Information (2020). Available at: https://www.ncbi.nlm.nih.gov/gene/2571. • KELLY, C. D. et al. Nucleotide sequence and chromosomal assignment of a cDNA encoding the large isoform of human glutamate decarboxylase. Ann. Hum. Genet. (1992). doi:10.1111/j.1469-1809.1992.tb01150.x • Giorda, R., Peakman, M., Tan, K. C., Vergani, D. & Trucco, M. Glutamic acid decarboxylase expression in islets and brain. The Lancet (1991). doi:10.1016/0140-6736(91)92781-V • Dirkx, R. et al. Targeting of the 67-kDa isoform of glutamic acid decarboxylase to intracellular organelles is mediated by its interaction with the NH2- terminal region of the 65-kDa isoform of glutamic acid decarboxylase. J. Biol. Chem. (1995). doi:10.1074/jbc.270.5.2241 • Bu, D. F. & Tobin, A. J. The exon-intron organization of the genes (gad1 and gad2) encoding two human glutamate decarboxylases (gad67and gad65) suggests that they derive from a common ancestral gad. Genomics (1994). doi:10.1006/geno.1994.1246 • Demakova, E. V, Korobov, V. P. & Lemkina, L. M. Determination of gamma-aminobutyric acid concentration and activity of glutamate decarboxylase in blood serum of patients with multiple sclerosis. Klin. Lab. Diagn. (2003). • Asada, H. et al. Mice lacking the 65 kDa isoform of glutamic acid decarboxylase (GAD65) maintain normal levels of GAD67 and GABA in their brains but are susceptible to seizures. Biochem. Biophys. Res. Commun. (1996). doi:10.1006/bbrc.1996.1898 • McHale, D. P. et al. A Gene for Autosomal Recessive Symmetrical Spastic Cerebral Palsy Maps to Chromosome 2q24-25. Am. J. Hum. Genet. (1999). doi:10.1086/302237

MAO-A

• Kim, S. K. et al. Association study between monoamine oxidase A (MAOA) gene polymorphisms and schizophrenia: Lack of association with schizophrenia and possible association with affective disturbances of schizophrenia. Mol. Biol. Rep. (2014). doi:10.1007/s11033-014-3207-5 • Anton, R. F. et al. Pharmacogenomics. Nat. Genet. 16, 268–278 (2008). • Karmakar, A. et al. Pilot study indicate role of preferentially transmitted monoamine oxidase gene variants in behavioral problems of male ADHD probands. BMC Med. Genet. (2017). doi:10.1186/s12881-017-0469-5 • Bortolato, M. & Shih, J. C. Behavioral outcomes of monoamine oxidase deficiency: Preclinical and clinical evidence. in International Review of Neurobiology (2011). doi:10.1016/B978-0-12-386467-3.00002-9

MAO-B

• Ukraintseva, S. V., Arbeev, K. G., Michalsky, A. I. & Yashin, A. I. Antiaging treatments have been legally prescribed for approximately thirty years. in Annals of the New York Academy of Sciences (2004). doi:10.1196/annals.1297.014 • Shih, J. C. & Chen, K. MAO-A and -B gene knock-out mice exhibit distinctly different behavior. Neurobiology (Budapest, Hungary). (1999). Available at: https://www.ncbi.nlm.nih.gov/pubmed/10591056. • Riederer, P. & Laux, G. MAO-inhibitors in Parkinson's Disease. Exp. Neurobiol. (2011). doi:10.5607/en.2011.20.1.1 • Saura, J. et al. Increased monoamine oxidase b activity in plaque-associated astrocytes of Alzheimer brains revealed by quantitative enzyme radioautography. Neuroscience (1994). doi:10.1016/0306-4522(94)90311-5 • Mallajosyula, J. K., Chinta, S. J., Rajagopalan, S., Nicholls, D. G. & Andersen, J. K. Metabolic control analysis in a cellular model of elevated MAO-B: Relevance to parkinson's disease. Neurotox. Res. (2009). doi:10.1007/s12640-009-9032-2 • Nagatsu, T. & Sawada, M. Molecular mechanism of the relation of monoamine oxidase B and its inhibitors to Parkinson's disease: possible implications of glial cells. J. Neural Transm. Suppl. (2006). doi:10.1007/978-3-211-33328-0_7 • Kumar, M. J. & Andersen, J. K. Perspectives on MAO-B in Aging and Neurological Disease: Where Do We Go From Here? Mol. Neurobiol. (2004). doi:10.1385/MN:30:1:077 • Shih, J. C., Chen, K. & Ridd, M. J. MONOAMINE OXIDASE: From Genes to Behavior. Annu. Rev. Neurosci. (1999). doi:10.1146/annurev.neuro.22.1.197 • MAOB monoamine oxidase B [Homo sapiens (human)] - Gene - NCBI. National Center for Biotechnology Information Available at: https://www.ncbi.nlm.nih.gov/gene/4129. • Bortolato, M. & Shih, J. C. Behavioral outcomes of monoamine oxidase deficiency: Preclinical and clinical evidence. in International Review of Neurobiology (2011). doi:10.1016/B978-0-12-386467-3.00002-9 • Bortolato, M., Godar, S. C., Davarian, S., Chen, K. & Shih, J. C. Behavioral disinhibition and reduced anxiety-like behaviors in monoamine oxidase b-deficient mice. Neuropsychopharmacology (2009). doi:10.1038/npp.2009.118 • Miller, G. M. The emerging role of trace amine-associated receptor 1 in the functional regulation of monoamine transporters and dopaminergic activity. Journal of Neurochemistry (2011). doi:10.1111/j.1471-4159.2010.07109.x • Edmondson, D. E., Binda, C. & Mattevi, A. Structural insights into the mechanism of amine oxidation by monoamine oxidases A and B. Archives of Biochemistry and Biophysics (2007). doi:10.1016/j.abb.2007.05.006 • Nolen, W. A., Hoencamp, E., Bouvy, P. F. & Haffmans, P. M. Reversible Monoamine Oxidase-A Inhibitors In Resistant Major Depression. Clinical Neuropharmacology 15, (1992).