



Gene Comprehensive Nutrigenomic Report

Accession Number: #####
Specimen Collected: ##/##/####
Specimen Received: ##/##/####
Report Generated: March 28, 2019
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.

– 34 – Male

(-/-) No clinical abnormality

(+/-) Heterozygous result

(+/+) Homozygous result

rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result	Highly Recommended Therapeutics / Neurobiologix Formulas	Provider Discretion: As Needed Formula Recommendations	Lifestyle Recommendations	Laboratory Recommendations
Women's Health							
Vitamin Conversion and Delivery							
rs2071010	FOLR1	-/-	Methyltetrahydrofolate (5-MTHF)	Methyl Folate Plus™ Twice Daily			
rs651933	FOLR2	+/-					
rs1076991	MTHFD1	+/-					
rs1801131	MTHFR A1298C	+/+					
rs1801133	MTHFR C677T	-/-					
rs1051266	SLC19A1	+/-					
rs526934	TCN1	+/-	Methyl B12, Adenosyl B12	Methylation Pro Topical™ OR Methylation Complete Fast Dissolves™ twice daily			Consider Routine Plasma B12 Level
rs1801198	TCN2	+/+					
Clot Risk							
rs6025	FACTOR V	-/-	Potential Increased Risk of Thrombosis				
rs3211719	FACTOR X	-/-					
rs268	LPL	-/-	Increased Risk of Thromboembolisms and Hyperlipidemia				

– 34 – Male

(-/-) No clinical abnormality

(+/-) Heterozygous result

(+/-) Heterozygous result

rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result	Highly Recommended Therapeutics / Neurobiologix Formulas	Provider Discretion: As Needed Formula Recommendations	Lifestyle Recommendations	Laboratory Recommendations
Estrogen Metabolism and Clearance							
rs1800440	CYP1B1	+/-	Increased Levels of 4-hydroxy Estrogen, Endometriosis and Osteoporosis	DIM Pro (Di-indoyl Methane) if Estrogen Dominant		Be Cautious With High Dose Estrogen Birth Control or Estrogen Supplementation Due To Increased Production of 4-OH Estrogen Metabolites	Consider Estrogen Metabolite Testing
rs1048943	CYP1A1 L4889G	-/-					
rs4680	COMT V158M	+/-					
rs1695	GSTP1 I105V	+/+					
Follicular Sensitivity							
rs6165	FSHR	+/+	Decreased FSH Sensitivity Higher Risk of PCOS, Estrogen Dominance and Premature Ovarian Failure	D-Chiro Inositol or Metabolic Stimulator™		Monitor for PCOS and Premature Ovarian Failure. May need supplemental progesterone during pregnancy.	Routine Mid Cycle Fractionated Estrogen, Progesterone, Testosterone
Hormone Metabolism							
rs4646	CYP19A1	+/+	High activity of Aromatase, Higher Risk of Endometriosis and Estrogen Dominance	Consider DIM Pro™ or Aromatase Inhibitor if Necessary		Testosterone Therapy May Produce Higher Levels of Estrogen	Routine Mid Cycle Fractionated Estrogen, Progesterone, Testosterone
rs166050	SRD5A1	-/-	Be Cautious with Estrogen, Testosterone and DHEA therapy due to potential increase in DHT				

– 34 – Male

(-/-) No clinical abnormality

(+/-) Heterozygous result

(+/+) Homozygous result

rsID	Gene	Genetic Result	Therapeutics Associated With Positive Result	Highly Recommended Therapeutics / Neurobiologix Formulas	Provider Discretion: As Needed Formula Recommendations	Lifestyle Recommendations	Laboratory Recommendations
Metabolic Risk Factor							
rs1867277	FOXE1	-/-	Iodine, Selenium				
rs510432	ATG5	+/+	Curcumin, Resveratrol, Sulfuraphane, Ginseng, Catechins, D-Chiro Inositol	D-Chiro Inositol or Metabolic Stimulator™ N.A.S Enhancer™	Metformin may be Beneficial Spironolactone may be Beneficial	Increased Risk of Insulin Resistance, PCOS, Gestational Diabetes 12-15 hour Fasting Routine Exercise	Routine Fasting Blood Sugar, Insulin and Hgb A1c
rs26538	ATG12	+/-					
rs10210302	ATG16L1	+/-					
Hypertension/Risk/Other							
rs4343	ACE	+/-	Increased risk of salt retention and hypertension				
rs699	AGT	+/-					
Vitamin D Transport							
rs731236	VDR Taq	+/-	Vitamin D	Vitamin D3+K2 Cofactor Complex™ OR D3+K2 Drops	Vitamin D3+K2 Cofactor Complex™ OR D3+K2 Drops		Consider Routine Vitamin D
rs2282679	GC or DBP	+/-	Vitamin K				

Summary for Women's Health

Highly Recommended Therapeutics / Neurobiologix Formulas

- Methyl Folate Plus™ Twice Daily
- Methylation Pro Topical™ OR Methylation Complete Fast Dissolves™ twice daily
- DIM Pro (Di-indoyl Methane) if Estrogen Dominant
- D-Chiro Inositol or Metabolic Stimulator™
- Consider DIM Pro™ or Aromatase Inhibitor if Necessary
- N.A.S Enhancer™
- Vitamin D3+K2 Cofactor Complex™ OR D3+K2 Drops

Provider Discretion

- Metformin may be Beneficial
- Spironolactone may be Beneficial
- Vitamin D3+K2 Cofactor Complex™ OR D3+K2 Drops

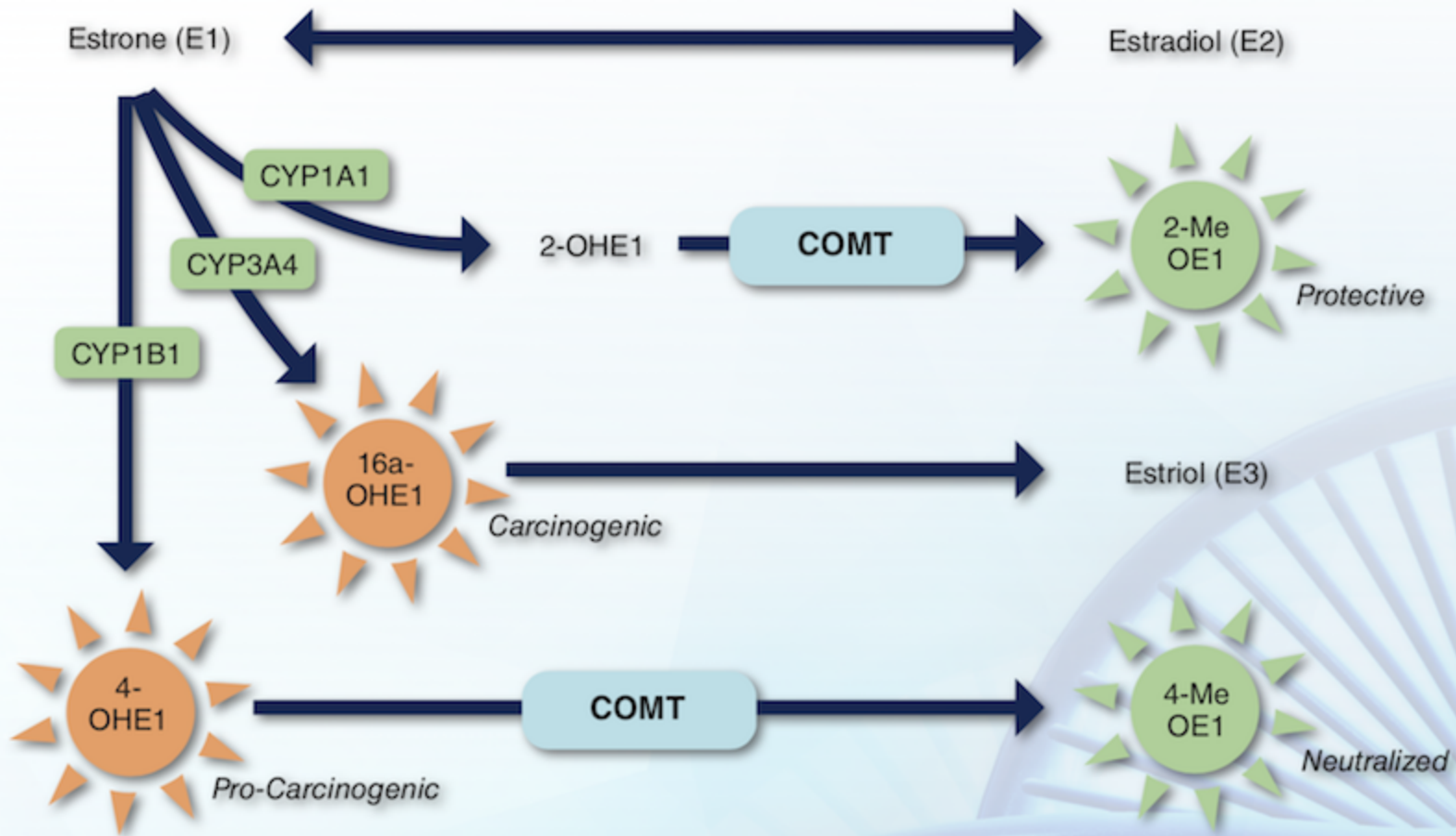
Lifestyle Recommendations

- Be Cautious With High Dose Estrogen Birth Control or Estrogen Supplementation Due To Increased Production of 4-OH Estrogen Metabolites
- Monitor for PCOS and Premature Ovarian Failure.
- May need supplemental progesterone during pregnancy.
- Testosterone Therapy May Produce Higher Levels of Estrogen
- Increased Risk of Insulin Resistance
- PCOS
- Gestational Diabetes
- 12-15 hour Fasting
- Routine Exercise

Laboratory Recommendations

- Consider Routine Plasma B12 Level
- Consider Estrogen Metabolite Testing
- Routine Mid Cycle Fractionated Estrogen
- Progesterone
- Testosterone
- Routine Fasting Blood Sugar
- Insulin and Hgb A1c
- Consider Routine Vitamin D

Phase I and II - Estrogen Metabolism



Gene Information Key

rsID	Gene	"-" variant	"+" variant
rs4343	ACE	A	G
rs699	AGT	A	G
rs26538	ATG12	T	C
rs10210302	ATG16L1	C	T
rs510432	ATG5	C	T
rs4680	COMT V158M	G	A
rs4646	CYP19A1	C	A
rs1048943	CYP1A1 L4889G	T	C
rs1800440	CYP1B1	T	C
rs6025	FACTOR V	C	T
rs3211719	FACTOR X	A	G
rs2071010	FOLR1	G	A
rs651933	FOLR2	A	G
rs1867277	FOXE1	G	A

rsID	Gene	"-" variant	"+" variant
rs6165	FSHR	C	T
rs2282679	GC or DBP	T	G
rs1695	GSTP1:I105V	A	G
rs268	LPL	A	G
rs1076991	MTHFD1	C	T
rs1801131	MTHFR:A1298C	T	G
rs1801133	MTHFR:C677T	G	A
rs1051266	SLC19A1	T	C
rs166050	SRD5A1	A	G
rs526934	TCN1	A	G
rs1801198	TCN2	C	G
rs731236	VDR Taq	A	G

Definitions

CLOT RISK	
Factor V	A single nucleotide polymorphism 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.
LPL	The lipoprotein lipase (LPL) gene encodes a protein involved in the breakdown of triglycerides into fatty acids. Mutations in the LPL gene are associated with many disorders of metabolism
DETOXIFICATION	Detoxification enzymes are responsible for clearing environmental chemicals and metabolites from our body. Accumulation of these chemicals and by-products can damage intracellular biochemical functions. Alterations in these systems can have a significant negative effect on the nervous system and immune systems functions. These polymorphisms can result in decreased "quality of life" and even decreased "life-span".
GSTP1	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 properties. 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.
DEVELOPMENTAL	
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	
CYP1A1	The CYP1A1 gene encodes a member of the cytochrome P450 family of enzymes. CYP1A1, also known as the aryl hydrocarbon hydroxylase, is essential for detoxifying xenobiotics and normal hormonal metabolism.
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.
HORMONE METABOLISM	
CYP19A1	The CYP19A1 gene encodes a special member of the cytochrome P450 family of enzymes: aromatase. Aromatase is a membrane-bound enzyme that converts androgens to estrogen. By controlling when and where aromatase is expressed during development, the genome carefully sculpts tissue-specific estrogen-responsive phenotypes. SNPs in aromatase (rs4646) are thought to predict a wide range of estrogen-sensitivity effects such as breast cancer risk, toxicity of aromatase inhibitors, and even female pattern hair loss.
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.
AGT	The AGT gene codes for the angiotensinogen protein, a key regulator of blood pressure and body fluid homeostasis. Individuals carrying two copies of the rs699 C allele are at increased risk of hypertension-related disorders such as pre-eclampsia.
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.
ATG16L1	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.

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 significant immune weakness and increased cancer risk, as well as, early bone loss, an increased risk of cognitive decline and mood disorders.
METHYLATION	Methylation is a primary biochemical process in the body that involves the addition of a "methyl" chemical group to a vitamin or neurotransmitter. The addition of the "methyl" group allows for very specific biochemical interactions. Poor "methylation" function alters the effectiveness, delivery and function of many vitamins and important chemicals in the cell.
FOLR1	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.
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	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.
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.
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.
VITAMIN / MINERAL ESSENTIAL	
GC or DBP	GC aka DBP (Vit. D Binding Protein) gene codes for Vit. D binding protein. This protein belongs to the albumin family and is a multifunctional protein found in plasma, ascitic fluid, cerebrospinal fluid and on the surface of many cell types. It is manufactured in the hepatic parenchymal cells. DBP is capable of binding to all forms of Vit D including ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3), the 25-hydroxylated forms (calcifediol) and the active hormonal product, 1,25-dihydroxyvitamin D (calcitriol). The major proportion of vitamin D in blood is bound to this protein. It transports vitamin D metabolites between skin, liver and kidney, and then on to the various target tissues. It binds to vitamin D and its plasma metabolites and transports them to target tissues. Polymorphisms in this gene decrease the affinity of the protein to Vit. D which reduces the response rate to Vit. D therapy. Patients with these polymorphisms require high doses of Vit D supplementation.

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

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 Neurobiologix 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.

DISCLAIMER:

These products are not approved by the Food and Drug Administration and are not intended to diagnose, treat, cure or prevent a disease. These recommendations are for report purposes only and an individual is not required to use such products. These are recommendations only and do not replace the advisement of your own healthcare practitioner.

GX Sciences SNP References

CLOT RISK SNP References

LPL

• Hu, Y., Liu, W., Huang, R. & Zhang, X. A systematic review and meta-analysis of the relationship between lipoprotein lipase Asn291Ser variant and diseases. *J. Lipid Res.* (2006). doi:10.1194/jlr.M600108-JLR200 • Gao, R. R. et al. Impact of LPL gene rs283 polymorphism on exercise-induced changes in metabolism of obese adolescents and the regulatory mechanisms behind it. *Exp. Physiol.* (2015). doi:10.1113/EP085127 • Pirim, D. et al. Lipoprotein lipase gene sequencing and plasma lipid profile. *J. Lipid Res.* (2014). doi:10.1194/jlr.M043265

DETOXIFICATION SNP References

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] • Strange, R. C. & Fryer, A. A. The glutathione S-transferases: influence of polymorphism on cancer susceptibility. *IARC Sci. Publ.* (1999). • 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 • 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 • 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

DEVELOPMENTAL SNP References

ATG12

• 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).

ESTROGEN METABOLISM AND CLEARANCE SNP References

CYP1A1

• Anton, R. F. et al. Pharmacogenomics. *Nat. Genet.* 16, 268–278 (2008). • Zeng, W., Li, Y., Lu, E. & Ma, M. CYP1A1 rs1048943 and rs4646903 polymorphisms associated with laryngeal cancer susceptibility among Asian populations: a meta-analysis. *J. Cell. Mol. Med.* 20, 287–293 (2016). • Abbas, M., Srivastava, K., Imran, M. & Banerjee, M. Association of CYP1A1 gene variants rs4646903 (T>C) and rs1048943 (A>G) with cervical cancer in a North Indian population. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 176, 68–74 (2014).

HEALTH PRECAUTIONS SNP References

ACE

• 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) • The ACE gene and human performance: 12 years on. Puthuchery 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. • 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) • Angiotensin-converting enzyme inhibition by perindopril in the treatment of cardiovascular disease. (PMID: 19379059) Brugs J.J. ... Simoons M.L.(Expert Rev Cardiovasc Ther 2009) • 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)

CYP1B1

• 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 • 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 • Wiggs, J. L., Langguth, A. M. & Allen, K. F. Carrier frequency of CYP1B1 mutations in the United States (an American Ophthalmological Society thesis). *Trans. Am. Ophthalmol. Soc.* (2014). • 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 • 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 • 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 • Zahid, M. et al. Unbalanced estrogen metabolism in ovarian cancer. *Int. J. Cancer* (2014). doi:10.1002/ijc.28565 • 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 • 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 • Samavat, H. & Kurzer, M. S. Estrogen metabolism and breast cancer. *Cancer Lett.* (2014). doi:10.1016/j.canlet.2014.04.018 • 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

F10

• PANTELEEV, M. A., SAENKO, E. L., ANANYEVA, N. M. & ATAULLAKHANOVA, 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 • 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). • 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 • 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 • 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 • 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 • 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 • 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 • 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

F5

• 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). • 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 • 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 • 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.ijh.2012.07.006 • 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 • 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 • Simone, B. et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetetrahydrofolate 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 • Ruigrok, Y. M., Sooter, 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 • 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 • 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 • 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 • 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 • Soría, J. M. et al. Multilocus genetic risk scores for venous thromboembolism risk assessment. *J. Am. Heart Assoc.* (2014). doi:10.1161/JAHA.114.001060 • Sode, B. F., Allin, K. H., Dahl, M., Gyntheberg, 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 • 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

FOXE1

• Genetic Predisposition to Papillary Thyroid Carcinoma: Involvement of FOXE1, TSHR, and a Novel lincRNA Gene. *PTSC2* 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 • The investigation of foxe1 variations in papillary thyroid carcinoma Erkan Somuncu, Adem Karatas, Sina Ferahman, Neslihan Saygılı, Eren Yılmaz, Oguz Ozturk, Metin Kapan *Int J Clin Exp Pathol.* 2015; 8(10): 13458–13464. Published online 2015 Oct 1. • 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-Mondejar, Roberto Castello, Isabella Merante-Boschin, Maria-Rosa Pelizzo, Didac Mauricio, Giuseppe Poocher, Cristina Rodríguez-Antona, Anna González-Neira, Xavier Matias-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 • 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 • 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 • 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. Mays, 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 • FOXE1 Association with Differentiated Thyroid Cancer and Its Progression Marissa Penna-Martinez, Friederike Epp, Heinrich Kahles, Elizabeth Ramos-Lopez, Nora Hirsch, Martin-Leo Hansmann, Ivan Selkinski, Frank Grünwald, Katharina Holzer, Wolf O. Bechstein, Stefan Zeuzem, Christian Vorfänder, Klaus Badenhoop *Thyroid.* 2014 May 1; 24(5): 845–851. doi: 10.1089/thy.2013.0274

HORMONE METABOLISM SNP References

CYP19A1

• Artigalás, O., Vanni, T., Hutz, M. H., Ashton-Prolla, P. & Schwartz, I. V. Influence of CYP19A1 polymorphisms on the treatment of breast cancer with aromatase inhibitors: a systematic review and meta-analysis. *BMC Med.* 13, 139 (2015). • Garcia-Casado, Z. et al. A polymorphism at the 3'-UTR region of the aromatase gene defines a subgroup of postmenopausal breast cancer patients with poor response to neoadjuvant letrozole.

HYPERTENSION SNP References

AGT

• Ahluwalia, Tarunveer Singh, Monica Ahuja, Taranjit Singh Rai, Harbir Singh Kohli, Anil Bhansali, Kamal Sud, and Madhu Khullar. 2009. "ACE Variants Interact with the RAS Pathway to Confer Risk and Protection against Type 2 Diabetic Nephropathy." *DNA and Cell Biology* 28 (3): 141–50. <https://doi.org/10.1089/dna.2008.0810>. • Anton, Raymond F, Gabor Orozsi, Stephanie O'Malley, David Couper, Robert Swift, Helen M Pettinati, David Goldman, et al. 2008. "Pharmacogenomics." Edited by Yoshiaki Tsuji. *Nature Genetics* 16 (1). Public Library of Science: 268–78. <https://doi.org/10.1016/j.ejca.2015.06.122>.

INFLAMMATORY SNP References

ATG16L1

• 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 • Csöngéi, 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 • Stappenbeck, T. S. et al. Crohn disease: A current perspective on genetics, autophagy and immunity. *Autophagy* (2011). doi:10.4161/auto.7.4.13074 • 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 • Rosenthal, D. C. et al. Role of autophagy genetic variants for the risk of Candida infections. *Med. Mycol.* (2014). doi:10.1093/mmy/myt035 • 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 • 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 • 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 • 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 • 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 • 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

ATG5

• Martin, L. J. et al. Functional Variant in the Autophagy-Related 5 Gene Promoter is Associated with Childhood Asthma. *PLoS One* 7, e33454 (2012). • 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). • 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).

VDRtaq

• 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>. • 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.jsmb.2010.01.015 • 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 • 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 • 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 • Germain, P., Staelb, B., Daquet, C., Spedding, M. & Laudet, V. Overview of Nomenclature of Nuclear Receptors. *Pharmacol. Rev.* (2006). doi:10.1124/pr.58.4.2 • 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 • 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 • 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

METHYLATION SNP References

FLOR1

• 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 • 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). • 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 • Kélemen, 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 • Henderson, G. B. Folate-binding proteins. *Annu. Rev. Nutr.* (1990). doi:10.1146/annurev.nutr.10.1.319 • 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

FLOR2

• 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 • Henderson, G. B. Folate-binding proteins. *Annu. Rev. Nutr.* (1990). doi:10.1146/annurev.nutr.10.1.319 • Ragoussis, J., Senger, G., Trowsdale, J. & Campbell, I. G. Genomic organization of the human folate receptor genes on chromosome 11q13. *Genomics* (1992). doi:10.1016/S0888-7543(05)80236-8 • Freisheim, J. H., Price, E. M. & Ratnam, M. Folate coenzyme and antifolate transport proteins in normal and neoplastic cells. *Adv. Enzyme Regul.* (1989). doi:10.1016/0065-2571(89)90091-5 • Ratnam, M., Marquardt, H., Duhring, J. L. & Freisheim, J. H. Homologous membrane folate binding proteins in human placenta: cloning and sequence of a cDNA. *Biochemistry* (1989). • Shen, F., Ross, J. F., Wang, X. & Ratnam, M. Identification of a novel folate receptor, a truncated receptor, and receptor type beta in hematopoietic cells: cDNA cloning, expression, immunoreactivity, and tissue specificity. *Biochemistry* (1994). doi:10.1021/bi00171a021 • Page, S. T., Owen, W. C., Price, K. & Elwood, P. C. Expression of the Human Placental Folate Receptor Transcript is Regulated in Human Tissues. *Journal of Molecular Biology* 229, 1175–1183 (1993). • Strausberg, R. L. et al. Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. *Proc. Natl. Acad. Sci. U. S. A.* (2002). doi:10.1073/pnas.242603899 • Nakashima-Matsushita, N. et al. Selective expression of folate receptor beta and its possible role in methotrexate transport in synovial macrophages from patients with rheumatoid arthritis. *Arthritis Rheum.* (1999). doi:10.1002/1529-0131(199908)42:83.0.CO;2-L

MTHFD1

• 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 • Sutherland, H. G. et al. Association study of MTHFD1 coding polymorphisms R134K and R653Q with migraine susceptibility. *Headache* (2014). doi:10.1111/head.12428 • 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 • Silva, L. M. R. D. da et al. Head and neck carcinogenesis : impact of MTHFD1 G1958A polymorphism. *Head Neck Carcinog.* (2011). • 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). • 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 • 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 • Field, M. S., Kamylnina, 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.1414556112 • Zheng, J. et al. MTHFD1 polymorphism as maternal risk for neural tube defects: a meta-analysis. *Neurol. Sci* (2015). • 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

MTHFR

• 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 • 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 • Mischoulon, D. & Raab, M. F. The role of folate in depression and dementia. *Journal of Clinical Psychiatry* (2007). • E. Trimmer, E. Methylenetetrahydrofolate Reductase: Biochemical Characterization and Medical Significance. *Curr. Pharm. Des.* (2013). doi:10.2174/1381612811319140008 • 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 • 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 • 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 • 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 • 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). • Födingner, M., Hörl, W. H. & Sunder-Plassmann, G. Molecular biology of 5,10-methylenetetrahydrofolate reductase. *Journal of Neurology* (2000). doi:10.5860/CHOICE.39-4838 • Goyette, P. et al. Human methylenetetrahydrofolate reductase: Isolation of cDNA, mapping and mutation identification. *Nat. Genet.* (1994). doi:10.1038/ng0694-195 • 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 • 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/gmb.2011.0318 • 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

SLC19A1

• Lima, Aurea et al. 2014. "SLC19A1, SLC46A1 and SLC01B1 Polymorphisms as Predictors of Methotrexate-Related Toxicity in Portuguese Rheumatoid Arthritis Patients." *Toxicological Sciences* 142(1): 196–209. • Bohanec Grabar, Petra et al. 2012. "Genetic Variation in the SLC19A1 Gene and Methotrexate Toxicity in Rheumatoid Arthritis Patients." *Pharmacogenomics* 13: 1583–94. <http://www.ncbi.nlm.nih.gov/pubmed/23148635>. • Liu, Jun et al. 2017. "Single Nucleotide Polymorphisms in SLC19A1 and SLC25A9 Are Associated with Childhood Autism Spectrum Disorder in the Chinese Han Population." *Journal of Molecular Neuroscience* 62(2): 262–67.

TCN1

• 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 • 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. Transcriptional 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 • Furger, E., Frei, D. C., Schibli, R., Fischer, E. & Protá, A. E. Structural basis for universal corrinoid recognition by the cobalamin transport protein haptocorrin. *J. Biol. Chem.* (2013). doi:10.1074/jbc.M113.483271 • 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 • 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 • Carmel, R. Haptocorrin (transcobalamin I) and cobalamin deficiencies [10]. *Clinical Chemistry* (2007). doi:10.1373/clinchem.2006.078808

TCN2

• 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 • Tepiltits, 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. & Nexø, 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., Födingner, 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> • Hofbrand, 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). • 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. Idiopathic pulmonary fibrosis and polymorphisms of the folate pathway genes. *Clin. Biochem.* (2013). doi:10.1016/j.clinbiochem.2012.10.009 • 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 • 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 • 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 • Mills, J. L. et al. Folate-related genes and omphalocele. *Am. J. Med. Genet.* (2005). doi:10.1002/ajmg.a.30772 • Regec, A., Quadros, E. V., Platica, O. & Rothenberg, S. P. The cloning and characterization of the human transcobalamin II gene. *Blood* (1995).

NEUROTRANSMITTER SNP References

COMT

• Golan, D. E., Armstrong, E. J. & Armstrong, A. W. Principles of pharmacology: the pathophysiologic basis of drug therapy. (Wolters Kluwer Health, 2017). • 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 • 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 • 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). • 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 • 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 • 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 • Robinson, S., Goddard, L., Ditschel, B., Wisley, M. & Howlin, P. Executive functions in children with Autism Spectrum Disorders. *Brain Cogn.* (2009). doi:10.1016/j.bandc.2009.06.007 • 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 • 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 • 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

VITAMIN / MINERAL ESSENTIAL SNP References

GC or DBP

• Cheung, C. L., Lau, K. S., Sham, P. C., Tan, K. C. & Kung, A. W. Genetic variant in vitamin D binding protein is associated with serum 25-hydroxyvitamin D and vitamin D insufficiency in southern Chinese. *Journal of Human Genetics* 58, 749–751 (2013). • Wang, W., Ingles, S. A., Torres-Mejia, G., Stern, M. C., Stanczyk, F. Z., Schwartz, G. G., ... John, E. M. (2014). Genetic variants and non-genetic factors predict circulating vitamin D levels in Hispanic and non-Hispanic White women: The breast cancer health disparities study. *International Journal of Molecular Epidemiology and Genetics*. • Trummer, O., Langsenlehner, U., Krenn-Pilko, S., Pieber, T. R., Obermayer-Pietsch, B., Gerger, A., ... Langsenlehner, T. (2016). Vitamin D and prostate cancer prognosis: a Mendelian randomization study. *World Journal of Urology*. <https://doi.org/10.1007/s00345-015-1646-9> • Theodoratou, E., Palmer, T., Zgaga, L., Farrington, S. M., McKeigue, P., Din, F. V. N., ... Campbell, H. (2012). Instrumental variable estimation of the causal effect of plasma 25-hydroxy-vitamin D on colorectal cancer risk: A Mendelian randomization analysis. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0037662> • Slater, N. A., Rager, M. L., Havrda, D. E. & Harralson, A. F. Genetic Variation in CYP2R1 and GC Genes Associated with Vitamin D Deficiency Status. *Journal of Pharmacy Practice* 30, 31–36 (2017). • Szkandera, J. et al. Association of common gene variants in vitamin D modulating genes and colon cancer recurrence. *Journal of Cancer Research and Clinical Oncology* 139, 1457–1464 (2013). • Nimitphong, Hataikarn, Chanika Sritara, La Or Chailurkit, Suwannee Chanprasertyothin, Wipa Ratanachaiwong, Piyamitr Sritara, and Boonsong Ongphiphadhanakul. 2015. "Relationship of Vitamin D Status and Bone Mass According to Vitamin D-Binding Protein Genotypes." *Nutrition Journal* 14 (1), BioMed Central Ltd. doi:10.1186/s12937-015-0016-1. • Leong, A., Rehman, W., Dastani, Z., Greenwood, C., Timpson, N., Langsetmo, L., ... Richards, J. B. (2014). The Causal Effect of Vitamin D Binding Protein (DBP) Levels on Calcemic and Cardiometabolic Diseases: A Mendelian Randomization Study. *PLoS Medicine*. <https://doi.org/10.1371/journal.pmed.1001751> • Elkum, N., Alkayal, F., Noronha, F., Ali, M. M., Melhem, M., Al-Arouj, M., ... Abubaker, J. (2014). Vitamin D insufficiency in Arabs and South Asians positively associates with polymorphisms in GC and CYP2R1 genes. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0113102> • Davies, J. R., Field, S., Randerson-Moor, J., Harland, M., Kumar, R., Anic, G. M., ... Newton-Bishop, J. (2014). An inherited variant in the gene coding for vitamin D-binding protein and survival from cutaneous melanoma: A BioGenoMEL study. *Pigment Cell and Melanoma Research*. <https://doi.org/10.1111/pcmr.12193> • Wang, Y., Wang, O., Li, W., Ma, L., Ping, F., Chen, L., & Nie, M. (2015). Variants in Vitamin D binding protein gene are associated with gestational diabetes mellitus. *Medicine (United States)*. <https://doi.org/10.1097/MD.0000000000001693>