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

COGNITION

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

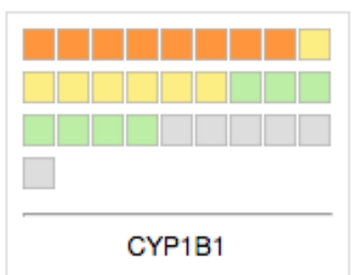
When it comes to a particular disease or syndrome, most SNPs have rather small ORs. This does not mean that they are unworthy of attention, but rather that the findings must be interpreted as part of an integrated whole, including: other SNP results that also support the conclusion; lifestyle factors; 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:

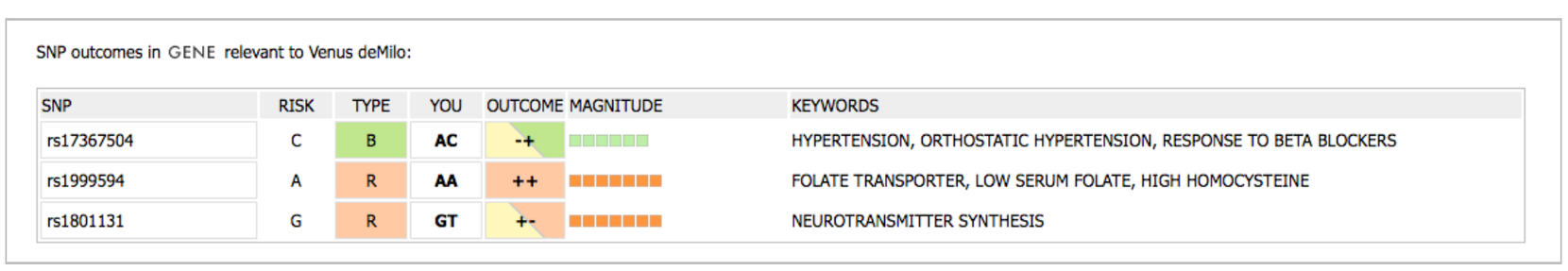
The data provided by Opus23 Explorer is for informational purposes only and is not designed or intended to suggest the treatment or diagnosis of any disease or condition. Opus23 Explorer and Datapunk Bioinformatics, LLC, take no responsibility for any harm arising from incorrect data being uploaded to 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.

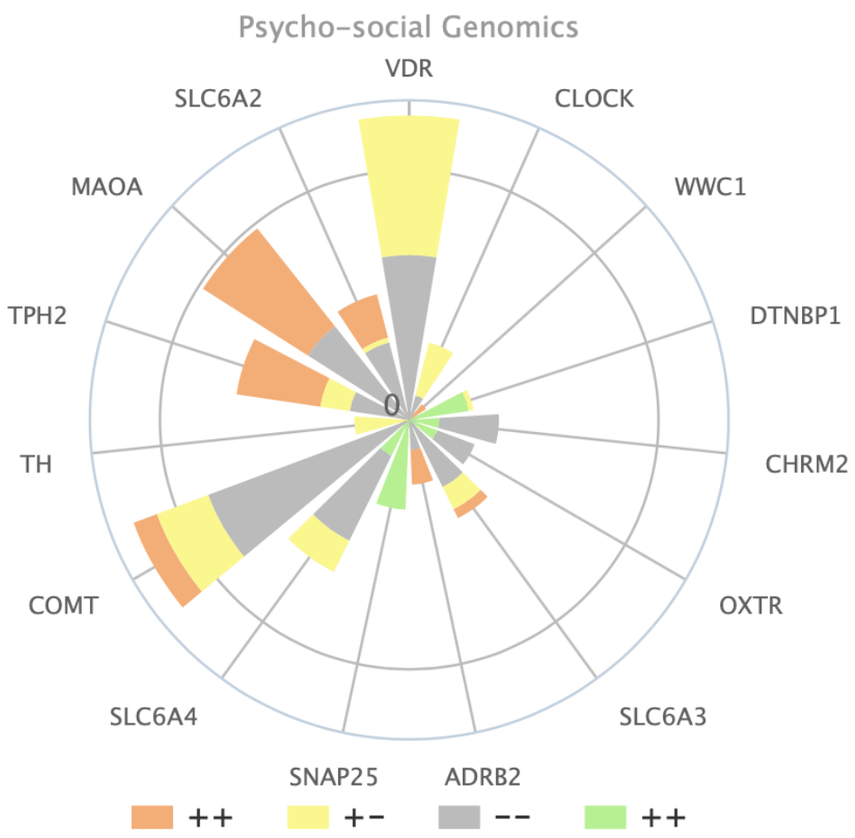
For example, a simple macro to determine if you should get out of bed might be:

- 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.

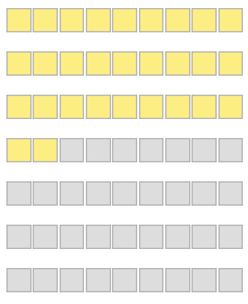


COGNITION

Psycho-social Genomics

Humans are social creatures, though some more than others. Even in infancy, humans vary dramatically in their proclivity to seek and accept comfort from caregivers. These ordinary variations, readily observable in infancy, are associated with a wide range of individual differences in psychological functioning in adults. Infants who rely on their caregivers with ease and confidence, compared with infants who do not, are more likely to experience stronger cognitive and language development , healthier interpersonal relations, and decreased risk of later mental health problems such as mood disorders, externalizing disorders, and dissociative and attentional disorders. Although scientists have devoted considerable effort to identifying the foundations of these differences, much remains unknown. Intelligence has been one of the most studied quantitative behavioral traits for more than 100 years. We are only now becoming able to identify genomic areas of interest which may help determine cognitive ability, preference in types of learning and memory.

VDR



vitamin D (1,25- dihydroxyvitamin D3) receptor

The VDR gene provides instructions for making a protein called vitamin D receptor (VDR), which allows the body to respond appropriately to vitamin D. This vitamin can be acquired from foods in the diet or made in the body with help from sunlight. Vitamin D is involved in maintaining the proper balance of several minerals in the body, including calcium and phosphate, which are essential for the normal formation of bones and teeth. One of vitamin D's major roles is to control the absorption of calcium and phosphate from the intestines into the bloodstream. Vitamin D is also involved in several process unrelated to bone formation.

VDR attaches (binds) to the active form of vitamin D, known as calcitriol. This interaction allows VDR to partner with another protein called retinoid X receptor (RXR). The resulting complex of proteins then binds to particular regions of DNA, known as vitamin D response elements, and regulates the activity of vitamin D-responsive genes. By turning these genes on or off, VDR helps control calcium and phosphate absorption and other processes.

A VDR variant FokI is involved with Blood sugar regulation. Certain VDR mutations oppose COMT mutations in the regulation of dopamine levels. A VDR TaqI++ mutation means that a person is less sensitive to mood swings when taking methyl group supplement levels. A VDR Taq1 mutation can result in behaviors opposite to certain COMT mutations.

The vitamin D receptor plays an important role in regulating the hair cycle. Loss of VDR is associated with hair loss in experimental animals. Glucocorticoids are known to decrease expression of VDR, which is expressed in most tissues of the body and regulate intestinal transport of calcium, iron and other minerals. The VDR BsmI variant has been associated with low bone mineral density and osteoporosis.

Mutations in the VDR gene cause vitamin D-dependent rickets type 2 (VDDR2), also known as hereditary vitamin D-resistant rickets (HVDRR). This disorder of bone development is characterized by low levels of calcium (hypocalcemia) and phosphate (hypophosphatemia) in the blood, which lead to soft, weak bones (rickets) that are prone to fracture. A common feature of this condition is bowed legs.

The VDR gene mutations that cause this condition prevent the VDR protein from functioning properly. Some changes in the VDR gene lead to an abnormally short version of the VDR protein; others result in the production of an abnormal receptor that cannot bind to calcitriol, to RXR, or to DNA. Despite plenty of calcitriol in the body, the altered VDR cannot stimulate gene activity important for mineral absorption. The lack of calcium and phosphate absorption in the intestines slows deposition of these minerals into developing bone (bone mineralization), which leads to soft, weak bones and other features of VDDR2. Hypocalcemia also causes muscle weakness and seizures in some affected individuals. Most VDR gene mutations impair hair growth, leading to alopecia; however, mutations that block VDR's ability to interact with calcitriol do not cause alopecia, indicating that calcitriol is not necessary for the receptor's role in hair development.

SNP outcomes in VDR relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs3847987	A	R	**CC**	**--**		COPD, PULMONARY, LUNG, VITAMIN D, T1D, TYPE 1 DIABETES, DIABETES, DEFICIENCY, CHRONIC OBSTRUCTIVE PULMONARY DISEASE
rs731236	G	R	**AG**	**-+**		TAQ1 DOPAMINE SYNTHESIS, BREAST CANCER SUSCEPTIBILITY
rs1540339	T	R	**CC**	**--**		INCREASED CYP1A2 ACTIVITY
rs2238135	G	R	**CC**	**--**		CANCER
rs1544410	T	R	**CT**	**-+**		BONE DENSITY RESPONSE TO ESTROGENS AND ALENDRONATE, HASHIMOTOS THYROIDITIS, INFERTILITY
rs7139166	G	R	**CG**	**-+**		
rs4516035	T	R	**CT**	**-+**		MELANOMA
rs2107301	A	R	**GG**	**--**		CANCER

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 *receptor* is a molecule in a cell membrane, that responds specifically to a particular neurotransmitter, hormone, antigen, or other substance.
- A *mutation* is an alteration of genetic material such that a new variation is produced.
- A *methyl group* is one of the commonest structural units of organic compounds, consisting of three hydrogen atoms bonded to a carbon atom, which is linked to the remainder of the molecule.
- *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.

CLOCK

clock homolog (mouse)

The protein encoded by CLOCK plays a central role in the regulation of circadian rhythms. Polymorphisms in this gene may be associated with behavioral changes in certain populations and with obesity and metabolic syndrome. CLOCK protein has been found to play a central role as a transcription factor in the circadian pacemaker. CLOCK has been implicated in sleep disorders, metabolism, pregnancy, and mood disorders. Circadian rhythms allow organisms to anticipate and prepare for precise and regular environmental changes, usually in alignment with the cycles of light and darkness. Studies have shown that light has a direct effect on human health because of the way it influences the circadian rhythms.

SNP outcomes in CLOCK relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs6832769	A	R	**AG**	**+-**		LESSENED AGREEABLNESS
rs3749474	T	R	**CT**	**-+**		DIETARY FAT RESTRICTION
rs1801260	G	R	**AA**	**--**		ADHD, CIRCADIAN RHYTHM, SLEEP, PATTERN, HEART, CORONARY ARTERY DISEASE

New concepts:

- *Transcription* is the first step of gene expression, in which a particular segment of DNA is copied into RNA
- A *Circadian rhythm* is a daily rhythmic activity cycle, based on 24-hour intervals, that is exhibited by many organisms.

WWC1

WW and C2 domain containing 1

The protein encoded by this gene is a cytoplasmic phosphoprotein that interacts with PRKC-zeta and dynein light chain-1. Alleles of this gene have been found that enhance memory in some individuals. Three transcript variants encoding different isoforms have been found for this gene.
SNP outcomes in WWC1 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs17070145	C	R	**CC**	**++**		REDUCED MEMORY PERFORMANCE

New concepts:

- *Cytoplasm* is the material or protoplasm within a living cell, excluding the nucleus.

CHRM2

cholinergic receptor, muscarinic 2

The muscarinic cholinergic receptor 2 (CHRM2) is involved in mediation of bradycardia and a decrease in cardiac contractility. Variation have been linked to stress-related health issues, depression and over-activation of the hypothalamus-pituitary axis (fight or flight response).

SNP outcomes in CHRM2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
No significant SNP mutations to report						

SLC6A3

solute carrier family 6 (neurotransmitter transporter, dopamine), member 3

This gene encodes a dopamine transporter which is a member of the sodium- and chloride-dependent neurotransmitter transporter family. The 3' UTR of this gene contains a 40 bp tandem repeat, referred to as a variable number tandem repeat or VNTR, which can be present in 3 to 11 copies. Variation in the number of repeats is associated with idiopathic epilepsy, attention-deficit hyperactivity disorder, dependence on alcohol and cocaine, susceptibility to Parkinson disease and protection against nicotine dependence.
SNP outcomes in SLC6A3 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs27072	T	R	**CC**	**--**		DOPAMINE TRANSPORTER BIPOLAR, PROTECTIVE AGAINST ADHD, NICOTINE DEPENDENCE
rs464049	A	R	**GG**	**--**		DOPAMINE TRANSPORTER, SCHIZOPHRENIA

New concepts:

- The term *idiopathic* denotes any disease or condition that arises spontaneously or for which the cause is unknown.

ADRB2

adrenergic, beta-2-, receptor, surface

This gene encodes beta-2-adrenergic receptor which is a member of the G protein-coupled receptor superfamily. This receptor is directly associated with one of its ultimate effectors, the class C L-type calcium channel Ca(V)1.2. This receptor-channel complex also contains a G protein, an adenylyl cyclase, cAMP-dependent kinase, and the counterbalancing phosphatase, PP2A. The assembly of the signaling complex provides a mechanism that ensures specific and rapid signaling by this G protein-coupled receptor. This gene is intronless. Different polymorphic forms, point mutations, and/or downregulation of this gene are associated with nocturnal asthma, obesity and type 2 diabetes.

SNP outcomes in ADRB2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs1042714	G	R	**CC**	**--**		HYPERTENSION, DIET, OBESITY, ASTHMA, VENOUS THROMBOEMBOLISM, AUTISM, STROKE, ISCHEMIC STROKE, ATENOLOL AND BETA BLOCKER RESPONSE
rs1042713	A	R	**AA**	**++**		OBESITY, SERUM HOMOCYSTEINE HYPERTENSION, EXERCISE, ASTHMA, INHALER, PEDIATRIC ASTHMA,

New concepts:

- *Introns* are sections of DNA in-between the protein-coding sequences of a gene; these sequences are transcribed into RNA but are cut out of the message before it is translated into protein. Sometimes (erroneously) called 'Junk DNA'.
- *Ribonucleic acid (RNA)* is a chemical found in the nucleus and cytoplasm of cells; it plays an important role in protein synthesis and other chemical activities of the cell.

SNAP25

synaptosomal-associated protein, 25kDa

Synaptic vesicle membrane docking and fusion is mediated by SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) located on the vesicle membrane (v-SNAREs) and the target membrane (t-SNAREs). The assembled v-SNARE/t-SNARE complex consists of a bundle of four helices, one of which is supplied by v-SNARE and the other three by t-SNARE. For t-SNAREs on the plasma membrane, the protein syntaxin supplies one helix and the protein encoded by this gene contributes the other two. Therefore, this gene product is a presynaptic plasma membrane protein involved in the regulation of neurotransmitter release. Two alternative transcript variants encoding different protein isoforms have been described for this gene. [provided by RefSeq, Jul 2008]

SNP outcomes in SNAP25 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs363043	T	B	**TT**	**++**		INTELLIGENCE / IQ (NON-VERBAL)
rs363050	A	B	**AA**	**++**		INTELLIGENCE / IQ (NON-VERBAL)
rs363039	G	B	**GG**	**++**		INTELLIGENCE / IQ (NON-VERBAL)

SLC6A4

solute carrier family 6 (neurotransmitter transporter, serotonin), member 4

SLC6A4 encodes a protein that terminates the action of serotonin and recycles it in a sodium-dependent manner. This protein is a target of psychomotor stimulants, such as amphetamines and cocaine, and is a member of the sodium:neurotransmitter symporter family. A repeat length polymorphism in the promoter of this gene has been shown to affect the rate of serotonin uptake and may play a role in sudden infant death syndrome, aggressive behavior in Alzheimer disease patients, and depression-susceptibility in people experiencing emotional trauma. The activation region of the SLC6A4 gene contains a polymorphism with "short" and "long" repeats in a region: 5-HTT-linked polymorphic region (5-HTTLPR or SERTPR). The short variation has 14 repeats of a sequence while the long variation has 16 repeats. The short variation leads to less transcription for SLC6A4, and it has been found that it can partly account for anxiety-related personality traits.

SNP outcomes in SLC6A4 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs25532	G	R	--	--		MAJOR ALLELE OBSESSIVE COMPULSIVE DISORDER (OCD) HAPLOTYPE FROM HIGHER SEROTONIN TRANSPORT FUNCTION, ALCOHOL DEPENDENCE
rs216250	A	R	**GG**	--		SEROTONIN TRANSPORTER, GABA TRANSPORTER
rs1042173	C	B	**AC**	-+		SEROTONIN TRANSPORTER,, RUMINATION PERSONALITY TRAIT
rs140701	T	R	**TC**	+-		SEROTONIN TRANSPORTER, PANIC, ANXIETY, MOOD
rs4251417	T	R	**CC**	--		PLACEBO EFFECT

New concepts:

- *Amines* are organic compounds contain a basic nitrogen atom. Important amines include amino acids, histamine, dopamine and serotonin.
- In genetics, a *promoter* is a region of DNA that initiates transcription of a particular gene.
- A *polymorphism* is a difference in DNA sequence among individuals.

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:

- 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.

TPH2

tryptophan hydroxylase 2

The TPH2 gene provides instructions for making a protein that enables the first step in the biosynthesis of serotonin, an important hormone and neurotransmitter. This step is also rate-limiting, which means that any reduction in efficiency of TPH2 will affect the rate of production of serotonin. TPH2 is primarily found in the neurons of the brain which are serotonergic, that is, the nerve cells which have nerve ending that release and are stimulated by serotonin. Drugs that alter serotonin levels are used in treating depression, generalized anxiety disorder and social phobia. Depletion of serotonin is common between disorders such as obsessive-compulsive disorder, depression and anxiety.

SNP outcomes in TPH2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs4290270	T	R	**AA**	**--**		ADDICTION, HEROIN, DEPRESSION, BIPOLAR DISORDER
rs4760816	C	R	**CC**	**++**		HEROIN ADDICTION
rs4565946	C	R	**CC**	**++**		CFS, FIBROMYALGIA, EARLY ONSET OCD
rs2171363	A	R	**AA**	**++**		ANTIDEPRESSANT RESPONSE, BORDERLINE PERSONALITY DISORDER, BIRTH WEIGHT
rs4570625	G	R	**GT**	**+-**		OBSESSIVE COMPULSIVE DISORDER (OCD), PLACEBO RESPONSE
rs7963720	T	R	**CC**	**--**		ADDICTION, HEROIN, HISPANICS

MAOA

monoamine oxidase A

Intolerance to methylfolate supplementation is due to slower breakdown of neurotransmitters including serotonin, dopamine, norepinephrine can lead to low/high levels causing mood swings, OCD, anxiety, aggression, insomnia and depression. Despite feeling depleted patients have a feeling of being overstimulated. This gene has also been associated with a variety of other psychiatric disorders, including antisocial behavior. This enzyme requires B2 (riboflavin) in sufficient levels to function normally. Because this is on the X chromosome, males will have only one allele and is why mutations have an enhanced effect. ACE deletions will also increase anxiety and lower frustration thresholds.

SNP outcomes in MAOA relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2235186	G	R	**GG**	**++**		ADHD
rs909525	T	R	**TT**	**++**		WARRIOR GENE, ANGER, AGGRESSION, SUICIDE, SUICIDALITY, METHYL TRAPPING
rs1137070	T	R	**CC**	**--**		ESTROGEN DOMINANCE AND LOW OXIDATIVE DEAMINATION OF AMINES, SUCH AS DOPAMINE, NOREPINEPHRINE, AND SEROTONIN
rs5953210	G	R	**AA**	**--**		SUBSTANCE ABUSE, GOUT
rs6323	T	R	**TT**	**++**		WILD-TYPE MAOA, CATECHOLAMINES METHYL TRAPPING ANTI-DEPRESSANT RESPONSE, MAJOR DEPRESSIVE DISORDER
rs2072743	T	R	**CC**	**--**		MAJOR DEPRESSIVE DISORDER ADHD
rs2283725	A	R	**GG**	**--**		GOUT

SLC6A2

solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2

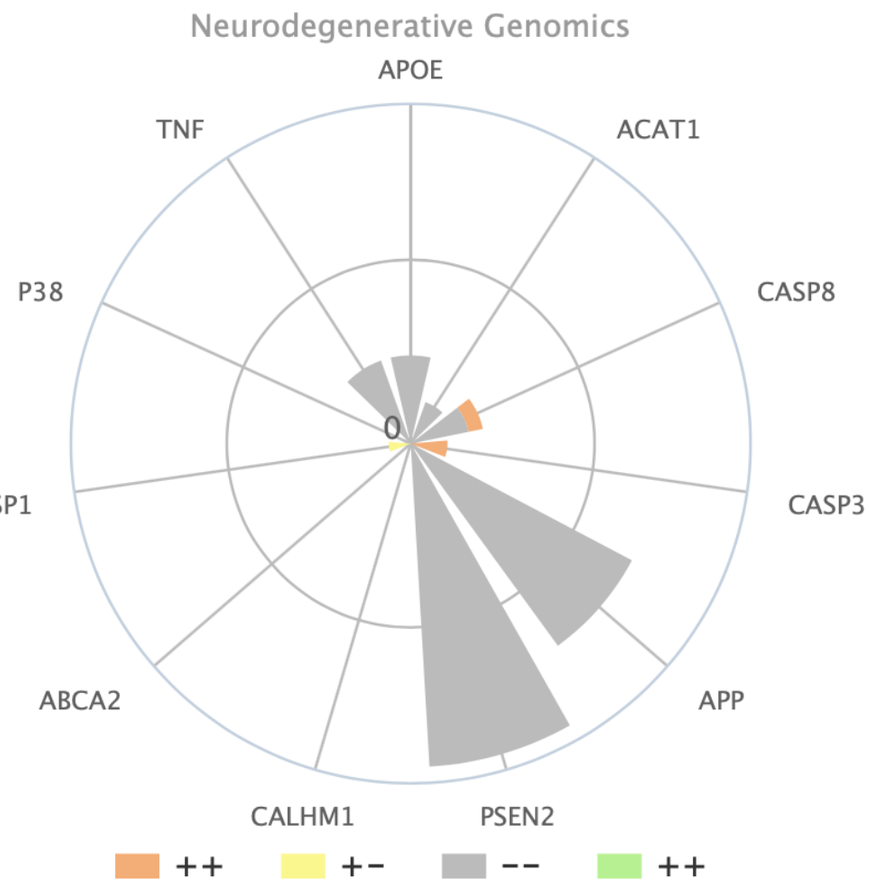
SLC6A2 encodes a cell membrane protein, which is responsible for reuptake of norepinephrine into presynaptic nerve terminals and is a regulator of norepinephrine balance. Mutations in this gene cause orthostatic intolerance, a syndrome characterized by lightheadedness, fatigue, altered mentation, syncope and orthostatic intolerance . Orthostatic intolerance (OI) is a disorder of the autonomic nervous system (a subcategory of dysautonomia) characterized by the onset of symptoms upon standing. Symptoms include fatigue, lightheadedness, headache, weakness, increased heart rate/heart palpitations, anxiety, and altered vision. There is evidence that single-nucleotide polymorphisms in the NET gene (SLC6A2) may be an underlying factor in some of these disorders.

SNP outcomes in SLC6A2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs5568	C	R	**CC**	**++**		NOREPINEPHRINE TRANSPORTER PROTEIN OXALATE
rs3785143	T	R	**CC**	**--**		ADHD
rs2242447	C	R	**TT**	**--**		NOREPINEPHRINE TRANSPORTER PROTEIN ADHD

New concepts:

- 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.



COGNITION

Neurodegenerative Genomics

Alzheimer's disease (AD) is a chronic disorder that slowly destroys neurons and causes serious cognitive disability. AD is associated with senile plaques and neurofibrillary tangles (NFTs). Amyloid-beta (Abeta), a major component of senile plaques, has various pathological effects on cell and organelle function. The extracellular Abeta oligomers may activate caspases through activation of cell surface death receptors. Alternatively, intracellular Abeta may contribute to pathology by facilitating tau hyper-phosphorylation, disrupting mitochondria function, and triggering calcium dysfunction. To date genetic studies have revealed four genes that may be linked to autosomal dominant or familial early onset AD (FAD). These four genes include: amyloid precursor protein (APP), presenilin 1 (PS1), presenilin 2 (PS2) and apolipoprotein E (ApoE). All mutations associated with APP and PS proteins can lead to an increase in the production of Abeta peptides, specfically the more amyloidogenic form, Abeta42. FAD-linked PS1 mutation downregulates the unfolded protein response and leads to vulnerability to ER stress.

CASP3

caspase 3, apoptosis-related cysteine peptidase

Caspases are proteins involved in the programmed cell death, known as apoptosis. The CASP3 protein is a member of the cysteine-aspartic acid protease (caspase) family. It is a critical component in the process of programmed cell death. Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis. Caspases exist as inactive proenzymes that undergo proteolytic processing at conserved aspartic residues to produce two subunits, large and small, that dimerize to form the active enzyme. CASP3 cleaves and activates caspases 6 and 7; and the protein itself is processed and activated by caspases 8, 9, and 10. It is the predominant caspase involved in the cleavage of amyloid-beta 4A precursor protein, which is associated with neuronal death in Alzheimer's disease.

SNP outcomes in CASP3 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2019978	A	R	**AA**	**++**		BREAST CANCER

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.
- *Proteolysis* (proteolytic) is the breakdown of proteins into smaller polypeptides or amino acids.

APP

amyloid beta (A4) precursor protein

The APP gene provides instructions for making a protein called amyloid precursor protein. This protein is found in many tissues and organs, including the brain and spinal cord (central nervous system). Little is known about the function of amyloid precursor protein. Researchers speculate that it may bind to other proteins on the surface of cells or help cells attach to one another. Studies suggest that in the brain, it helps direct the movement (migration) of nerve cells (neurons) during early development.

Amyloid precursor protein is cut by enzymes to create smaller fragments (peptides), some of which are released outside the cell. Two of these fragments are called soluble amyloid precursor protein (sAPP) and amyloid beta (β) peptide. Recent evidence suggests that sAPP has growth-promoting properties and may play a role in the formation of nerve cells (neurons) in the brain both before and after birth. The sAPP peptide may also control the function of certain other proteins by turning off (inhibiting) their activity. Amyloid β peptide is likely involved in the ability of neurons to change and adapt over time (plasticity). Other functions of sAPP and amyloid β peptide are under investigation.

More than 50 different mutations in the APP gene can cause early-onset Alzheimer disease, which begins before age 65. These mutations are responsible for less than 10 percent of all early-onset cases of the disorder.

The most common APP mutation changes one of the protein building blocks (amino acids) in the amyloid precursor protein. This mutation replaces the amino acid valine with the amino acid isoleucine at protein position 717 (written as Val717Ile or V717I). Mutations in the APPgene can lead to an increased amount of the amyloid β peptide or to the production of a slightly longer and stickier form of the peptide. When these protein fragments are released from the cell, they can accumulate in the brain and form clumps called amyloid plaques. These plaques are characteristic of Alzheimer disease. A buildup of toxic amyloid β peptide and amyloid plaques may lead to the death of neurons and the progressive signs and symptoms of this disorder.

At least six mutations in the APP gene have been found to cause hereditary cerebral amyloid angiopathy, a condition characterized by stroke and a decline in intellectual function (dementia), which begins in mid-adulthood. These mutations change single amino acids in the amyloid precursor protein. All of the APP gene mutations that cause hereditary cerebral amyloid angiopathy lead to changes near the beginning of the protein sequence. Each of these mutations causes a different type of the condition. The Dutch type, the most common of all the types, is caused by the replacement of the amino acid glutamic acid with the amino acid glutamine at position 22 in the protein sequence (written as Glu22Gln or E22Q). The Italian type and Arctic type are also caused by changes to glutamic acid at position 22. In the Italian type, glutamic acid is replaced with the amino acid lysine (written as Glu22Lys or E22K) and in the Arctic type, glutamic acid is replaced with the amino acid glycine (written as Glu22Gly or E22G). The Flemish type is caused by replacement of the amino acid alanine with glycine at position 21 (written as Ala21Gly or A21G). In the Iowa type, the amino acid aspartic acid is switched with the amino acid asparagine at position 23 (written as Asp23Asn or D23N). The Piedmont type of hereditary cerebral amyloid angiopathy is caused by the replacement of the amino acid leucine at position 34 with the amino acid valine (written as Leu34Val or L34V).

The result of all of these mutations is the production of an amyloid β peptide that is more prone to cluster together (aggregate) than the normal peptide. The aggregated protein forms amyloid deposits known as plaques that accumulate in the blood vessels of the brain. The amyloid plaques replace the muscle fibers and elastic fibers that give blood vessels flexibility, causing the blood vessels to become weak and prone to breakage. In the brain, such a break causes bleeding (hemorrhagic stroke), which can lead to brain damage and dementia. Amyloid plaques in specific parts of the brain can interfere with brain function, leading to seizures, movement problems, and other neurological features in some people with hereditary cerebral amyloid angiopathy.

SNP outcomes in APP relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs63751039	C	R	**TT**	**--**		ALZHEIMER'S DISEASE
rs63750643	C	R	**TT**	**--**		ALZHEIMER'S DISEASE
rs63750973	A	R	**GG**	**--**		ALZHEIMER'S DISEASE
rs63750064	T	R	**CC**	**--**		ALZHEIMER'S DISEASE
rs63750734	T	R	**CC**	**--**		ALZHEIMER'S DISEASE
rs63750399	C	R	**TT**	**--**		ALZHEIMER'S DISEASE

New concepts:

- *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.

PSEN2

presenilin 2 (Alzheimer disease 4)

Alzheimer's disease (AD) patients with an inherited form of the disease carry mutations in the presenilin proteins (PSEN1 or PSEN2) or the amyloid precursor protein (APP). These disease-linked mutations result in increased production of the longer form of amyloid-beta (main component of the deposits found in Alzheimer's disease brains). Presenilins are postulated to regulate amyloid processing through their effects on gamma-secretase, an enzyme that cleaves amyloid protein.

SNP outcomes in PSEN2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs28936379	G	R	**AA**	**--**		ALZHEIMERS, AD, ALZHEIMER'S DISEASE
rs63749851	C	R	**AA**	**--**		ALZHEIMER'S DISEASE, ALZHEIMERS, AD
rs28936380	G	R	**CC**	**--**		ALZHEIMER'S DISEASE, ALZHEIMERS, AD
rs63750110	C	R	**AA**	**--**		ALZHEIMERS, ALZHEIMER'S DISEASE, AD
rs63750197	T	R	**CC**	**--**		ALZHEIMERS, AD, ALZHEIMER'S DISEASE, DILATED CARDIOMYOPATHY
rs63750048	T	R	**CC**	**--**		ALZHEIMERS, ALZHEIMER'S DISEASE, AD
rs63750812	A	R	**GG**	**--**		ALZHEIMERS, ALZHEIMER'S DISEASE, AD
rs63749884	A	R	**GG**	**--**		ALZHEIMERS, ALZHEIMER'S DISEASE, AD

NFE2L2

nuclear factor (erythroid-derived 2)-like 2

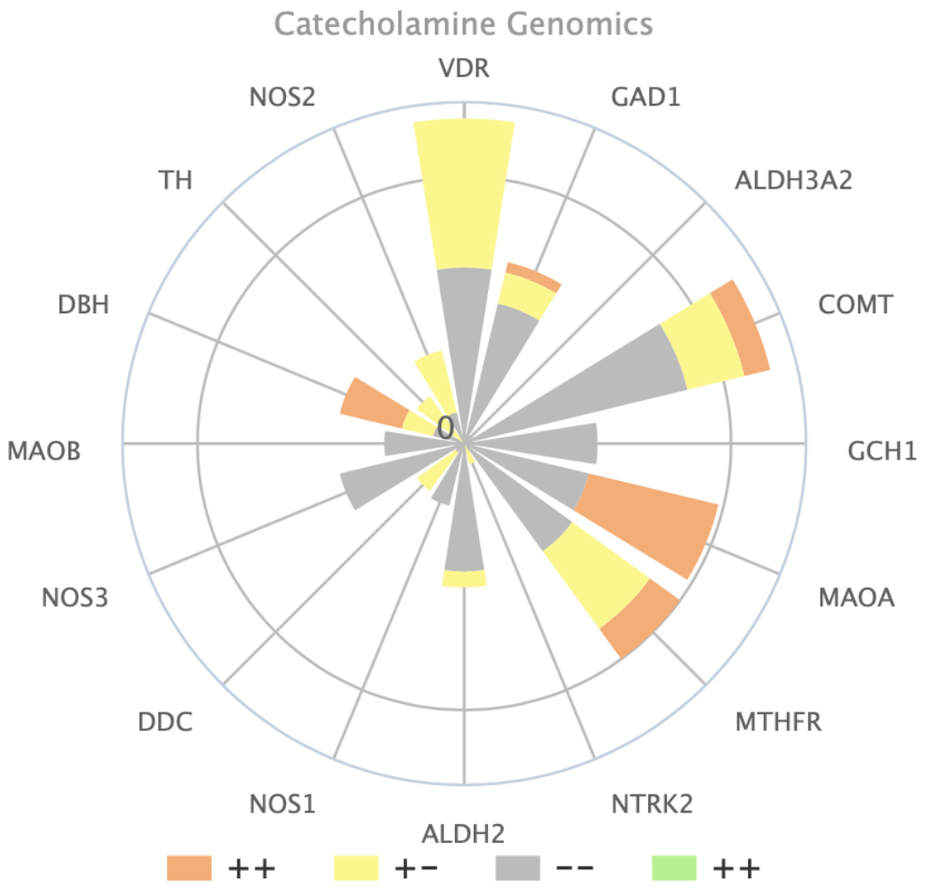
NFE2L2 is a transcription factor (i.e a molecule that activates the production of a gene product) that in humans is encoded by the NFE2L2 gene. It is central to the action of the body's own endogenous (internal) anti-oxidant production. The NFE2L2 protein regulates the expression of the body's antioxidant proteins that protect against oxidative damage triggered by injury and inflammation. Several drugs that stimulate the NFE2L2 pathway are being studied for treatment of diseases that are caused by oxidative stress. The NFE2L2 transcription factor regulates genes which contain antioxidant response elements (ARE); many of these genes encode proteins involved in response to injury and inflammation that result in the production of free radicals.

SNP outcomes in NFE2L2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs10183914	T	R	**CC**	**--**		NRF2
rs1962142	A	R	**GG**	**--**		

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.

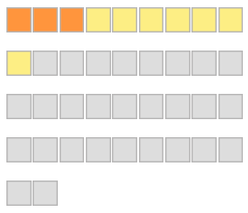


COGNITION

Catecholamine Genomics

A catecholamine is a monoamine, an organic compound that has a catechol (benzene with two hydroxyl side groups at carbons 1 and 2) and a side-chain amine. Catechol can be either a free molecule or a substituent of a larger molecule, where it represents a 1,2-dihydroxybenzene group.Catecholamines are derived from the amino acid tyrosine, which is derived from dietary sources as well as synthesis from phenylalanine. Catecholamines are water-soluble and are 50%-bound to plasma proteins in circulation.Included among catecholamines are epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine. Release of the hormones epinephrine and norepinephrine from the adrenal medulla of the adrenal glands is part of the fight-or-flight response. Tyrosine is created from phenylalanine by hydroxylation by the enzyme phenylalanine hydroxylase. Tyrosine is also ingested directly from dietary protein. Catecholamine-secreting cells use several reactions to convert tyrosine serially to L-DOPA and then to dopamine. Depending on the cell type, dopamine may be further converted to norepinephrine or even further converted to epinephrine.

GAD1



glutamate decarboxylase 1 (brain, 67kDa)

This gene encodes one of several forms of glutamic acid decarboxylase, which is a major target for the autoimmune response in insulin-dependent diabetes. This enzyme is responsible for the conversion of L-glutamic acid into gamma-aminobutyric acid (GABA), a neurotransmitter whose principle role is as a inhibitor of excitability in the nervous system and as a regulator of muscle tone. As a result, this gene is thought to play a role in the "Stiff Man Syndrome." Deficiency in the enzyme encoded by this gene has been shown to lead to dependency on Vitamin B6 with seizures.

SNP outcomes in GAD1 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2241165	C	R	**TT**	**--**		ANXIETY DISORDERS, MAJOR DEPRESSION, NEUROTICISM
rs769407	C	R	**GG**	**--**		ANXIETY DISORDERS, MAJOR DEPRESSION, NEUROTICISM
rs2058725	C	R	**TT**	**--**		ANXIETY DISORDERS, MAJOR DEPRESSION, NEUROTICISM
rs1978340	A	R	**AG**	**+-**		HEROIN ADDICTION
rs3791851	C	R	**TT**	**--**		ANXIETY DISORDERS, MAJOR DEPRESSION, NEUROTICISM

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.

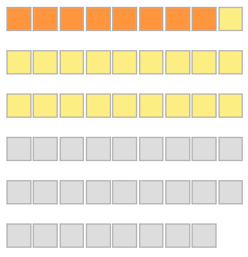
Additionally, a reduction in GTP cyclohydrolase 1 activity disrupts the production of certain neurotransmitters in the brain. Because neurotransmitters are necessary for normal brain function, changes in the levels of these chemicals contribute to intellectual disability in people with GTPCH1 deficiency.

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

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 *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.
- *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.

ALDH2

aldehyde dehydrogenase 2 family (mitochondrial)

Aldehyde dehydrogenase is the second enzyme of the major metabolic pathway of alcohol metabolism. There are two major forms of aldehyde dehydrogenase, the cellular and mitochondrial forms. Most Caucasians have both major major forms while approximately 50% of Orientals have one. A remarkably higher frequency of acute alcohol intoxication among Asians than among Caucasians could be related to the absence of a the missing form in Asian populations. Variation in ALDH2 may contribute to esophageal cancer.

SNP outcomes in ALDH2 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2238152	T	R	**GG**	**--**		HYPERTENSION, ALCOHOL INTOLERANCE
rs968529	T	R	**CC**	**--**		PARKINSON'S DISEASE, PESTICIDE TOXICITY
rs16941667	T	R	**CC**	**--**		GASTRIC CANCER
rs671	A	R	**GG**	**--**		ALCOHOL FLUSH IN ASIANS, ESOPHOGEAL CANCER, GASTRIC CANCER, SMOKING

New concepts:

- *Mitochondria* are a cell constitutent (organelle) found in large numbers in most cells, in which the biochemical processes of respiration and energy production occur.
- A *dehydrogenase* is an enzyme that accelerates the removal of hydrogen from metabolites and its transfer to other substances.

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

New concepts:

- A *pathogen* is a bacterium, virus, or other microorganism that can cause disease.

DBH

dopamine beta-hydroxylase (dopamine beta-monooxygenase)

DBH converts dopamine to norepinephrine. Excessive levels are associated with restlessness and anxiety due to the loss of dopamine and the increase in norepinephrine. DBH shows variability by ABO blood type, being much more active in those with blood type O. DBH activity can be modulated with regular exercise, a higher protein diet and a low-wheat diet. The supplement panthetine has been show to help modulate DBH activity.

SNP outcomes in DBH relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2519152	C	R	**TC**	**-+**		BIPOLAR
rs2873804	C	R	**CC**	**++**		RESPONSE TO ATOMOXETINE IN ADHD
rs1108580	A	R	**GG**	**--**		BIPOLAR
rs1611115	C	R	**CC**	**++**		T ALLELE DECREASED DBH DOPAMINE TO NOREPINEPHRINE CONVERSION ACTIVITY, C HIGH CONVERSION TO NOREPINEPHRINE RELATED TO IMPULSIVENESS, BIPOLAR, SUBSTANCE WITHDRAWAL SYNDROME, ALCOHOLISM, NALTREXONE EFFICACY

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

QDPR

quinoid dihydropteridine reductase

The QDPR gene provides instructions for making an enzyme called quinoid dihydropteridine reductase. This enzyme helps carry out one step in the chemical pathway that recycles a molecule called tetrahydrobiopterin (BH4). The QDPR gene belongs to a family of genes called SDR (short chain dehydrogenase/reductase superfamily).

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. Because it helps enzymes carry out chemical reactions, tetrahydrobiopterin is known as a cofactor.

When tetrahydrobiopterin interacts with enzymes during chemical reactions, the cofactor is altered and must be recycled to a usable form. Quinoid dihydropteridine reductase is one of two enzymes that help recycle tetrahydrobiopterin in the body.

More than 30 mutations in the QDPR gene have been found to cause tetrahydrobiopterin deficiency. When this condition results from QDPR gene mutations, it is known as dihydropteridine reductase (DHPR) deficiency. DHPR deficiency accounts for about one-third of all cases of tetrahydrobiopterin deficiency.

Most QDPR gene mutations change single amino acids in quinoid dihydropteridine reductase, although some mutations insert small amounts of DNA into the QDPR gene or disrupt the way the gene's instructions are used to make the enzyme. Changes in quinoid dihydropteridine reductase greatly reduce or eliminate the enzyme's activity. Without enough of this enzyme, tetrahydrobiopterin is not recycled properly. 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 quinoid dihydropteridine reductase activity disrupts the production of certain neurotransmitters in the brain. Because neurotransmitters are necessary for normal brain function, changes in the levels of these brain chemicals contribute to intellectual disability in people with DHPR deficiency.

SNP outcomes in QDPR relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs104893863	T	R	**CC**	--		DIHYDROPTERIDINE REDUCTASE DEFICIENCY, BH2 TO BH4 CONVERSION
rs1031326	T	R	**CC**	--		BH2 TO BH4 CONVERSION
rs104893867	T	R	**CC**	--		DIHYDROPTERIDINE REDUCTASE DEFICIENCY, BH2 TO BH4 CONVERSION
rs104893864	C	R	**AA**	--		DIHYDROPTERIDINE REDUCTASE DEFICIENCY, BH2 TO BH4 CONVERSION
rs11722315	A	R	**CC**	--		BH2 TO BH4 CONVERSION

COGNITION

MULTI-SNP MACROS

APOE E3/E3 genotype

Genes	APOE
Repute:	NEUTRAL
Magnitude:	2
Frequency:	57.4~41.7~74.6~APOE%

INTERPRETATION: You have 2 APOE-ε3 alleles, the most common form of APOE. It is considered the 'neutral' genotype, with E2 having lower risk and E4 having higher risk of Alzheimer's disease.

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

Your results: rs429358 (**TT**) rs7412 (**CC**)

Oxytocin 'social/ empathy' polymorphism

Genes	OXTR
Repute:	BENEFIT
Magnitude:	3
Frequency:	N/A

INTERPRETATION: rs53576 is a silent G to A change in the oxytocin receptor (OXTR) gene. You have the GG genotype, which appears to predispose to gaining benefits in the managment of stress form seeking social support. Understress, individuals with with one or more copies of the G version of rs53576 were more likely to seek emotional support from their friends, compared to those with two copies of the A version. Studies have demonstrated that individuals with the G allele are more empathetic, feel less lonely, employ more sensitive parenting techniques, and have lower rates of autism. GG genotype rs53576 also tend to be on average more optimistic and empathetic and handle stress well.

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

Your results: rs53576 (**GG**)

Risk and intensity of functional somatic syndromes (CFS, FM)

Genes	TPH2,HTR2A
Repute:	SEE CHART
Magnitude:	2.2
Frequency:	N/A

INTERPRETATION: 1 Functional somatic syndromes (FSS) are a way of classifying people with medically unexplained symptoms including, among others, fibromyalgia (FM), chronic widespread pain (CWP) and chronic fatigue syndrome (CFS). Two genes, serotonin receptor 2A gene (HTR2A) and the serotonin biosynthesis gene (TPH2) are linked with more somatic symptoms and a risk of having several FSS.

The G allele of SNP rs6313 in the serotonin receptor 2A gene HTR2A has been associated with an increased risk of FM, CFS and Temporomandibular joint disorder.

In the serotonin biosynthesis gene, TPH2, each copy of the minor allele (C) of rs4565946 in the TPH2 gene and rs7305115 was associated with an increase in the number of somatic symptoms.

A heterozygous genotype (AG) for SNP rs6313 (T102C), in the serotonin receptor 2A gene HTR2A was associated with a decrease in the number of somatic symptoms.

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

Your results: rs4565946 (**CC**) rs6313 (**AG**)

Minimally or non-responsive to the placebo effect

Genes	COMT
Repute:	NEUTRAL
Magnitude:	3
Frequency:	60%

INTERPRETATION: This client is heterozygous for the COMT rs4680(GG) genotype variant (often referred to as 'val/val' or 'val158'). This variation retains the valine codon, resulting in a thermostable COMT enzyme that exhibits a fully COMT activity. Higher COMT enzymatic activity results lower dopamine levels; higher pain threshold and better stress resiliency, albeit with a modest reduction in executive cognition performance under most conditions. People with Val alleles have increased COMT activity and lower prefrontal extracellular dopamine compared with those with the Met substitution. Val158 alleles may be associated with an advantage in the processing of aversive stimuli (the so-called 'warrior' strategy). A recent study showed that as the number of COMT val158 alleles increased progressively from rs4680(AA) to rs4680(AG) to rs4680(GG), and COMT activity increased (theoretically making less dopamine available in the prefrontal cortex), placebo responses decreased in a linear fashion.

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

Your results: rs4680 (**GG**)

No heightened placebo effect

Genes	COMT,TPH2
Repute:	NEUTRAL
Magnitude:	3
Frequency:	61%

INTERPRETATION: This client is homozygous for the COMT rs4680(GG). Unlike the COMT rs4680(AA) variant the GG genotype does not produce a significant increase in the placebo effect. People with GG genotype have increased COMT activity and lower prefrontal extracellular dopamine compared with those with the AA substitution. GG genotypes may be associated with an advantage in the processing of aversive stimuli (the so-called 'warrior' strategy). Yet this genotype also appears to be also more efficient at processing information under most conditions. val158met has been associated with a more 'exploratory' personality'. A recent study showed that as the number of rs4680(GG) alleles increased progressively from rs4680(AA) to rs4680(AG) to rs4680(GG), and COMT activity increased (theoretically making less dopamine available in the prefrontal cortex), placebo responses decreased in a linear fashion .

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

Your results: rs4680 (**GG**) rs4633 (**CC**) rs4570625 (**GT**)

Stress/ Cognition macro algorithms returning as false:

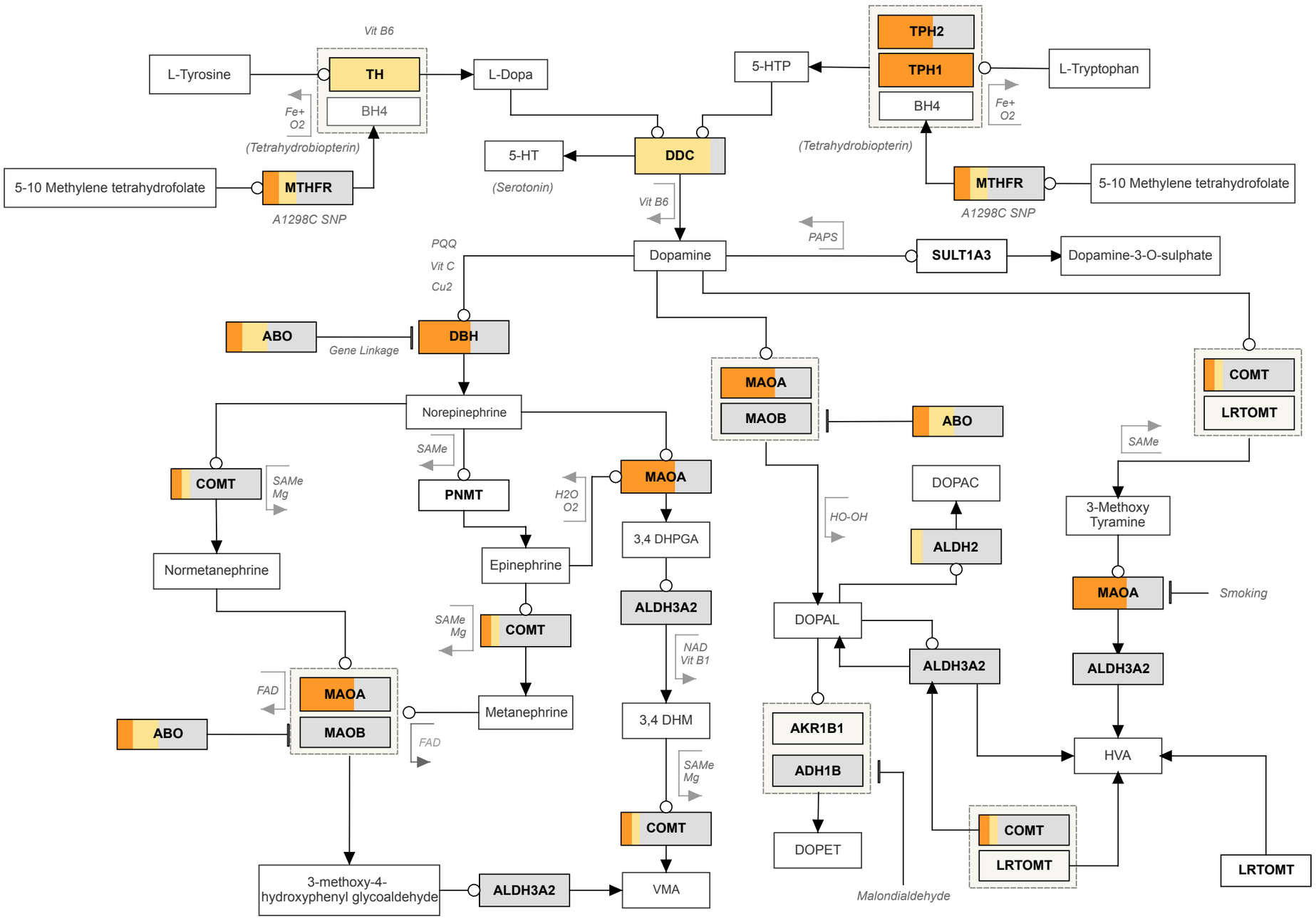
- Two short form 5-HTTLPR

COGNITION

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).

Catecholamine Metabolism



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.	Vitamin D (calciferols)	
2.	Binge drinking	
3.	Vitamin B-2 (riboflavin)	
4.	Acorus tatarinowii	
5.	Curcumin	
6.	Rhodiola rosea	
7.	Theanine	
8.	Resveratrol	
9.	Quercetin	
10.	Ashwagandha (Withania somnifera)	
11.	Berberine	
12.	Lithium orotate	
13.	Lactobacillus plantarum	
14.	Vitamin B-1 (thiamine)	
15.	Incremental Carbohydrate:Protein meals	
16.	Bacopa monnieri	
17.	Arecoline	
18.	Estrogen	
19.	Luteolin	
20.	7-ethyl-8-methylflavin	
21.	Coptis rhizome	
22.	Iron	
23.	Resveratroloside	
24.	Testosterone	
25.	Guaiacol	

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