Client Report

Venus deMilo

Opus23 Explorer

Opus23 Explorer™ is a fully functional version of the well-regarded and widely used Opus23 Pro™ genomic exploration software designed and programmed by Dr. Peter D'Adamo and distributed under license to Diagnostic Solutions Lab (DSL) by Datapunk Bioinformatics LLC for use in the interpretation of genomic raw data produced by the DSL 'Opus' genomic microarray chip.

Opus23 Explorer scans over 20 peer-reviewed, evidence-based scientific databases and cross-references their information with the results of your raw data. This report summarizes the findings from your genomic data that have been curated by your clinical team into a human-understandable format. However, before we begin, let's introduce a few genetic concepts to set the stage and advance your understanding a bit.

REPORT FOCUS

DETOXIFICATION

Welcome to your owner's manual

Opus23 Explorer is a very sophisticated computer program that looks for very simple things: variations in the code of DNA (the A, T, C, and G of the genetic alphabet) that can exist between people. Not all of our DNA varies from person to person, but about 9% of it can. The variations are called 'snips' (SNPs) which stands for single nucleotide polymorphism.

Although SNPs are the 'letters' of individuality, genes are in fact the words and vocabulary. After all, it is the genes that have to do the work, coding for the construction for a myriad of enzymes and proteins. Because gene function is central to any sort of biochemical prediction, Opus 23 Pro groups all the SNP outcomes under their parent gene, and presents its results as a reflection of their combined influence on the effectiveness of that gene. Although SNPs are pretty much unchangeable, our genes can be influenced (for better or worse) by lifestyle, diet, emotions and nutritional supplementation.

The DNA in our bodies is a double-stranded molecule, meaning that for every location that we might find a SNP there exists two letters, one for each strand. Taken together, these two letters comprise the **genotype** for that location. Over the years, much research has been done to examine whether a particular SNP variation (or mutation) can be shown to result in an effect on our health. For example, let's look at two different people, John and Jane. At location 12345678 on chromosome #1 most people, as does John, have the 'AA' genotype. It has been noticed that 15% of the population have one 'G' (genotype 'AG') while 5% of the population have genotype 'GG'. Separate studies show that people with at least one 'G' genotype have an increased risk of eczema. Jane's genotype at this location is 'GA' so she may have this susceptibility. As you might have noticed, genotypes come in two types: two identical letters ('GG', 'AA') known as *homozygous* and one of each letter ('GA' or 'AG') known as *heterozygous*.

Because the presence of a 'G' at this SNP location is associated with a condition, for this SNP 'G' is known as the *risk nucleotide* or *risk allele*. Most of the time, having the risk allele negatively impacts the function of its parent gene, but sometimes the mutations can convey a benefit or advantage.

Something like 99.6% of the human genome is identical in all people. This is true of everyone, regardless of race or heritage. However, it is at the SNP location that variation does take place. SNPs only make up a tiny portion of the genome (0.4%) but because the genome is so enormous, this equals over 12 million locations. It's the differences at these SNP locations that make each of us unique. If your genotype at SNP rs17822931 is TT, then you probably have dry earwax. If you have any other genotype at this SNP, then you have wet earwax.

By the way, you're **CT** for the rs17822931 SNP.

This owner's manual was produced by your clinician who, using the Opus23 Explorer software, has curated what, in the great sea of data that Opus23 Explorer provides, they believe is most important to your health care. It would be untrue (and unkind) to pretend that much of the material in this report is easy to understand. Although the editors of Opus23 Explorer try to provide explanations in layperson terminology when and where possible, things can get quite technical. Don't panic! Make note of your questions and remeber to discuss these with your clinician next opportunity. Also, use online resources such as Google and Wikipedia as research tools.

Genetics can be complicated to the layperson. Sometimes a word is used to describe a gene function that you might not recognize. If *Opus23 Explorer* thinks that you might need some help with a technical term, 'Mr. Smart Owl' will try to explain it to you.

Now, a few caveats

Depending on how your health professional has decided to structure this report, you might find the information that follows to be intimidating or even potentially disturbing. For example, nobody enjoys hearing that they may have an increased risk for a disease or health complication. While Opus23 Explorer cannot guarantee that all of its findings will be of a positive nature, it's important to understand what this information can and cannot do. Let's discuss a few facts that you should keep in mind.

Advances in genetic technology have made the process of discovering new SNPs very easy. However the process of linking a SNP to particular trait or illness requires epidemiologic studies that are far more expensive and labor intensive. Thus there is a large gap between the SNPs we know and what in fact we know about them. Opus 23 Pro is constantly updated with new information and your health care provider can very easily update your data to include any new information as it arrives. Opus23 Pro strives to provide the most accurate possible data interpretation. As part of this mission, we constantly monitor and refine our data analysis algorithms. When an improvement is identified, the new algorithm becomes available immediately on creation. In that event, a corrected report will be available to your health care provider. Such re-analysis of patient data may lead to reclassification of your results.

Opus23 Explorer can only supply correlations and relationships

Opus23 Explorer can only compare your genetic data with published data linking your results to the outcomes in the research. It can't diagnose disease. Nor should it. However, it can point the way to areas of possible further clinical interest, and perhaps guide both you and your health care professional in the process of developing a more evidence-based approach to prevention. The etiology (cause) of many diseases is multifactorial; that is, disease can occur as a result of various factors, including both inherited and acquired genetic variants, diet, lifestyle choices and age.

Opus23 Explorer results are as good as the starting data

The interpretations given by Opus23 Explorer are the result of evaluated inherited genetic variants in data uploaded to our server, and interpretations are only as accurate as the data received from the genomic test. It is possible that inaccuracies in the genomic test results could lead to false interpretations. It is also possible that variants in genes and genetic regions not tested in the DNA sequencing test may contribute to an individual’s risk for disease. Therefore, a negative result in a gene where no pathogenic variants are detected does not eliminate the individual’s disease risk.

Genetic findings can only report the starting point

Your genome is similar to the blueprint for a house that is yet to be built. If the builder follows the architect's instructions exactly, the house will match the blueprint perfectly. However, all throughout the construction process alterations will most certainly be made: For example, if the new owners are running short on funds, perhaps the original plans for an expensive slate roof may have to be altered to a less expensive, though still-functional, asphalt version. It's the same with genomics, although variations in your gene data may reflect an increased or decreased risk of a health issue, many of these risks may have been altered by environmental factors (such as your pre-existing lifestyle and health habits) acting epigenetically to control the expression of these genes. If you've carefully watched your diet over time and kept your weight at a healthy level, a finding that you are at risk for obesity might do nothing more than encourage you to continue what you are already doing.

Genetic findings can only reflect probabilities

Very few gene mutations result in a direct, absolutely certain, health consequence. Most of the time, they instead reflect a change to your odds of developing a particular health condition. This is defined as the 'risk' for a certain event. This is usually expressed as an 'odds ratio' (OR). Understanding the meaning of an OR for a particular risk is a key to minimizing stress when encountering dire results. For example, being told you are 110% more likely to get struck by lightning (OR=1.1) is much less distressing when you realize that:

- This is a very small difference from normal
- Very few people get struck by lightning regardless

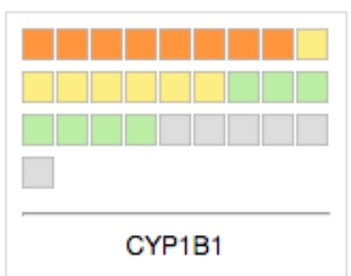
When it comes to a particular disease or syndrome, most SNPs have rather small ORs. This does not mean that they are unworthy of attention, but rather that the findings must be interpreted as part of an integrated whole, including: other SNP results that also support the conclusion; lifestyle factors; family history, and environmental exposures. Further, a positive test result does not guarantee an occurrence of disease since the SNP variants in most genes are not 100% penetrant (even genes with several risk SNPs will very likely function to some degree). Rather, pathogenic variants may predispose a person to a higher or lower risk of disease. The results of genomic testing must be interpreted in the context of your clinical history. Genetic counseling is recommended for the individual and for other at-risk family members.

And now, the usual indemnification statement:

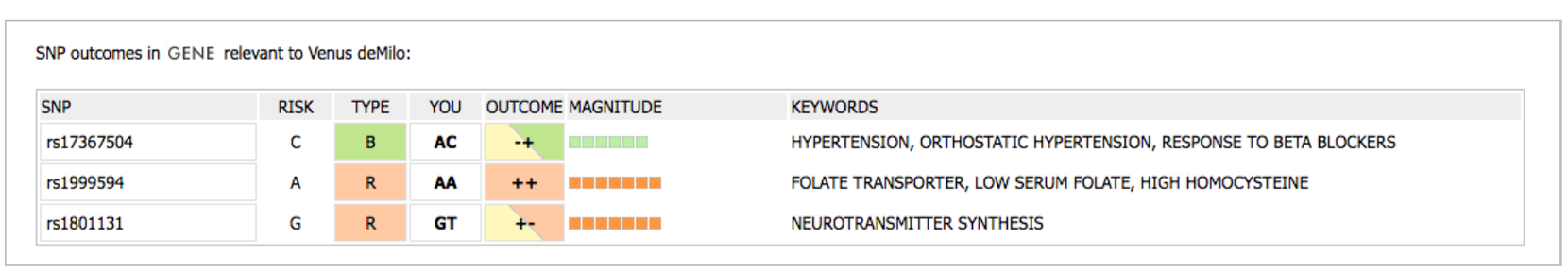
The data provided by Opus23 Explorer is for informational purposes only and is not designed or intended to suggest the treatment or diagnosis of any disease or condition. Opus23 Explorer and Datapunk Bioinformatics, LLC, take no responsibility for any harm arising from incorrect data being uploaded to our server or incorrect data interpretation, errors, or omissions by the software. By agreeing to access this Opus 23 Pro report you hereby agree to indemify Opus23 Explorer and Datapunk Bioinformatics, LLC from any consequences resulting fro the use or misuse of this information. The statements made on this page have not been evaluated by the FDA (U.S. Food & Drug Administration). This material is presented for informational and education purposes only and is not intended to diagnose, cure or prevent any disease.

Understanding the report

Each gene is depicted as a grid showing the result of its SNPs:



- The sum of the significant SNPs in the gene that indicate a higher (homozygous) risk are the orange squares
- The sum of the significant SNPs in the gene that indicate a lower (heterozygous) risk are the yellow squares
- The sum of the significant SNPs that are working just fine (no problem polymorphisms) risk are the gray squares
- You might even find that for some genes you may have a polymorphism that conveys some benefit. These are the green squares



SNP outcomes in GENE relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs17367504	C	B	AC	-+		HYPERTENSION, ORTHOSTATIC HYPERTENSION, RESPONSE TO BETA BLOCKERS
rs1999594	A	R	AA	++		FOLATE TRANSPORTER, LOW SERUM FOLATE, HIGH HOMOCYSTEINE
rs1801131	G	R	GT	+-		NEUROTRANSMITTER SYNTHESIS

Multi SNP macros

Macros (algorithms) are perhaps the most significant and flexible aspect of your Opus 23 data. They are usually the easiest result for the non-medical person to understand, because their conclusions are usually simplified statements in everyday language.

Many correlations between SNPs and various traits exist as 'haplotypes,' clusters of SNPs, often on different genes, that must be evaluated as 'true' or 'false' based on their total outcome values. Some algorithms may identify risks for certain problems, while others identify special strengths or benefits you might possess. It's helpful to think of an Opus 23 algorithm as a tiny flowchart, that depending on which way the result branches, generates a 'true or false' result.

For example, a simple macro to determine if you should get out of bed might be:

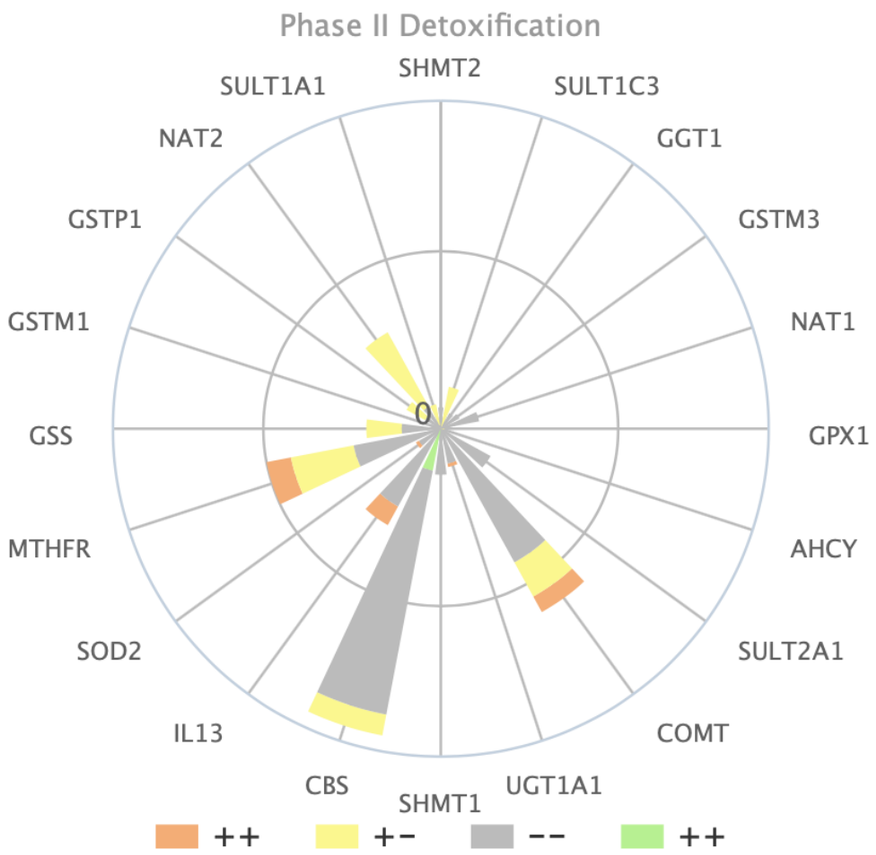
- If you hear the alarm clock, open your eyes.
- If it's dark outside, go back to bed.
- If it's light outside, check the time.
- If it's earlier than 7AM, go back to bed.
- If it's later than 7AM, get up, check calendar
- If it's Saturday, go back to bed.

As can be seen, there are a lot of ways you can go back to bed with this algorithm! And this is also true as well for the Opus 23 Pro algorithms: In order for an algorithm to be true, it must fufill all of several conditions. *If even one condition fails, the whole algorithm will be false.*

Each macro algorithm is displayed in its own box, and contain information about the genes and SNPs used in its creation. The title of the algorithm is generally its conclusion. Typically, your report contains only true algoriths, although your clinical team may choose to include false algorithms as well, especially if it would be helpful to make you aware of something you're likely to not be prone to. Thus:

- An algorithm that returns a **true** will have a 'check' icon in the bottom left-hand box. The conclusions of these algorithms **pertain** to you based on your genomic data results.
- An algorithm that returns a **false** will have a 'cross' icon in the bottom left-hand box. The conclusions of these algorithms **do not pertain** to you based on your genomic data, other than perhaps the added knowledge that this is one less thing in life to worry about.

DETOXIFICATION



Phase II Detoxification

Following oxidation, reduction or hydrolysis by phase I reactions transforming toxic hydrophobic products into hydrophilic products, toxicants and drugs are then subjected to phase II detoxification conjugation reactions. Phase II metabolites are less metabolically active than phase I metabolites, enabling their transport and excretion from the body via Phase III. Phase II reactions involve attachment of a molecule such as glucuronic acid, sulfate, or glycine to form water-soluble compounds. Conjugation mechanisms include methylation, sulfation, acetylation, glucuronidation and glutathione or glycine conjugation.

Phase II enzymes exhibit redundancy: a particular phase I product can be metabolised by more than one phase II enzyme. Genetic polymorphism is an important cause of variations in drug response, and increased phase I CYP activity in turn increases the burden on phases II and III. Exposure to phase I, phase II, and phase III inducers may trigger cellular stress response, leading to an increase in gene expression and ultimately enhancing the elimination and clearance of these xenobiotics.

UGTs, GSTs, and SULTs catalyze the bulk of human detoxification reactions. Several other phase II enzymes contribute to the process to a lesser although still significant extent, including:

- Methyltransferase enzymes catalyze methylation reactions using S-adenosyl-L-methionine (SAMe) as a substrate, such as COMT. Methylation reactions are one of the few phase II reactions that decrease water solubility
- Arylamine N-acetyltransferases (NATs) detoxify carcinogenic aromatic amines and heterocyclic amines
- Amino acid conjugating enzymes: Acyl-CoA synthetase and acyl-CoA amino acid N-acyltransferases (NATs) attach amino acids (most commonly glycine or glutamine) to xenobiotics. Benzoic acid, a preservative in food and personal care products is an example of a toxin metabolized by amino acid conjugation

SULT1C3

sulfotransferase family, cytosolic, 1C, member 3

SULT1C3 (Sulfotransferase Family, Cytosolic, 1C, Member 3) is a protein coding gene. Among its related pathways are biological oxidations and sulfation biotransformation reactions. GO annotations related to this gene include aryl sulfotransferase activity and alcohol sulfotransferase activity. An important paralog of this gene is SULT1B1. This sulfotransferase utilizes 3-phospho-5-adenylyl sulfate (PAPS) as a sulfonate donor, and has low sulphotransferase activity towards various substrates with alcohol groups (in vitro). SULT1C3 catalyzes the sulfate conjugation of xenobiotic compounds and endogenous substrates.

Sulfotransferases catalyze sulfonation reactions is expressed in human intestine associated with colorectal adenocarcinoma [PMID: 24335392]. SULT1C3 can sulfonate p-nitrophenol, 1-naphthol, 2-ethylphenol, 2-n-propylphenol, and 2-sec-butylphenol, as well as the steroid-related compounds α-zearalenol and lithocholic acid. SULT1C3 appears to be most active with α-zearalenol and 2-ethylphenol, which suggests its contribution to the metabolism of steroid and phenolic compounds [PMID: 17425406].

Phase II reactions include sulfation and glucuronidation, which are key to human detoxification, along with glutathione conjugation, methylation, amino acid conjugation, and acetylation. Phase II detoxification typically involves biochemical conjugation, in which various enzymes sulfotransferases, glucuronosyltransferase and acetyltranferases in the liver attach small chemical moieties to the toxin. The conjugation reaction neutralizes toxins and reactive intermediates left over from Phase I detoxification.

Sulfotransferases are inhibited by quercetin, red wine, black tea, green tea and caffeine and carmoisine in red food coloring.(1)

Reference:

1. Wang LQ, James MO. Inhibition of sulfotransferases by xenobiotics. Curr Drug Metab. 2006 Jan;7(1):83-104. Review. PubMed PMID: 16454694.

SNP outcomes in SULT1C3 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs6722745	C	R	**CT**	**+-**		
rs2219078	A	R	**AG**	**+-**		

New concepts:

- The *gene* is the fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific product (i.e., a protein).
- A *xenobiotic* is a chemical compound foreign to the body. Xenobiotics include drugs, and environmental compounds such as pollutants that are not produced by the body. In the environment, xenobiotics include synthetic pesticides, herbicides, and industrial pollutants that would not be found in nature.
- To *Catalyze* is to cause or accelerate (a reaction) by acting as a catalyst.
- A *paralog*is a duplicated or repetitive sequence of DNA, multiple copies of which are found in a single genome.
- *Methylation* is the addition of a single carbon and three hydrogen atoms (called a methyl group) to another molecule. The removal of a methyl group is called demethylation. Methylation is a key mechanism behind the regulation of gene expression.
- *Proteins* are large molecules composed of one or more chains of amino acids. Proteins are required for the structure, function, and regulation of the bodys cells, tissues, and organs, and each protein has unique functions. Examples are hormones, enzymes, and antibodies.
- *Amino acid* are small molecules that are the components of proteins. There are 20 different kinds of amino acids in living things. Proteins are composed of different combinations of amino acids assembled in chain-like molecules.

SULT2A1

sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring, member 1

This gene encodes a member of the sulfotranserase (SULT) family. SULTs aid in the metabolism of drugs and endogenous compounds by converting thsese substances into more soluble conjugates that can be easily excreted. The protein encoded by SULT2A1 may have a role in the inherited adrenal androgen excess in women with polycystic ovary syndrome.

SULT2A1 assists detoxification of compounds such as thyroid and adrenal hormones, serotonin, retinol, ascorbate and vitamin D by converting these substances into more easily excreted water soluble sulfate conjugates. In contrast to other phase II enxymes, SULT2A1 can convert a number of procarcinogens (such as heterocyclic amines from cooked meats) into highly reactive intermediates which may act as chemical carcinogens and mutagens.

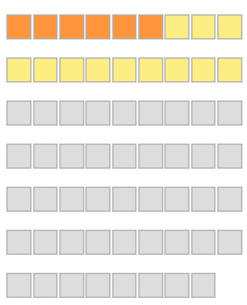
SNP outcomes in SULT2A1 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs4149452	T	R	**CC**	**--**		
rs4149449	T	R	**CC**	**--**		

New concepts:

- *Amines* are organic compounds contain a basic nitrogen atom. Important amines include amino acids, histamine, dopamine and serotonin.
- An *androgen* is any natural or synthetic compound, usually a steroid hormone, that stimulates or controls the development and maintenance of male characteristics.

COMT



catechol-O-methyltransferase

Catechol-O-methyltransferase (COMT) gene helps break down the neurotransmitters dopamine and norepinephrine. A defect due to certain variants in COMT will cause higher levels of dopamine due to slower breakdown, which can contribute to anxiety and insomnia. Individuals can be more susceptible to dopamine fluctuations, and therefore mood swings. People without COMT mutations are generally more even tempered. Studies of the COMT Val158Met polymorphism have shown the variant affects cognitive tasks rated as executive function, aggression, and working memory and ratings of subjective well-being. The Val158Met variant has also been found to influence the effect of aspirin and vitamin E to lower rates of incident CVD of 40%.

COMT is implicated in ADD/ADHD and bipolar disorders. A functioning FOKI SNP in the VDR gene and/or supplementing with vitamin D enhances dopamine formation.

COMT is important in the metabolism of catechol drugs used in the treatment of hypertension, asthma, and Parkinson disease. Catechol-estrogens like 4-OH estrone, and catechol-containing flavonoids are metabolised by this enzyme, and play a role in the risk of cancer.

Persons with the G allele have an increase in risk of ADD/ADHD, Anxiety, Aggressiveness, Internet Gaming, OCD, Oppositional Defiant Disorder, Panic Disorder, and Pathological Aggression, and an increase in addiction to cannabis, cocaine, glucose (sugar cravings), Nicotine, Opioids, and Stimulants.

Persons with the A allele have an increase in addiction to alcohol, and an increase in stress intolerance / PTSD, homocysteine levels, CVD risk, testosterone requirements, anxiety, neuroticism, and postoperative pain.

SNP outcomes in COMT relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs769224	A	R	**GG**	**--**		CATECHOLAMINES DEGRADATION
rs4633	T	R	**CC**	**--**		RS4680 PAIN SENSITIVITY, PARANOID SCHIZOPHRENIA, HYPERACTIVITY, CHRONIC FATIGUE SYNDROME, ENDOMETRIAL CANCER
rs165774	A	R	**GG**	**--**		HIGH EPINEPHRINE VARIANT, BUT CATALYTICALLY ACTIVE TO DOPAMINE AND NOREPINEPHRINE DEGRADATION
rs4680	A	R	**GG**	**--**		DOPAMINE, STRESS, ESTROGEN BLOOD METABOLITES, BREAST CANCER, PAIN, MEMORY, ATTENTION, WARRIOR VS WORRIER, NICOTINE RESPONSE, PAIN SENSITIVITY, ENDOMETRIAL CANCER, REDUCED CVD RISK ON ASPIRIN AND VITAMIN E
rs6269	G	R	**GG**	**++**		HYPERACTIVITY PARKINSON'S DISEASE SCHIZOPHRENIA MAJOR DEPRESSIVE DISORDER
rs4646312	T	R	**CC**	**--**		ESTROGEN ANDROGEN METABOLIZING

New concepts:

- A *mutation* is an alteration of genetic material such that a new variation is produced.
- A *polymorphism* is a difference in DNA sequence among individuals.
- An *allele* is one of two or more alternative forms of a gene at the same site in a chromosome, which determine alternative characters in inheritance.

CBS

cystathionine-beta-synthase

Cystathionine β-synthase, or the CBS enzyme that begins the transsulfuration pathway to provide sulfur groups needed for detoxification, neuroprotection by making glutathione and hydrogen sulfide, as well as for neurotransmitter and hormone modification. Sulfation can be blocked by non-steroidal anti-inflammatory drugs (e.g. aspirin), tartrazine (yellow food dye) and molybdenum deficiency.

CBS enzyme activation needs pyridoxal-5' phosphate, the active form of vitamin B6. S-adenosyl methionine regulates enzyme activity. The downstream pathway from CBS is the sulfite oxidase enzyme, made by the SUOX gene, requires molybdenum produces sulfates from toxic sulfites. SUOX can be inactivated by tungsten toxicity.

CBS may be upregulated to produce hydrogen sulfide if persists can counter the neuroprotective effects of hydrogen sulfide and deplete cofactors needed to make glutathione. Elevated homocysteine or cysteine may contribute to brain fog. Some CBS SNPs are associated with midline defects.

Issues in the methionine and folate cycle may contribute to depletion of sulfur production in the transsulfation pathway. Other subunits of transsulfation and the sulfation pathways may be involved in neurotoxicity, or neurotransmitter dysregulation.

SNP outcomes in CBS relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs234715	T	R	**GG**	**--**		AUTISM NTD RISK IN HYPOMETHYLATION
rs121964962	T	R	**CC**	**--**		PYRIDOXINE RESISTANT HOMOCYSTEINURIA
rs234709	T	R	**CT**	**-+**		METABOLISM, ARSENIC METABOLISM, LUNG CANCER
rs121964970	T	R	**CC**	**--**		MILD HOMOCYSTEINURIA B-6 REPSONSIVE
rs2298758	A	R	**GG**	**--**		DOWNREGULATION, AUTISM, CLEFT, EHLERS-DANLOS SYNDROME
rs2851391	T	R	**CC**	**--**		BLOOD, METABOLITES, HOMOCYSTEINE, OBESITY
rs121964972	A	R	**GG**	**--**		B6 UNRESPONSIVE
rs4920037	A	R	**GG**	**--**		SLOW TRANSSULFATION
rs1801181	A	B	**AA**	**++**		TRANSSULFATION NO REDUCTION OF ACTIVITY
rs234706	A	B	**AG**	**+-**		NO REDUCTION OF ACTIVITY, B-6 RESPONSIVE, RESPONSIVE TO HCY LOWERING EFFECTS OF FOLIC ACID
rs28934891	T	R	**CC**	**--**		NORMAL CBS ACTIVITY
rs6586282	T	R	**CC**	**--**		HOMOCYSTEINURIA
i5003389	A	R	**GG**	**--**		B6 UNRESPONSIVE

IL13

interleukin 13

IL13 is one of a class of immune hormones known as 'cytokines'. IL13 down-regulates the activity of white blood cells known as 'macrophages', and thereby inhibits the production of pro-inflammatory cytokines and chemokines. This cytokine is found to be critical to the pathogenesis of allergen-induced asthma but operates through mechanisms independent of IgE and eosinophils. Dietary lectins have been shown to produce immunologic reactions due to their ability to stimulate IL13.

SNP outcomes in IL13 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs1295685	A	R	**GG**	**--**		PSORIASIS, AUTOIMMUNE
rs1800925	T	R	**CC**	**--**		IGE, PSORIASIS, AUTOIMMUNE, PEDIATRIC ASTHMA
rs20541	A	R	**GG**	**--**		ELEVATED IGE LEVELS IMMUNOGLOBULIN E, HIGH IGE, PEDIATRIC ASTHMA
rs848	C	R	**CC**	**++**		CROHNS

New concepts:

- *Pathogenesis* is the development of a disease and the chain of events leading to that disease.
- *Cytokines* are chemicals important in cell signaling. They are released by cells and affect the behavior of other cells. Cytokines include chemokines, interferons and interleukins. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes and T lymphocytes.
- A *pathogen* is a bacterium, virus, or other microorganism that can cause disease.

MTHFR

methylenetetrahydrofolate reductase (NAD(P)H)

Perhaps the most studied SNP-containing gene of all, Methylene tetrahydrofolate reductase (MTHFR) allows conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, needed for conversion of homocysteine (HCy) to the protein-building amino acid methionine via methylation, in the rate-limiting step of the methyl cycle. MTHFR is a highly polymorphic gene, and genetic variation influences susceptibility to occlusive vascular disease, neural tube defects, colon cancer and acute leukemia, and mutations in this gene are associated with methylenetetrahydrofolate reductase deficiency. Lower MTHFR enzyme activity results in lower levels of methylated folate, leading to elevated homocysteine (HCy). Natural variation in this gene is common in healthy people. Although some variants have been reported to influence susceptibility to occlusive vascular disease, neural tube defects, Alzheimer's disease and other forms of dementia, colon cancer, and acute leukemia, findings from small early studies have not been consistently reproduced. Two of the most investigated are C677T (rs1801133) and A1298C (rs1801131) single nucleotide polymorphisms (SNPs).

- Individuals with two copies of 677C (677CC) have the most common genotype. 677TT individuals (homozygous) have lower MTHFR activity than CC or CT (heterozygous) individuals.
- 1298AA is the "normal" homozygous, 1298AC the heterozygous, and 1298CC the homozygous for the "variant". The C mutation does not appear to affect the MTHFR protein. It does not result in thermolabile MTHFR and does not appear to affect homocysteine levels. It does, however, affect the conversion of MTHF to BH4 (tetrahydrobiopterin), an important cofactor in the production of neurotransmitters, production of nitric oxide, and detoxification of ammonia.

SNP outcomes in MTHFR relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs1801133	A	R	**GG**	**--**		HOMOCYSTEINE, AUTOIMMUNITY, CANCER MIGRAINE HEADACHE
rs17367504	G	R	**AG**	**-+**		HYPERTENSION, ORTHOSTATIC HYPERTENSION, RESPONSE TO BETA BLOCKERS
rs2274976	T	R	**CC**	**--**		
rs2066470	T	R	**GG**	**--**		HOMOCYSTEINE, CARDIOVASCULAR RISK
rs1999594	A	R	**AA**	**++**		FOLATE TRANSPORTER, LOW SERUM FOLATE, HIGH HOMOCYSTEINE
rs1801131	G	R	**GT**	**+-**		NEUROTRANSMITTER SYNTHESIS

New concepts:

- The *genotype* is the genetic makeup of an individual. Genotype can refer to a person's entire genetic makeup or the alleles at a particular locus
- A *nucleotide* is subunit of DNA or RNA consisting of a nitrogenous base (adenine, guanine, thymine, or cytosine), a phosphate molecule, and a sugar molecule. Thousands of nucleotides are linked to form a DNA or RNA molecule.
- A *homozygous* genotype has the same allele at the same locus (location) on both chromosomes. Homozygous also refers to a genotype consisting of two identical alleles of a gene for a particular trait.
- A *heterozygous* genotype consists of two different alleles of a gene for a particular trait. Individuals who are heterozygous for a trait are referred to as heterozygotes.
- The *rate limiting step* is the slowest step in a metabolic pathway or series of chemical reactions, which determines the overall rate of the other reactions in the pathway.

GSS

glutathione synthetase

Glutathione synthetase (GSS) is the second enzyme in the glutathione biosynthesis pathway, and important factor in Phase II detoxification. Glutathione is important for a variety of biological functions, including protection of cells from oxidative damage by free radicals, detoxification of xenobiotics, and transport of substances across the cell membrane. The protein encoded by this gene functions as a part of the second step of the synthesis of glutathione by the body, which is the conversion of gamma-L-glutamyl-L-cysteine to glutathione, a process which is dependent on the presence of ATP (adenosine triphosphate).

SNP outcomes in GSS relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2273684	G	R	**TG**	-+		
rs28938472	C	R	**TT**	--		HEMOLYTIC ANEMIA
rs6060124	A	R	**AC**	+-		
rs28936396	A	R	**GG**	--		GLUTATHIONE SNTHETASE HEMOLYTIC ANEMIA, NEUROLOGICAL SYMPTOMS, AUTISM

NAT2

N-acetyltransferase 2 (arylamine N-acetyltransferase)

NAT2 encodes a critical Phase II detoxification enzyme that functions to both activate and deactivate arylamine and hydrazine drugs and carcinogens. Polymorphisms in this gene are responsible for the N-acetylation polymorphism in which human populations segregate into rapid, intermediate, and slow acetylator phenotypes. Polymorphisms in this gene are also associated with higher incidences drug toxicity. Carcinogens resulting from grilled and barbequed foods are processed by NAT2 and compromised NAT2 function affords a higher risk for colorectal cancer in those eating well-cooked meats.

SNP outcomes in NAT2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs1801280	C	R	**CT**	+-		SLOW ACETYLATOR PHENOTYPE
rs1495741	G	R	**AG**	-+		SLOW ACETYLATOR
rs1208	G	R	**AG**	-+		NAT K FAST ACETYLATOR
rs1041983	T	R	**CT**	-+		SLOW ACETYLATOR
rs1799929	T	R	**CC**	--		SLOW ACETYLATOR PHENOTYPE

New concepts:

- *Phenotype* is the observable or detectable characteristics of an individual organism--the detectable expression of a genotype.

SULT1A1

sulfotransferase family, cytosolic, 1A, phenol-preferring, member 1

Sulfotransferase enzymes (SULTs) enable the addition of sulfate to many hormones, neurotransmitters, phenolic drugs, and toxic environmental compounds. SULT1A1 is an important phase II detoxificiation enzyme. They have protein-protein interactions with DIO1 and 2 enzymes. In contrast to other Phase II enzymes, SULT1A1 can convert a number of procarcinogens (such as heterocyclic amines from cooked meats) into highly reactive intermediates which may act as chemical carcinogens and mutagens. SULT1A1 helps the safe elimination of acetominophen. Sulfotransferases are inhibited by quercetin, red wine, black and green tea, caffeine and carmoisine in red food coloring.

SNP outcomes in SULT1A1 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs1042157	A	R	**AG**	**+-**		LIVER

SLC6A9

Solute Carrier Family 6 (Neurotransmitter Transporter, Glycine), Member 9

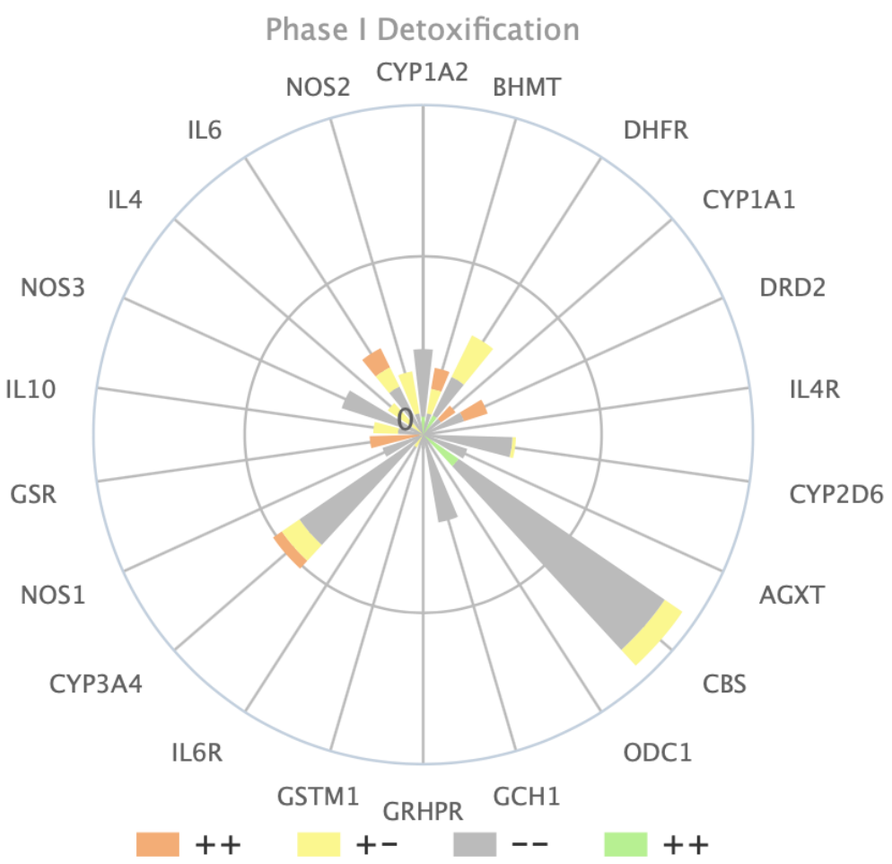
Solute Carrier Family 6 (Neurotransmitter Transporter, Glycine) Member 9 (SLC6A9) is found throughout the human intestine where it is responsible for some 30-50% of glycine uptake into intestinal epithelial cells across the basolateral membrane and appears to function to maintain glycine supply to enterocytes and colonocytes. SLC6A9 may have an essential role in glycine mediated cytoprotection (cell protective role) in intestinal absorptive cells. This may indicate a potential use of glycine for use as an anti-inflammatory, protective agent in the management of inflammatory bowel disease. SLC6A9 glycine and noradrenalin transporter which may potentiate NMDA receptor function, and a diseases associated with SLC6A9 is schizophrenia. Pharmacologically, glycine transporter inhibitors may have applications in the treatment of muscle tone defects, epilepsy, schizophrenia, pain and neurodegenerative disorders.

SNP outcomes in SLC6A9 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs9429225	C	R	**TT**	**--**		GLYCINE TRANSPORTER
rs2248829	A	R	**GG**	**--**		GLYCINE TRANSPORTER
rs7523468	A	R	**GG**	**--**		GLYCINE TRANSPORTER
rs6429644	T	R	**TT**	**++**		GLYCINE TRANSPORTER

New concepts:

- A *receptor* is a molecule in a cell membrane, that responds specifically to a particular neurotransmitter, hormone, antigen, or other substance.



DETOXIFICATION

Phase I Detoxification

Phase I Detoxification reactions transform a toxin into a chemical form that can be metabolized by the phase II detoxification enzymes. Phase I reactions are performed primarily by the cytochrome P450 enzymes (CYP). Some CYP polymorphisms result in an upregulation of the enzyme. Elevated levels of reactive oxygen species (ROS) may be detected by low serum SAM:SAH or low GSH:GSSG ratios. Several factors should to be

considered when aiming to reduce reactive oxygen species byproducts of Phase I:

- Phase I overproduction of ROS, superoxides and hydroxyl radical products by upregulated CYP450 species, due to inducers, cofactor availability (coenzymes and cofactor SNPs) and dietary deficiencies of trace minerals and vitamins, lipid peroxidation triggers including weight loss, infection, lipolysis, toxic metal displacement of cofactors, drug-diet interactions including hormone replacement therapy and birth control pills.
- Uncoupling of NOS resulting in nitrate and peroxynitrite overproduction due to nitric oxide synthase polymorphisms, low BH4:BH2 ratio (tetrahydrobiopterin:dihydrobiopterin from dihydrofolate reductase (DHFR), GTP cyclohydrolase 1 (GCH1), betaine-homocysteine S-methyltransferase (BHMT) polymorphisms.
- Neurotoxic effects of accumulated ammonia due to ornithine decarboxylase (ODC) in the urea cycle or glutathione depletion.
- Methylation issues including methyl trapping (inappropriate mega-dosing methylation supplements), synthetic folate intake, undermethylation (see the methylation scenario for MTHFR, MTR, MTRR, AHCY polymorphisms).
- High cytokine activity due to cytokines induced by chronic infection (H. Pylori, Epstein-Barr virus, Lyme Disease, etc.).
- Sulfation pathway deficiencies due to low protein diet, low nitrogen balance or polymorphisms in cystathionine beta synthase (CBS), sulfite oxidase (SUOX).
- Free radical reduction of xenobiotics, carcinogens, pollutants and drugs by glutathione conjugation by glutathione S-transferase theta 1 (GSTT1) and glutathione S-transferase mu 1 (GSMT1), and glutathione reduction by glutathione reductase (GSR).
- High levels of glyoxal formation or elevated oxalates by glyoxylate reductase/hydroxypyruvate reductase (GRHPR) and alanine-glyoxylate aminotransferase (AGXT) inhibit aldehyde dehydrogenases (ALDH family), GSR, and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) production which increase susceptibility to hydrogen peroxide and disrupt mitochondrial membrane potential.
- Mitochondrial membrane instability due to polymorphisms in cytochrome c oxidase subunit VIIIA (COX8A), NADH dehydrogenases (NDUF family), ubiquinol-cytochrome c reductase core protein II (UQCRC), ATP synthase subunits (ATP5 family), fatty acid dehydrogenase (FADH).

CYP1A2

cytochrome P450, family 1, subfamily A, polypeptide 2

This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are important detoxification enzymes which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Inducers bind to repressors of an enzyme and prevent it from being inhibited. The protein encoded by this gene is found in the endoplasmic reticulum and its expression is induced by some polycyclic aromatic hydrocarbons (PAHs), some of which are found in cigarette smoke. CYP1A2 helps metabolize many drugs, including antidepressants, NSAIDS (naproxen), blood pressure medications (propranolol), melatonin, caffeine and estradiol. It is inhibited by the herb St. John's Wort, tumeric, cumin and grapefruit juice. Production of the CYP1A2 enzyme also appears to be induced by various dietary constituents, including tobacco, broccoli, cabbage, cauliflower, brussels sprouts, echinacea, chargrilled meat, cauliflower and proton pump inhibitor ulcer medications.

CYP450 family member plays a much greater role in the regulation of oxidative stress due to its redox effects. When upregulated it is a major contributor of ROS and major consumer of reducing agent NADPH, important in glutathione recycling.

CYP1A2 is inhibited by saffron but only in males.

SNP outcomes in CYP1A2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs28399424	T	R	**CC**	**--**		DECREASED ACTIVITY, CAFFEINE, COFFEE
rs2069526	G	R	**TT**	**--**		DECREASED ACTIVITY, CAFFEINE, COFFEE
rs762551	A	B	**AA**	**++**		A A IS FAST METABOLIZER IN SMOKERS AND HABITUAL COFFEE DRINKERS
rs12720461	T	R	**CC**	**--**		CAFFEINE, COFFEE, DECREASED CYP1A2 ACTIVITY

New concepts:

- *Oxidative stress* reflects an imbalance between the levels of reactive oxygen species and the body's ability to readily detoxify the reactive intermediates or to repair the resulting damage.

BHMT

betaine--homocysteine S-methyltransferase

The BHMT gene (not BHMT2) provides instructions for making a protein that converts betaine (trimethylglycine) and homocysteine (a byproduct of the amino acid methionine, and toxic at high levels) to dimethylglycine and methionine, respectively. BHMT2 converts homocysteine to methionine, and the cofactor for this conversion is zinc. BHMT2 is inhibited by high levels of methionine, and does not use S-adenosylmethionine (SAMe) as a methyl donor. Defects in the BHMT gene could lead to elevated blood homocysteine levels. The product of this gene is central to the 'short cut' through the methylation cycle in helping to convert homocysteine to methionine. BHMT may therefore play a critical role in homocysteine homeostasis, or balance, when the manufacture of methionine, a folate-dependent process, is compromised by dietary or genetic influences.

The activity of the BHMT gene product can be affected by stress, by cortisol levels, and may play a role in ADD/ADHD through its affect on norepinephrine (adrenaline) levels. Phosphatidylcholine may be indicated.

SNP outcomes in BHMT relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs6875201	G	R	**AG**	**-+**		LIVER, METHYLATION,
rs567754	T	R	**TT**	**++**		FOLATE METABOLISM, FOLATES, HOMOCYSTEINURIA
rs3733890	A	R	**GG**	**--**		CHOLINE, OMPHALOCELE, NEURAL TUBE DEFECTS, NSCL, NSCP, CLEFT LIP, CLEFT PALATE, NONSYNDROMIC, SHORTER TELOMERES, REDUCED RISK OF CORONARY ARTERY DISEASE

New concepts:

- *Homeostasis* is the tendency of a system, especially the physiological system of higher animals, to maintain internal stability, owing to the coordinated response of its parts to any situation or stimulus that would tend to disturb its normal condition or function.

DHFR

dihydrofolate reductase

DHFR is an important enzyme in nucleic and amino acid synthesis and an extensively studied drug target over the past 50 years. It converts dihydrofolate (a form of folic acid) into tetrahydrofolate, an 'active' form of folic acid required for the synthesis of purines, thymidylic acid, and certain amino acids. Tetrahydrofolic acid is a cofactor in many reactions, especially in the metabolism of amino acids and nucleic acids. It acts as a donor of a group with one carbon atom. It gets this carbon atom by sequestering formaldehyde produced in other processes. The conversion of dihydrofolic acid to tetrahydrofolic acid by DHFR ultimately allows for the creation of 5-MTHF, the primary biologically active form of folate used at the cellular level for DNA reproduction, the cysteine cycle and the regulation of homocysteine. Methotrexate and sulfa-containing drugs like sulfamethoxazole and trimethoprim (brand name Septra or Bactrim) or sulfasalazine, or triamterene (found in Dyazide) inhibit DHFR.

Unmetabolized synthetic folic acid also inhibits DHFR. Intakes of synthetic folic acid higher than the Tolerable Upper Intake Level (1.0 mg), whether from a combination of supplements and fortified foods, or from high dose synthetic folic acid administered for therapeutic purposes, will considerably increase exposure to circulating unmetabolized folic acid.

SNP outcomes in DHFR relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs1677693	T	R	**TG**	**+-**		CANCER RISK UNPREDICTABLE WITH METHYLATED B VITAMINS, PRODUCES NADPH AND REDUCED FOLATE
rs1643659	C	B	**TC**	**-+**		PRODUCES NADPH AND REDUCED FOLATE
rs7743761	A	R	**CC**	**--**		PRODUCES NADPH AND REDUCED FOLATE
rs70991108	I	R	**DI**	**-+**		PRODUCES NADPH AND REDUCED FOLATE

CYP1A1

cytochrome P450, family 1, subfamily A, polypeptide 1

Phase I Detoxification reactions transform a toxin into a chemical form that can be metabolized by the phase II detoxification enzymes. CYP1A1 is involved in phase I xenobiotic and drug metabolism (one substrate of it is theophylline). It is inhibited by fluoroquinolones andmacrolides and induced by aromatic hydrocarbons. CYP1A1 is involved in the metabolic activation of aromatic hydrocarbons (polycyclic aromatic hydrocarbons, PAH), for example, benzo(a)pyrene (BP), by transforming it to an epoxide. MSG, arsenic, cadmium and chromium can make this enzyme more active.

CYP40 family members compete for activity and process hormones and xenobiotics variably in patients. CYP450 family member plays a much greater role in the regulation of oxidative stress due to its redox effects. When upregulated it is a major contributor of ROS and major consumer of reducing agent NADPH, important in glutathione recycling. They also plays a major role in cell danger signaling and cell turnover as it interacts electrically with the apoptosis mechanisms controlled by mitochondria.

SNP outcomes in CYP1A1 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2606345	A	R	**AA**	**++**		BILIARY STONES DEPRESSION
rs1799814	T	R	**GG**	**--**		LUNG CANCER, NON-SMALL CELL

New concepts:

- *Apoptosis* is the process of programmed cell death that may occur in multicellular organisms. In contrast to traumatic cell death from cellular injury, apoptosis is a highly regulated and controlled process that confers advantages during an organism's lifecycle.
- *Mitochondria* are a cell constitutent (organelle) found in large numbers in most cells, in which the biochemical processes of respiration and energy production occur.

DRD2

dopamine receptor D2

This gene encodes a dopamine receptor. A missense mutation in this gene causes the rare myoclonus dystonia; other mutations have been associated with schizophrenia.

SNP outcomes in DRD2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs6277	A	R	**AA**	**++**		SCHIZOPHRENIA, SUBSTANCE ABUSE, DOPAMINE

CYP2D6

cytochrome P450, family 2, subfamily D, polypeptide 6

CYP2D6 is a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are phase I detoxifying enzymes which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. CYP2D6 is known to metabolize as many as 25% of commonly prescribed drugs. Its substrates include antidepressants, antipsychotics, analgesics and antitussives, beta adrenergic blocking agents, antiarrythmics and antiemetics. The gene is highly polymorphic in the human population; certain variation result in the poor metabolizer phenotype, characterized by a decreased ability to metabolize the enzyme's substrates. Some individuals with the poor metabolizer phenotype have no functional protein since they carry 2 null alleles whereas in other individuals the gene is absent.

SNP outcomes in CYP2D6 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs5030656	D	R	**II**	**--**		DOUBLE REDUCED METABOLISM
rs5030655	D	R	**II**	**--**		POOR METABOLIZER DEXTROMORPHAN, SPARTEINE, NORTRIPTYLINE, VENLAFAXINE, CODEINE
rs28371725	T	R	**CC**	**--**		POOR METABOLIZER OF TAMOXIFEN, PRE-ECLAMPSIA

GCH1

GTP cyclohydrolase 1

The GCH1 gene provides instructions for making an enzyme called GTP cyclohydrolase 1. This enzyme is involved in the first of three steps in the production of a molecule called tetrahydrobiopterin (BH4). Other enzymes help carry out the second and third steps in this process.

Tetrahydrobiopterin plays a critical role in processing several protein building blocks (amino acids) in the body. For example, it works with the enzyme phenylalanine hydroxylase to convert an amino acid called phenylalanine into another amino acid, tyrosine. Tetrahydrobiopterin is also involved in reactions that produce chemicals called neurotransmitters, which transmit signals between nerve cells in the brain. Specifically, tetrahydrobiopterin is involved in the production of two neurotransmitters called dopamine and serotonin. Among their many functions, dopamine transmits signals within the brain to produce smooth physical movements, and serotonin regulates mood, emotion, sleep, and appetite. Because it helps enzymes carry out chemical reactions, tetrahydrobiopterin is known as a cofactor.

More than 140 mutations in the GCH1 gene have been found to cause dopa-responsive dystonia. This condition is characterized by a pattern of involuntary muscle contractions (dystonia), tremors, and other uncontrolled movements and usually responds to treatment with a medication called L-Dopa. Dopa-responsive dystonia results when one copy of the GCH1 gene is mutated in each cell. Most GCH1 gene mutations that cause this condition change single amino acids in the GTP cyclohydrolase 1 enzyme. Researchers believe that the abnormal enzyme may interfere with the activity of the normal version of GTP cyclohydrolase 1 that is produced from the copy of the gene with no mutation. As a result, the amount of working enzyme in affected individuals is reduced by 80 percent or more. A reduction in functional GTP cyclohydrolase 1 enzyme causes less dopamine and serotonin to be produced, leading to the movement problems and other characteristic features of dopa-responsive dystonia.

At least seven mutations in the GCH1 gene have been found to cause tetrahydrobiopterin deficiency. When this condition is caused by GCH1 gene mutations, it is known as GTP cyclohydrolase 1 (GTPCH1) deficiency. GTPCH1 deficiency accounts for about 4 percent of all cases of tetrahydrobiopterin deficiency.

GTPCH1 deficiency results when two copies of the GCH1 gene are mutated in each cell. Most of the mutations responsible for this condition change single amino acids in GTP cyclohydrolase 1. These mutations greatly reduce or eliminate the activity of this enzyme. Without enough GTP cyclohydrolase 1, little or no tetrahydrobiopterin is produced. As a result, this cofactor is not available to participate in chemical reactions such as the conversion of phenylalanine to tyrosine. If phenylalanine is not converted to tyrosine, it can build up to toxic levels in the blood and other tissues. Nerve cells in the brain are particularly sensitive to phenylalanine levels, which is why excessive amounts of this substance can cause brain damage.

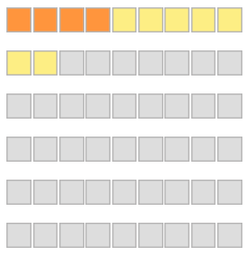
Additionally, a reduction in GTP cyclohydrolase 1 activity disrupts the production of certain neurotransmitters in the brain. Because neurotransmitters are necessary for normal brain function, changes in the levels of these chemicals contribute to intellectual disability in people with GTPCH1 deficiency.

Tetrahydrobiopterin deficiency is more severe than dopa-responsive dystonia likely because both copies of the GCH1 gene are mutated, which leads to a more severe enzyme shortage than in dopa-responsive dystonia, in which only one copy of the gene has a mutation.

SNP outcomes in GCH1 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs3783641	A	R	**TT**	**--**		TETRAHYDROBIOPTERIN BIOSYNTHESIS, HIGHER PAIN TOLERANCE
rs41298442	C	R	**TT**	**--**		DOPA-RESPONSIVE DYSTONIA
rs10483639	C	R	**GG**	**--**		TETRAHYDROBIOPTERIN COMT ACTIVITY

CYP3A4



cytochrome P450, family 3, subfamily A, polypeptide 4

CYP3A4 is an important enzyme in the body, mainly found in the liver and in the intestine. Its purpose is to oxidize small foreign organic molecules (xenobiotics), such as toxins or drugs, so that they can be removed from the body. While many drugs are deactivated by CYP3A4, there are also some drugs which are *activated* by the enzyme. Some substances, such as grapefruit juice and some drugs, interfere with the action of CYP3A4. These substances will therefore either amplify or weaken the action of those drugs that are modified by CYP3A4. This enzyme is involved in the metabolism of approximately half the drugs in use today, including acetaminophen, codeine, cyclosporin A, diazepam and erythromycin. The enzyme also metabolizes some steroids and carcinogens. In 1998, various researchers showed that grapefruit juice, and grapefruit in general, is a potent inhibitor of CYP3A4, which can affect the metabolism of a variety of drugs, increasing their bioavailability. In addition to grapefruit, other fruits have similar effects. Noni (M. citrifolia), for example, is a dietary supplement typically consumed as a juice and also inhibits CYP3A4; pomegranate juice has this effect as well.

CYP40 family members compete for activity and process hormones and xenobiotics variably in patients. CYP450 family member plays a much greater role in the regulation of oxidative stress due to its redox effects. When upregulated it is a major contributor of ROS and major consumer of reducing agent NADPH, important in glutathione recycling. They also plays a major role in cell danger signaling and cell turnover as it interacts electrically with the apoptosis mechanisms controlled by mitochondria.

SNP outcomes in CYP3A4 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs28371759	G	R	**AA**	**--**		INCREASED ACTIVITY
rs4986910	G	R	**AA**	**--**		
rs55785340	G	R	**AA**	**--**		
rs3091339	C	R	**TT**	**--**		
rs2740574	C	R	**TT**	**--**		INCREASED ACTIVITY
rs55901263	C	R	**GG**	**--**		
rs2246709	G	R	**AA**	**--**		
rs4646437	A	R	**AG**	**+-**		DRUG METABOLISM

GSR

glutathione reductase

GSR is a central enzyme of cellular antioxidant defense. Glutathione plays a key role in maintaining proper function and preventing oxidative stress in human cells. It can act as a scavenger for hydroxyl radicals, singlet oxygen, and various electrophiles. Reduced glutathione reduces the oxidized form of the enzyme glutathione peroxidase, which in turn reduces hydrogen peroxide (H2O2), a dangerously reactive species within the cell. In addition, it plays a key role in the metabolism and clearance of xenobiotics, acts as a cofactor in certain detoxifying enzymes, participates in transport, and regenerates antioxidants such and Vitamins E and C to their reactive forms. Some patients exhibit deficient levels of glutathione activity as a result of not consuming enough riboflavin in their diets.

SNP outcomes in GSR relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs3594	A	R	**AA**	**++**		ANEMIA, AUTISM
rs2551715	C	R	**CC**	**++**		LUPUS

New concepts:

- *Singlet oxygen* is a high energy form of oxygen. Singlet oxygen is one of the reactive oxygen species, which is linked to oxidation of LDL cholesterol and resultant cardiovascular effects.
- In chemistry, an *electrophile* (literally electron lover) is a molecule attracted to electrons. It participates in a chemical reaction by accepting an electron pair in order to bond to a other molecules that want to give them up.

NOS3

nitric oxide synthase 3 (endothelial cell)

NOS3 provides instructions for making a protein that produces nitric oxide (NO). This is a free radical, a molecule with a missing electron that can cause damage by oxidation when in excess inside the cells, but it is also essential for many functions within the body such as neurotransmitter function and helping the body deal with microbes and tumors. NOS3 is needed for normal urea cycle function and responsible for regulation of sulfate production for lipid oxidation sparing membrane-bound cholesterol sulfate vs. nitric oxide production in acute infection.

This enzyme is one of three similar types of protein that synthesize NO. The NO produced by NOS3 is known as endothelial NOS, or eNOS, and is mainly responsible for allowing the muscles of the blood vessels to relax. It is also important in cellular reproduction and in enabling the function of white blood cells and platelets.

Other types of nitric oxide synthases, NOS1 (nNOS) and NOS2 (iNOS) are more specific to the nervous system and immune defense against pathogens.

Impaired NO production is involved in the development of several diseases such as high blood pressure, pre-eclampsia, diabetes mellitus, obesity, erectile dysfunction, and migraine. Aluminum, mercury, lead and glyphosate may dysrupt endothelial Nitric oxide synthase function causing cellular injury by glycation or oxidative damage in cardiovascular disorders.

SNP outcomes in NOS3 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs7830	T	R	**GG**	**--**		ENOS
rs1800779	G	R	**AA**	**--**		ENOS, HYPOXIC-ISCHEMIC ENCEPHALOPATHY, LEUKOARAIOSIS
rs1800783	A	R	**TT**	**--**		DECREASED ENDOTHELIAL NITRIC OXIDE SYNTHASE ACTIVITY, DIABETIC NEPHROPATHY
rs2070744	C	R	**TT**	**--**		ENDOTHELIAL NOS, RECURRENT MISCARRIAGE, NEURALGIA-INDUCING CAVITATIONAL OSTEONECROSIS OF THE JAWS (NICO) FOR HOMOZYGOUS TT

IL6

interleukin 6 (interferon, beta 2)

IL6 is a cell signalling protein activated in response to various inflammatory triggers. A mutated SNP causes a fixed response with or without inflammatory triggers. Normally IL6 is a signalling protein secreted by T cells and macrophages to stimulate immune response, e.g. during infection and after trauma, especially burns or other tissue damage leading to inflammation, either an acute and chronic inflammation response. A mutated gene will induce chronicity.

IL6 encodes a cytokine that functions in inflammation and the maturation of B lymphocyte cells. In addition, the protein encoded by IL6 has been shown to be an endogenous pyrogen capable of inducing fever in people with autoimmune diseases or infections. The protein is primarily produced at sites of acute and chronic inflammation, where it is secreted into the serum and induces a transcriptional inflammatory response through interleukin 6 receptor, alpha. The functioning of this gene is implicated in a wide variety of inflammation-associated disease states, including suspectibility to diabetes mellitus and systemic juvenile rheumatoid arthritis.

Polymorphism (-174CC) predicts greater severity of common cold symtoms.

SNP outcomes in IL6 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2069837	G	R	**AA**	**--**		INFLAMMASOME CHRONIC HBV
rs2066992	T	R	**GT**	**-+**		INFLAMMASOME CHRONIC HBV
rs1800795	C	R	**GG**	**--**		HRV & RSV SEVERITY OF SYMPTOMS, ISCHEMIC STROKE, FIBRINOGEN LEVELS, HETEROZYGOUS SHOWED LESS EXPRESSED HSP70, DIABETES, CANCER, HYPERTENSION, ALZHEIMER'S, PERIODONTITIS, SUDDEN INFANT DEATH, CELIAC DISEASE IN GIRLS
rs2069852	G	R	**GG**	**++**		INFLAMMASOME CHRONIC HBV

New concepts:

- *Interleukins* are one of a large group of proteins produced mainly by T lymphocyte cells. Interleukins participate in communication among leukocytes and are important in the inflammatory response.
- *Transcription* is the first step of gene expression, in which a particular segment of DNA is copied into RNA

NOS2

nitric oxide synthase 2, inducible

NOS2 provides instructions for making a protein that produces nitric oxide (NO) from the amino acid arginine. NO is a free radical, a molecule with a free electron that can cause damage by oxidation, but it is also essential for many functions within the body such as neurotransmitter function and helping the body deal with microbes and tumors.

This enzyme is one of three similar types of protein that synthesize NO. The NO produced by NOS2 is known as inducible NOS, or iNOS, and is produced in large quantities when needed as an oxidant in immune defense.

Other types of nitric oxide synthases, NOS1 (nNOS) and NOS3 (eNOS) are more specific to the nervous system and blood circulation.

Impaired NO production is involved in the development of several diseases such as high blood pressure, pre-eclampsia, diabetes mellitus, obesity, erectile dysfunction, and migraine.

SNP outcomes in NOS2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2248814	A	R	**AG**	**+-**		IMMUNE NOS
rs2297518	A	R	**GG**	**--**		IMMUNE NOS
rs2274894	T	R	**TG**	**+-**		IMMUNE NOS

SUOX

sulfite oxidase

Downstream from the cystathionine beta synthase enzyme (CBS) is the sulfite oxidase enzyme, made by the SUOX gene. This requires molybdenum to produce sulfates from toxic sulfites. SUOX can be inactivated by tungsten toxicity. Sulfite sensitivity to sulfite-containing dried fruits and wines can be caused by SUOX mutations or from the bottleneck effect of up regulated transsulfation (CBS pathway) due to hyperglycemia (high blood sugar), infection and other conditions of oxidative stress.

SNP outcomes in SUOX relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs7297662	A	R	**AG**	**+-**		LEUKEMIAS IN TUNGSTEN AND ARSENIC TOXICITY

DETOXIFICATION

MULTI-SNP MACROS

CYP1A2 fast metabolizer

Genes	CYP1A2
Repute:	BENEFIT
Magnitude:	2
Frequency:	N/A

INTERPRETATION: You are a 'CYP1A2 fast metabolizer'. One well-known agent metabolized by CYP1A2 is caffeine; individuals who carry one or more CYP1A2 alleles are "slow" caffeine metabolizers, whereas carriers of the variant CYP1A2 are "fast" caffeine metabolizers. The same amount of caffeine will therefore tend to have more stimulating effect on CYP1A2 slow metabolizers than on you (a CYP1A2 fast metabolizer.) CYP1A2 metabolism is increased when CYP1A2 fast metabolizers consume coffee, cigarettes or omeprazole, whereas these substrates have less effect on slow metabolizers.

This algorithm is **true** and applies to you

Your results: rs762551 (**AA**) rs12720461 (**CC**) rs2069526 (**TT**) rs28399424 (**CC**)

CYP2D6*39 Normal Metabolizer

Genes	CYP2D6
Repute:	BENEFIT
Magnitude:	1
Frequency:	N/A

INTERPRETATION: You are a CYP2D6*39 'Normal Metabolizer.' The type of CYP2D6 function may influence your response to different doses of drugs that CYP2D6 metabolizes. The nature of the effect on the drug response depends not only on the type of CYP2D6 function, but also on the extent to which processing of the drug by CYP2D6 results in a chemical that has an effect that is similar, stronger, or weaker than the original drug, or no effect at all.

This algorithm is **true** and applies to you

Your results: rs1135840 (**GC**) rs16947 (**N/A**)

NAT2 Intermediate Metabolizer

Genes	NAT2
Repute:	NEUTRAL
Magnitude:	1
Frequency:	N/A

INTERPRETATION: You are a 'NAT2 intermediate metabolizer'. Generally this means you carry one rapid (normal) NAT2 allele plus one slow allele. This appears to be the most common form. Intermediate metabolizer may benefit by slightly lower than average drug dosages of the drugs metabolized by NAT2 for optimal therapeutic response. NAT2 is a phase II detoxifying enzyme that performs its work by 'acetylating' toxic compounds, allowing them to be excreted through the organs of elimination.

This algorithm is **true** and applies to you

Your results: rs1041983 (**CT**) rs1801280 (**CT**) rs1799929 (**CC**) rs1799930 (**AG**) rs1208 (**AG**) rs1799931 (**GG**) rs1495741 (**AG**)

Detoxification macro algorithms returning as false:

- CYP2D6*2 normal metabolism
- CYP2D6*7 double reduced metabolism
- GSTM1 'Null' Genotype
- CYP2C19 Extensive or Ultra-Fast Metabolizer
- CYP2D6*8 double reduced metabolism
- CYP2D6*10 reduced metabolism
- CYP2C9 poor metabolizer
- CYP3A5 non-expressor
- CYP2D6*41 decreased metabolism
- CYP2D6*6A poor metabolizer
- Poor warfarin metabolizer
- NAT2 Rapid Metabolizer
- NAT2 Slow Metabolizer
- CYP2D6*10 poor metabolizer
- CYP2D6*6A reduced metabolism
- CYP2C9 Intermediate Metabolizer
- Possible CYP3A5 non-expressor
- CYP2C19 normal/rapid metabolizer
- CYP1A2 'slow metabolizer' Caffeine sensitivity
- Intermediate warfarin metabolizer
- CYP2D6*8 reduced metabolism
- CYP2D6*9 double reduced metabolism
- CYP2D6*8 poor metabolizer

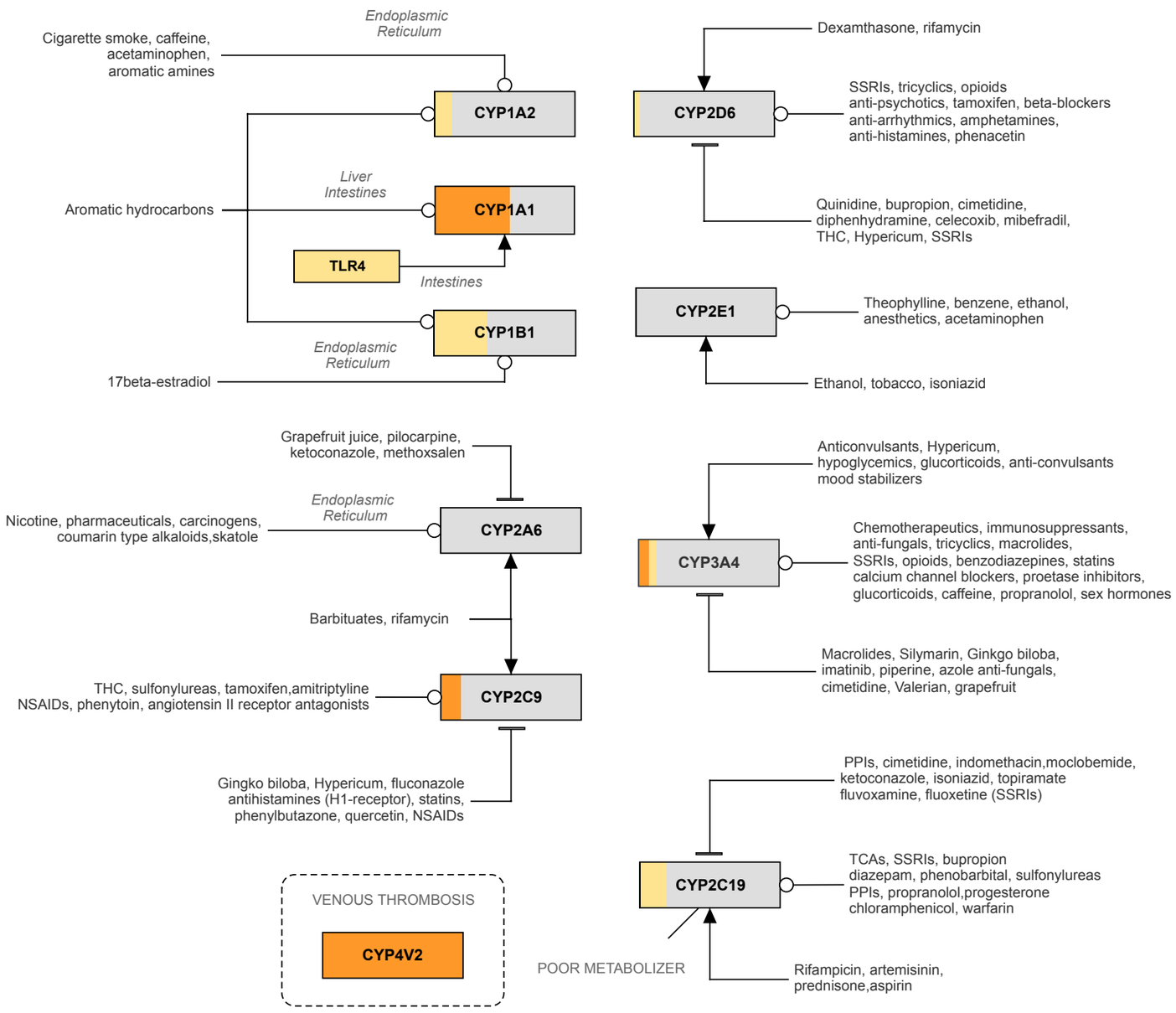
DETOXIFICATION

NETWORK MAPS

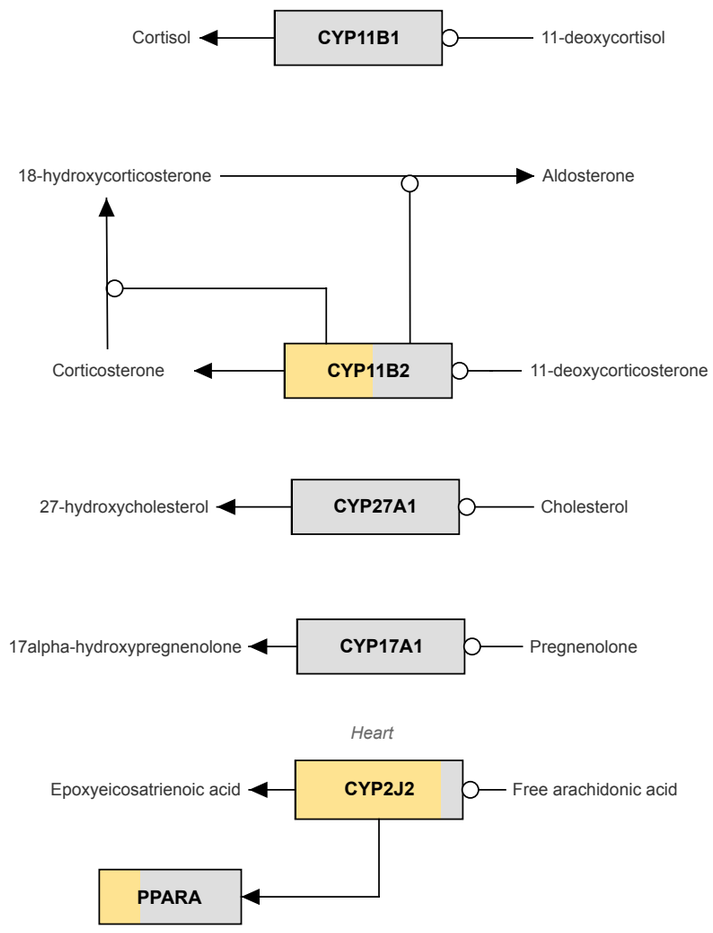
Network maps allow you to visualize how certain gene pathways interact and contribute to health maintenance. These network maps allows you to visualize your genomic data directly in a number of hand-curated pathway maps. Boxes in the map generally depict genes, and the box color(s) are determined by the percentage of SNP values that are homozygous recessive for risk (orange), heterozygous for risk (yellow) and negative for risk (gray).

Phase I: Cytochrome Metabolome

XENOBIOTIC FUNCTIONALIZATION

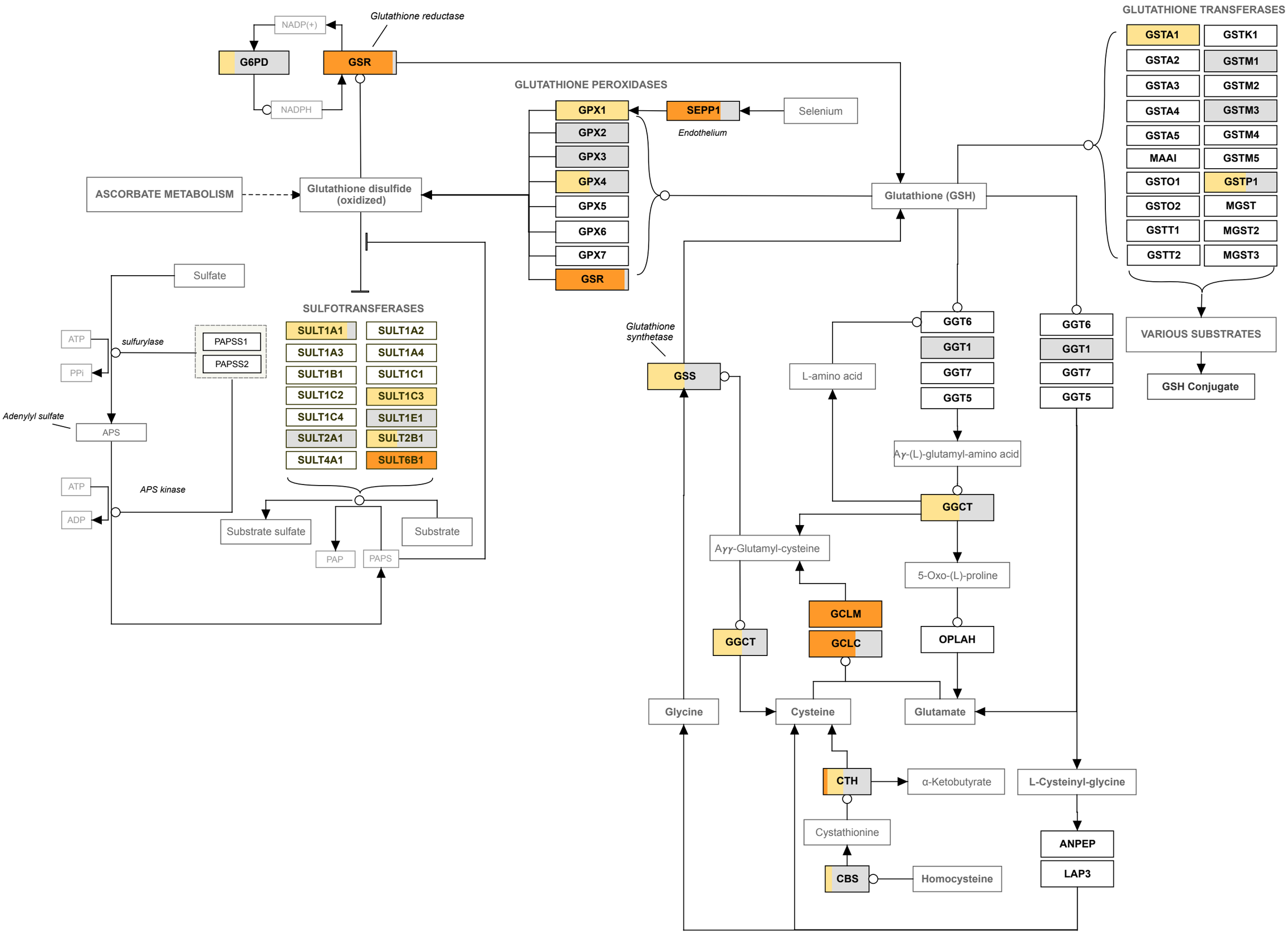


STEROL/ FATTY ACID FUNCTIONALIZATION



Phase II: Glutathione Conjugation and Sulfation

Phase II detoxification is called the 'conjugation pathway', whereby the liver cells add another substance (such as the amino acids cysteine, glycine or a sulphur molecule) to a toxic chemical or drug, which renders it less harmful. Phase II reactions conjugate (attach) the toxin to other water-soluble substances to increase its solubility. Each of the different types of phase II enzymes catalyzes a different type of conjugation reaction. This makes the toxin or drug water-soluble, so it can then be excreted from the body via watery fluids such as bile or urine.



NATURAL PRODUCTS

This section lists the top 25 natural products that may be worthy of attention as potentially valuable therapeutic agents:

RANK	AGENT	INDICATION VALUE
1.	Resveratrol	
2.	Sulforaphane	
3.	Curcumin	
4.	Theanine	
5.	Co-enzyme Q10	
6.	Vitamin B-9 (folic acid)	
7.	Vitamin B-2 (riboflavin)	
8.	Rhodiola rosea	
9.	Quercetin	
10.	Green Tea, Kukicha, Bancha	
11.	Pyridoxal 5' phosphate	
12.	Sea Vegetables, Spirulina	
13.	Glutathione	
14.	Epigallocatechin gallate (EGCG)	
15.	Silymarin	
16.	Eicosapentaenoic acid (EPA)	
17.	Citral	
18.	Cannabidiol	
19.	Betaine	
20.	N-acetylcysteine (NAC)	
21.	Multivitamin	
22.	Ginkgo (Ginkgo biloba)	
23.	Alpha-Linolenic acid ALA	
24.	Linoleic acid	
25.	Omega 3 Fatty Acids	

DRUG INTERACTIONS

This section documents potential drug interactions or complications you may be genetically susceptible to.

DRUG	SNP	GENE	RISK ALLELE	YOUR GENOTYPE	SIDE EFFECT
Acitretin	rs7412	APOE	C	**CC**	Psoriasis
Amitriptyline	rs4244285	CYP2C19	A	**AG**	Those with the AA or AG genotype are poor metabolizers of amitriptyline
Azathioprine	rs1800460	TPMT	T	**CT**	Hepatotoxicity
Azathioprine	rs1142345	TPMT	C	**CT**	Hepatotoxicity
Azathioprine	rs1142345	TPMT	C	**CT**	Patients with CC or CT genotype have decreased inactivation of thiopurines and increased risk of toxicity
Carbamazepine	rs3909184	FLOT1	G	**GG**	Patients with the CG or GG genotype (in Asian patients) were at a higher risk of Steven-Johnson Syndrome compared to those with the CC genotype (non-carriers of HLA-b*1502)
Cisplatin	rs1695	GSTP1	A	**AG**	Tinnitus, hearing impairment, Raynaud syndrome
Clobazam	rs4244285	CYP2C19	G	**AG**	Clobazem is metabolized into N-desmethylclobazem (NCLB) mostly by CYP3A4. NCLB is primarily metabolized by 2C19. Those with one 2C19*2 allele mutation (1*/2*) are intermediate metabolizers of NCLB. Those with two (2*/2*) mutations will metabolize NCLB poorly in comparisone to extensive metabolizers (1*/1*). Levels of NCLB can be five times higher in poor metabolizers, and two times higher in intermediate metabolizers as compared to individuals who are extensive metabolizers. The safety and efficacy of clobazem may be affected by polymorphic expression of CYP2C19*2.
Cyclosporine	rs231775	CTLA4	A	**AG**	Gingival overgrowth, periodontal disease
Fluorouracil	rs1695	GSTP1	A	**AG**	Hematological toxicity, gastrointestinal toxicity
Gefitinib	rs2231142	ABCG2	T	**GT**	Diarrhea
Gefitinib	rs2231142	ABCG2	T	**GT**	In non-small lung cancer patients, those that are heterozygous (ABCG2 421C>A) have a higher risk of diarrhea.
Irinotecan	rs4149056	SLCO1B1	C	**CT**	Diarrhea, leucopenia, neutropenia
Isoniazid	rs6413419	CYP2E1	GG	**GG**	Hepatotoxicity
Mercaptopurine	rs1800460	TPMT	T	**CT**	Hepatotoxicity
Mercaptopurine	rs1142345	TPMT	C	**CT**	Hepatotoxicity
Venlafaxine	rs5030655	CYP2D6	I	**II**	Nausea, vomiting diarrhea
Almotriptan	rs5443	GNB3	T	**CT**	Better response to drug treatment
Citalopram	rs1954787	GRIK4	C	**CC**	Improved response to antidepressant medication
Clopidogrel	rs4244285	CYP2C19	A	**AG**	Patients are poor metabolizers of clopidogrel. More likely to experience poor cardiovascular outcomes.
Clopidogrel	rs4244285	CYP2C19	A	**AG**	Patients are poor metabolizers of clopidogrel. More likely to experience poor cardiovascular outcomes.
Codeine	rs5030655	CYP2D6	I	**II**	Poor drug metabolizer, lower dose requirements
Dextromethorphan	rs5030655	CYP2D6	II	**II**	Poor drug metabolizer, lower dose requirements
Eletriptan	rs5443	GNB3	T	**CT**	Better response to drug treatment
Frovatriptan	rs5443	GNB3	T	**CT**	Better response to drug treatment
Infliximab	rs1801274	FCGR3A	GG	**GG**	Better ACR20 response
Modafinil	rs4680	COMT	GG	**GG**	Those with the GG genotype respond better to drug therapy (improved vigor and well being). Those with the AA genotype do not respond well to drug therapy
Morphine	rs1799971	OPRM1	A	**AA**	Better response to pain relief drugs
Naratriptan	rs5443	GNB3	T	**CT**	Better response to drug treatment
Rizatriptan	rs5443	GNB3	T	**CT**	Better response to drug treatment

Rosuvastatin	rs2231142	ABCG2	T	GT	Greater response to drug therapy
Sildenafil	rs5443	GNB3	T	CT	Better response to drug treatment
Sumatriptan	rs5443	GNB3	T	CT	Better response to drug treatment
Trastuzumab	rs351855	FGFR4	G	AG	Reduced response to herceptin
Venlafaxine	rs5030655	CYP2D6	I	II	Poor drug metabolizer, lower dose requirements, nausea, vomiting and diarrhea
Venlafaxine	rs5030655	CYP2D6	I	II	Poor drug metabolizer, lower dose requirements, nausea, vomiting and diarrhea
Zolmitriptan	rs5443	GNB3	T	CT	Better response to drug treatment