Client Report

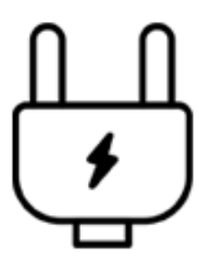
Venus deMilo

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



ENERGY/ METABOLISM

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

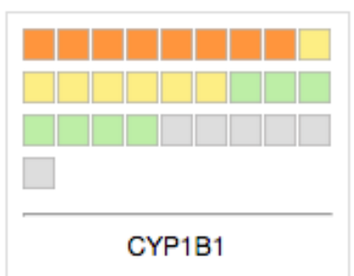
When it comes to a particular disease or syndrome, most SNPs have rather small ORs. This does not mean that they are unworthy of attention, but rather that the findings must be interpreted as part of an integrated whole, including: other SNP results that also support the conclusion; lifestyle factors;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

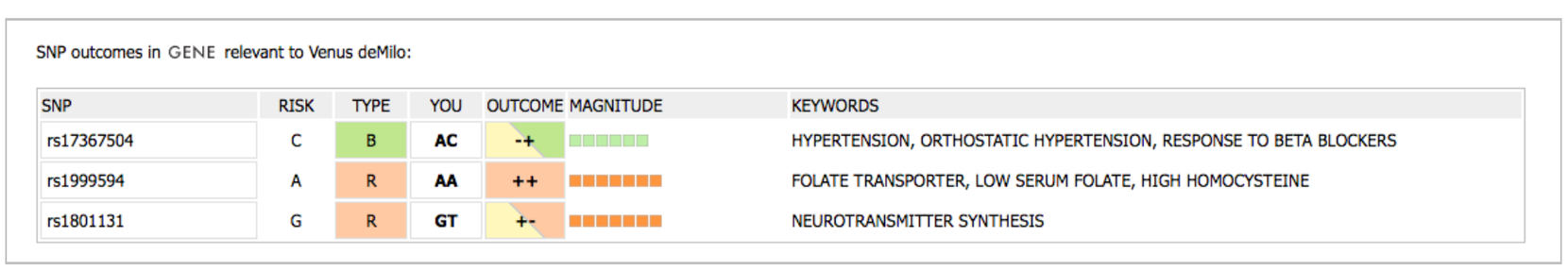
The data provided by Opus23 Explorer is for informational purposes only and is not designed or intended to suggest the treatment or diagnosis of any disease or condition. Opus23 Explorer and Datapunk Bioinformatics, LLC, take no responsibility for any harm arising from incorrect data being uploaded to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

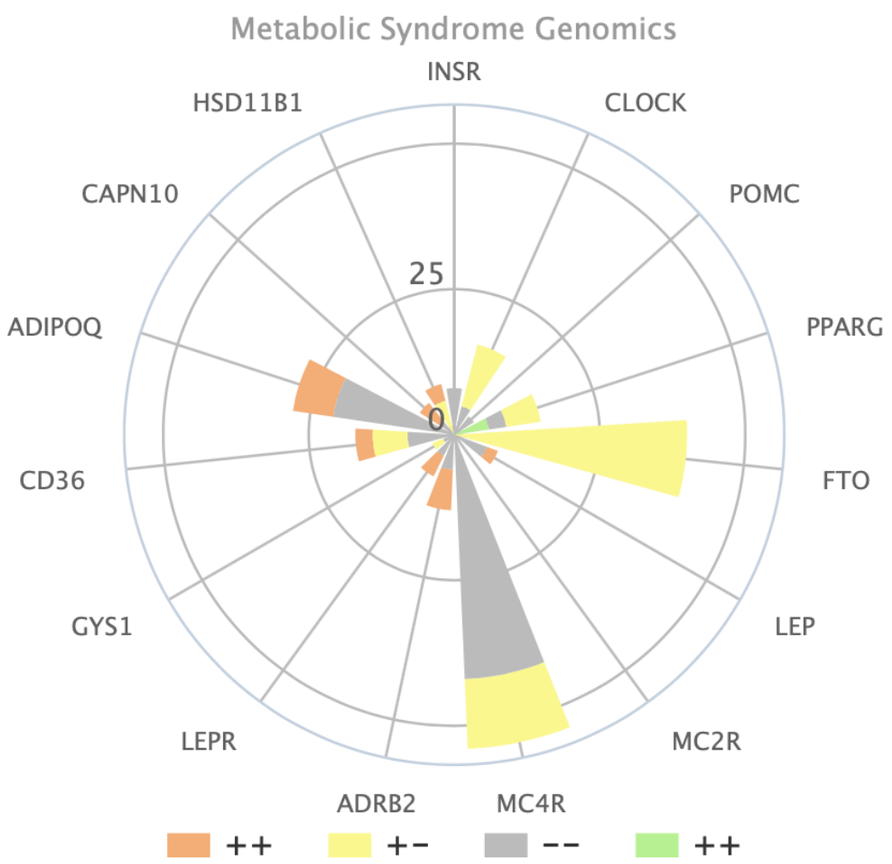
For example, a simple macro to determine if you should get out of bed might be:

- 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.



ENERGY/ METABOLISM

Metabolic Syndrome Genomics

Based on the thrifty genotype hypothesis, genes involved in efficiently storing and saving energy could predispose to metabolic syndrome. Several potential candidate genes have been suggested by their biologic relevance, such as genes in systems of energy balance, nutrient partitioning, lipid and insulin metabolism, lipolysis, thermogenesis, fuel oxidation, and glucose uptake in skeletal muscle. Many of these genes have been associated with metabolic syndrome in various ethnic populations. These candidate genes include but are not limited to peroxisome proliferator-activated receptor (PPAR γ), adiponectin, CD36, β-adrenergic receptors, insulin receptor substrates (IRS), 11 β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), CRP, tumor necrosis factor-α (TNF-α), calpain-10 (CAPN10), upstream transcription factor 1, and skeletal muscle glycogen synthase 1.

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:

- 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).
- *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.
- *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.

FTO

fat mass and obesity associated

Studies in mice and humans indicate a role in nervous and cardiovascular systems and a strong association with body mass index, obesity risk, and type 2 diabetes. in 2009 variants in the FTO gene were further confirmed to associate with obesity in two very large genome wide association studies of body mass index (BMI). A study of 38,759 Europeans for variants of FTO identified several obesity risk alleles. The presence of FTO variations was also found to be positively correlated with other symptoms of the metabolic syndrome, including higher fasting insulin, glucose, and triglycerides, and lower HDL cholesterol.

SNP outcomes in FTO relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs1121980	A	R	**AG**	**+-**		OBESITY RISK, HIGH BIRTH WEIGHT
rs8050136	A	R	**AC**	**+-**		DIABETES, TYPE 2 DIABETES, OBESITY
rs1558902	A	R	**AT**	**+-**		OBESITY, BMI, BODY MASS INDEX
rs17817449	G	R	**GT**	**+-**		OBESITY, SATIETY, HUNGER
rs9939609	A	R	**AT**	**+-**		OBESITY, DIABETES, TYPE 2 DIABETES, FAT GENE, SATIETY

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.

MC4R

melanocortin 4 receptor

The melanocortin 4 receptor is a protein that in humans is encoded by the MC4R gene. Defects in this gene are a cause of autosomal dominant obesity. It is found in higher levels in people with body mass indices greater than 30, making it the most commonly known genetic defect predisposing people to obesity. In 2009, two very large genome-wide association studies of body mass index (BMI) confirmed the association of variants of the MC4R gene with insulin resistance, obesity, and other anthropometric traits. Variants are linked with a preference for high fat or sweet food.

SNP outcomes in MC4R relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs17782313	C	R	**CT**	**+-**		OBESITY, BMI, DIABETES, ANTIPSYCHOTICS RESPONSE
rs12970134	A	R	**AG**	**+-**		BODY WEIGHT, BMI, INCREASED WAIST CIRCUMFERENCE
rs52804924	T	R	**GG**	**--**		OBESITY
rs121913557	T	R	**CC**	**--**		OBESITY
rs13447324	T	R	**GG**	**--**		SCHIZOPHRENIA, OBESITY
rs79783591	T	R	**AA**	**--**		OBESITY
rs13447336	T	R	**CC**	**--**		PARTIAL RECEPTOR ACTIVITY, TASTE PREFERENCE

New concepts:

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

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'.
- A *mutation* is an alteration of genetic material such that a new variation is produced.
- *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.

LEPR

leptin receptor

The leptin hormone regulates adipose-tissue mass through hypothalamus effects on hunger and energy use. It acts through the leptin receptor (LEP-R), a single-transmembrane-domain receptor of the cytokine receptor family. This protein is a receptor for leptin (an adipocyte-specific hormone that regulates body weight), and is involved in the regulation of fat metabolism. Variations in the leptin receptor have been associated with obesity. Excess secretion of Leptin due to stress increases glucocorticoids and decreases a-MSH allowing the stimulation of the hunger gene.

SNP outcomes in LEPR relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs2025804	G	R	**GG**	**++**		LEPTIN, OBESITY, HUNGER CRAVINGS, INCREASED SNACKING AND FOOD SEEKING BEHAVIOR
rs1137101	A	R	**GG**	**--**		HUNGER, OBESITY LEPTIN RECEPTOR POLYMORPHISM

New concepts:

- *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.

CD36

CD36 molecule (thrombospondin receptor)

CD36 may have important functions as a cell adhesion molecule. Below-normal levels of CD36 expression in the kidneys has been implicated as a genetic risk factor for hypertension (high blood pressure). It directly mediates cytoadherence of Plasmodium falciparum (malaria) infected red blood cells. CD36 also binds long chain fatty acids and may function in the transport and/or as a regulator of fatty acid transport. Mutations in this gene can cause platelet glycoprotein deficiency.

SNP outcomes in CD36 relevant to Venus deMilo:

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

ADIPOQ

adiponectin, C1Q and collagen domain containing

Adiponectin (AdipoQ) is a protein which in humans is encoded by the ADIPOQ gene. It is involved in regulating glucose levels as well as fatty acid breakdown. Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation. Adiponectin is exclusively secreted from adipose tissue (and also from the placenta in pregnancy) into the bloodstream and is very abundant in plasma relative to many hormones. Levels of the hormone are inversely correlated with body fat percentage in adults. Adiponectin exerts some of its weight reduction effects via the brain. This is similar to the action of leptin, but the two hormones perform complementary actions, and can have synergistic effects.

SNP outcomes in ADIPOQ relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs17366568	A	R	**GG**	**--**		ADIPONECTIN, OBESITY, BMI
rs1501299	G	R	**GG**	**++**		BREAST CANCER

New concepts:

- *Fatty acid oxidation* is the process of fatty acids breaking down, which releases energy.

CAPN10

calpain 10

Calpains represent a ubiquitous, well-conserved family of calcium-dependent cysteine proteases. The calpain proteins are heterodimers consisting of an invariant small subunit and variable large subunits. The large catalytic subunit has four domains: domain I, the N-terminal regulatory domain that is processed upon calpain activation; domain II, the protease domain; domain III, a linker domain of unknown function; and domain IV, the calmodulin-like calcium-binding domain. This gene encodes a large subunit. It is an atypical calpain in that it lacks the calmodulin-like calcium-binding domain and instead has a divergent C-terminal domain. It is similar in organization to calpains 5 and 6. This gene is associated with type 2 or non-insulin-dependent diabetes mellitus (NIDDM), and is located within the NIDDM1 region. Multiple alternative transcript variants have been described for this gene.
SNP outcomes in CAPN10 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs3792267	A	R	**AA**	**++**		OBESITY, DIABETES, TYPE 2 DIABETES, POLYCYSTIC OVARY SYNDROME,

HSD11B1

hydroxysteroid (11-beta) dehydrogenase 1

HSD11B1 catalyzes the conversion of the stress hormone cortisol to the inactive metabolite cortisone. In addition, the encoded protein can catalyze the reverse reaction, the conversion of cortisone to cortisol. Too much cortisol can lead to central obesity, and a particular variation in this gene has been associated with obesity and insulin resistance in children.

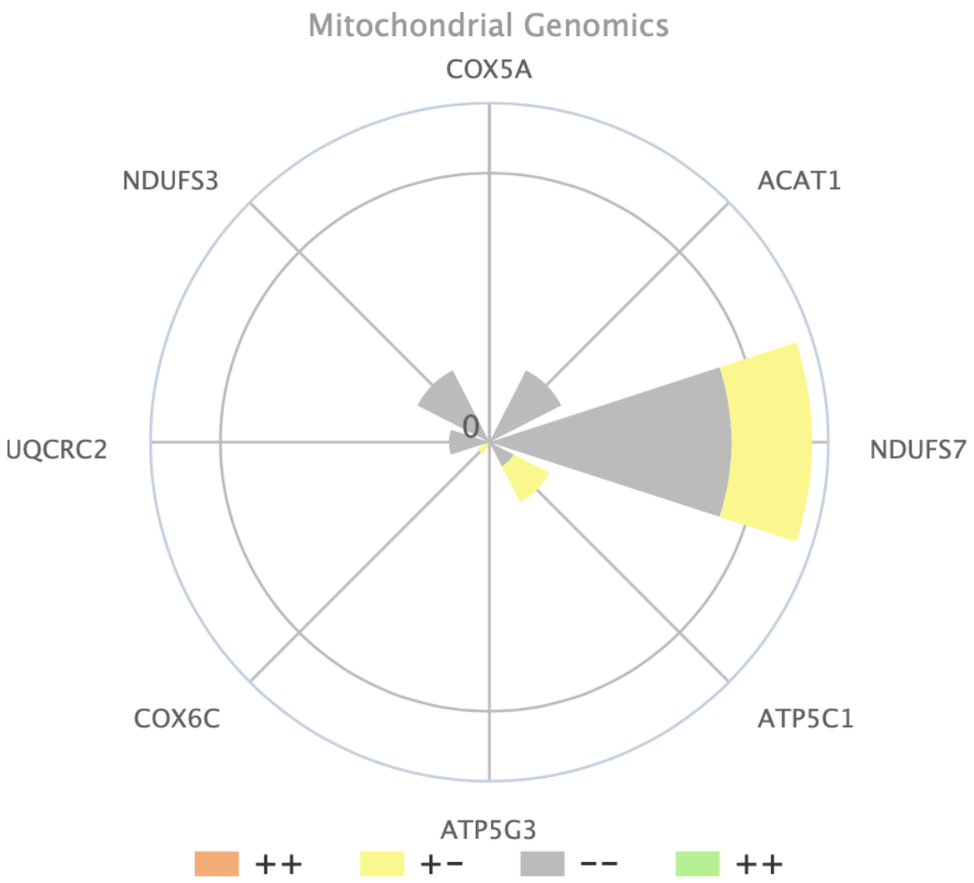
SNP outcomes in HSD11B1 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs846906	T	R	**TC**	**+-**		

New concepts:

- To *Catalyze* is to cause or accelerate (a reaction) by acting as a catalyst.
- A *metabolite* is a product of metabolism; a substance essential to the metabolism of a particular organism or to a particular metabolic process.

ENERGY/ METABOLISM



Mitochondrial Genomics

Mitochondria contain their own genome, an indication that they are derived from bacteria through endosymbiosis. However, the ancestral endosymbiont genome has lost most of its genes so that the mitochondrial genome is one of the most reduced genomes across organisms. Damage and subsequent dysfunction in mitochondria is an important factor in a range of human diseases due to their influence in cell metabolism. Mitochondrial disorders often present themselves as neurological disorders, including autism. They can also manifest as myopathy, diabetes, multiple endocrinopathy, and a variety of other systemic disorders. In other diseases, defects in nuclear genes lead to dysfunction of mitochondrial proteins. This is the case in Friedreich's ataxia, hereditary spastic paraplegia, and Wilson's disease. These diseases are inherited in a dominance relationship, as applies to most other genetic diseases. A variety of disorders can be caused by nuclear mutations of oxidative phosphorylation enzymes, such as coenzyme Q10 deficiency and Barth syndrome. Environmental influences may interact with hereditary predispositions and cause mitochondrial disease. For example, there may be a link between pesticide exposure and the later onset of Parkinson's disease. Other pathologies with etiology involving mitochondrial dysfunction include schizophrenia, bipolar disorder, dementia, Alzheimer's disease, Parkinson's disease, epilepsy, stroke, cardiovascular disease, chronic fatigue syndrome, retinitis pigmentosa, and diabetes mellitus. Mitochondria-mediated oxidative stress plays a role in cardiomyopathy in Type 2 diabetics. Increased fatty acid delivery to the heart increases fatty acid uptake by cardiomyocytes, resulting in increased fatty acid oxidation in these cells. This process increases the reducing equivalents available to the electron transport chain of the mitochondria, ultimately increasing reactive oxygen species (ROS) production. ROS increases uncoupling proteins (UCPs) and potentiate proton leakage through the adenine nucleotide translocator (ANT), the combination of which uncouples the mitochondria. Uncoupling then increases oxygen consumption by the mitochondria, compounding the increase in fatty acid oxidation. Given the role of mitochondria as the cell's powerhouse, there may be some leakage of the high-energy electrons in the respiratory chain to form reactive oxygen species. This was thought to result in significant oxidative stress in the mitochondria with high mutation rates of mitochondrial DNA (mtDNA). Hypothesized links between aging and oxidative stress are not new and were proposed in 1956, which was later refined into the mitochondrial free radical theory of aging.

NDUFS7

NADH dehydrogenase (ubiquinone) Fe-S protein 7, 20kDa (NADH-coenzyme Q reductase)

This gene encodes a protein that is a subunit of one of the complexes that forms the mitochondrial respiratory chain. This protein is one of over 40 subunits found in complex I, the nicotinamide adenine dinucleotide (NADH):ubiquinone oxidoreductase. This complex functions in the transfer of electrons from NADH to the respiratory chain, and ubiquinone is believed to be the immediate electron acceptor for the enzyme. Mutations in this gene cause Leigh syndrome due to mitochondrial complex I deficiency, a severe neurological disorder that results in brain lesions and associated symptoms.

SNP outcomes in NDUFS7 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs11666067	A	R	**CC**	**--**		MITOCHONDRIA COMPLEX I NADH : UBIQUINONE OXIREDUCTASE
rs7254913	G	R	**AG**	**-+**		MITOCHONDRIA COMPLEX I NADH : UBIQUINONE OXIREDUCTASE
rs1142530	T	R	**CC**	**--**		MITOCHONDRIA COMPLEX I NADH : UBIQUINONE OXIREDUCTASE
rs809359	G	R	**AA**	**--**		MITOCHONDRIA COMPLEX I NADH : UBIQUINONE OXIREDUCTASE

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 *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.

NDUFS8

NADH dehydrogenase (ubiquinone) Fe-S protein 8, 23kDa (NADH-coenzyme Q reductase)

The KCNJ11 gene provides instructions for making a part of NADH:ubiquinone oxidoreductase, or Complex I in the mitochondria, the energy-producing part of the cell. Mutations in this gene have been associated with Leigh syndrome, an early-onset progressive disorder involving degeneration of the nervous system.

SNP outcomes in NDUFS8 relevant to Venus deMilo:

SNP	RISK	TYPE	YOU	OUTCOME	MAGNITUDE	KEYWORDS
rs1104739	C	R	**CC**	**++**		MITOCHONDRIA COMPLEX I NADH : UBIQUINONE OXIREDUCTASE
rs2075626	C	R	**TT**	**--**		MITOCHONDRIA COMPLEX I NADH : UBIQUINONE OXIREDUCTASE
rs999571	A	R	**GG**	**--**		MITOCHONDRIA COMPLEX I NADH : UBIQUINONE OXIREDUCTASE

ENERGY/ METABOLISM

MULTI-SNP MACROS

Lower circulating levels of adiponectin

Genes	ARL15,KNG1,ADIPOQ
Repute:	RISK
Magnitude:	2
Frequency:	N/A

INTERPRETATION: Adiponectin controls blood glucose levels and breaks down fatty acids. You have at least one variant SNP affecting adiponectin production in the ARL15, KNG1 or ADIPOQ genes from the following: rs6444175-A; rs1851665-A; rs4311394-G, which are linked to lower levels of adiponectin in the blood. These mutations may be linked to a higher risk of coronary heart disease and type 2 diabetes, as well as several traits relating to metabolic problems.

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

Your results: rs6444175 (**GG**) rs1851665 (**AA**) rs4311394 (**AA**)

Problematic effects from high fat diet

Genes	PPARG
Repute:	RISK
Magnitude:	2.5
Frequency:	21%

INTERPRETATION: Metabolic syndrome is when a person has at least three out of five of the following medical conditions: abdominal obesity, high blood pressure, high fasting blood glucose, high triglycerides, and low high-density lipoprotein (HDL) levels. Metabolic syndrome is associated with the risk of developing cardiovascular disease and diabetes. A study found a common SNP in the peroxisome proliferator-activated receptor PPARG gene, rs1801282 (G) or Pro12Ala to be associated with metabolic syndrome, but other studies have not been able to replicate this finding. Homozygous (GG) genotypes for Pro12Ala are in fact a bit leaner than the other genotypes, but this benefit disappears when a high fat diet is consumed. On the plus side, mice with the Pro12Ala variant live longer than the non-variant mice, but only when they ate a normal diet, not a high-fat diet.

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

Your results: rs1801282 (**CG**)

Any type of exercise results in weight loss

Genes	ADRB2,ADRB3
Repute:	BENEFIT
Magnitude:	2.5
Frequency:	12%

INTERPRETATION: 88% of peoples' bodies resist burning fat during low intensity exercise. You are part of the 12% of the population who can lose weight with any type of exercise.

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

Your results: rs1042713 (**AA**) rs4994 (**AA**)

Increased risk of metabolic syndrome/ consequences

Genes	GNB3
Repute:	RISK
Magnitude:	4
Frequency:	55.1%

INTERPRETATION: rs5443, a SNP in the G-protein beta3 subunit (GNB3) gene that is more commonly known as the C825T variant, has been linked to a number of metabolic conditions including obesity, coronary artery disease, insulin resistance and therefore diabetes, left ventricular hypertrophy, and hypertension.

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

Your results: rs5443 (**CT**)

Lower serum vitamin D levels

Genes	GC,CYP2R1,NADSYN1,C10orf88
Repute:	RISK
Magnitude:	1.5
Frequency:	N/A

INTERPRETATION: You have one or more mutations on a series of genes that have been shown in a large study to be linked to a 2.8% change in vitamin D levels. Your risk is of lower vitamin D levels.

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

Your results: rs6599638 (**AA**) rs2060793 (**AG**) rs3829251 (**GG**) rs2282679 (**GG**)

Lower serum levels of vitamin B12

Genes	FUT2
Repute:	RISK
Magnitude:	3.1
Frequency:	77%

INTERPRETATION: You are a secretor of your blood type as a result of having the FUT2 (fucosyltransferase 2) secretor phenotype. There is a link with FUT2 secretor status and infection with the H. pylori bacteria, a risk factor for inflammation of the stomach. Being a secretor of your blood type is associated with lower vitamin B12 levels in the blood, potentially due to inactivation of the intrinsic factor (GIF) needed for B12 absorption. [PMID: 23402911]

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

Your results: rs601338 (**GG**)

30-40% increase in MnSOD activity in mitochondria

Genes	SOD2
Repute:	BENEFIT
Magnitude:	2.3
Frequency:	16%

INTERPRETATION: Superoxide is produced as a byproduct of using oxygen in the body, and if not regulated, causes cell damage. Superoxide dismutase (SOD) is an antioxidant enzyme that helps break down the damaging superoxide free radical into either ordinary molecular oxygen (O2) or hydrogen peroxide (H2O2). SOD is an important antioxidant defense in cells exposed to oxygen. Mitochondria, the energy-producing parts of the cell, use a type of SOD called SOD2 that uses manganese in its structure. The rs4880(A) allele in SOD2 is the more common SNP, but the rs4880(G) allele was shown to increase SOD2 activity by 30-40% in mitochondria, resulting in a lower risk of coronary artery disease and acute myocardial infarction.

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

Your results: rs4880 (**GG**)

exercise performance with caffeine intake

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

INTERPRETATION: Caffeine is frequently used by athletes because of its reported performance-enhancing or ergogenic effects. You have the AA genotype ('fast metabolizer') for rs762551 snp on gene CYP1A2, one of the main genes involved in detoxification. Recent findings show that caffeine improves exercise performance (10-km cycling time) but only in those with the AA genotype for rsrs762551 on gene CYP1A2. Caffeine had no effect in those with the AC genotype and diminished performance in those with the CC genotype.

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

Your results: rs762551 (**AA**)

Intermediate carotenoid conversion/ slightly lower macular pigment optical density.

Genes	PKD1L2,BCO1
Repute:	RISK
Magnitude:	2.3
Frequency:	N/A

INTERPRETATION: Carotenoids such as beta carotene are converted to vitamin A by the Beta-Carotene Oxygenase 1 (BCO1) gene. Variants in the gene play a role in the uptake of macular pigments lutein and zeaxanthin in the eye. This can have significant effects on the risk of developing age-related macular degeneration (AMD) and its subsequent progression. In a study of healthy participants, macular pigment optical density (MPOD) levels can be related to high and low beta-carotene conversion BCO1 genotypes.

You have the rs11645428(AG), rs6420424(AG), rs6564851(GT) genotype, which is considered an 'intermediate' genotype with on average slightly lower macular pigment optical density (MPOD) compared to those with the other genotypes. This genotype will have higher levels of beta-carotene and alpha-carotene levels and slightly lower levels of the carotenoids lycopene, zeaxanthin and lutein.

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

Your results: rs11645428 (**AG**) rs6420424 (**AG**) rs6564851 (**GT**)

Increased risk of elevated uric acid levels and gout

Genes	ABCG2
Repute:	RISK
Magnitude:	3
Frequency:	23%

INTERPRETATION: The T variant of rs2231142 is a mutation in the ABCG2 gene (a transporter protein), indicating a lack of gene function. It is associated with higher uric acid levels and gout, and may account for at least 10% of all gout cases in whites

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

Your results: rs2231142 (**GT**)

Benefits from low-fat diet

Genes	PPARG,ADRB2,ADRB3
Repute:	BENEFIT
Magnitude:	2
Frequency:	39%

INTERPRETATION: You will lose 2.5 times as much weight on a low fat diet.

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

Your results: rs1042713 (**AA**) rs4994 (**AA**) rs1801282 (**CG**) rs1042714 (**CC**)

Reduced conversion of beta-carotene to retinol

Genes	BCO1
Repute:	RISK
Magnitude:	2
Frequency:	N/A

INTERPRETATION: A study of women with at least one 'T' allele on both SNPs of the BCO1 gene (rs7501331 and rs12934922) have a 69% lower ability to convert Beta-carotene into retinyl esters, the active form of vitamin A. Those with mutations in rs12934922 (R267S) and rs7501331 (A379V) have their ability to convert beta-carotene to retinyl esters reduced by 57%. Those carrying just the T variant of rs7501331 have a 32% lower ability to convert Beta-carotene into retinyl esters.

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

Your results: rs12934922 (**AT**) rs7501331 (**CC**)

Significantly lower arachidonic acid and linoleic acid levels and higher interleukin (IL)-6 levels

Genes	FADS1
Repute:	RISK
Magnitude:	2.1
Frequency:	16%

INTERPRETATION: You have a T allele on the rs174537 SNP, which is on the Fatty Acid Desaturase 1 (FADS1) gene. This gene regulates the saturation of fatty acids, and mutations in this SNP are associated with lower concentrations of long-chain polyunsaturated fatty acids.

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

ADDITIONAL THERAPEUTICS:
This client would probably benefit from a fish oil or other omega-3 oil supplement.

Your results: rs174537 (**GT**)

Energy/ Metabolism macro algorithms returning as false:

- Carrier for hereditary fructose intolerance
- Higher serum levels of vitamin B12
- Benefits from low-carb diet
- Increased risk of elevated uric acid levels and gout
- Lower levels of tetrahydrobiopterin
- Balanced diet works best
- High-protein diet conveys significant benefits for weight loss
- Better weight loss with reduced dietary fat intake

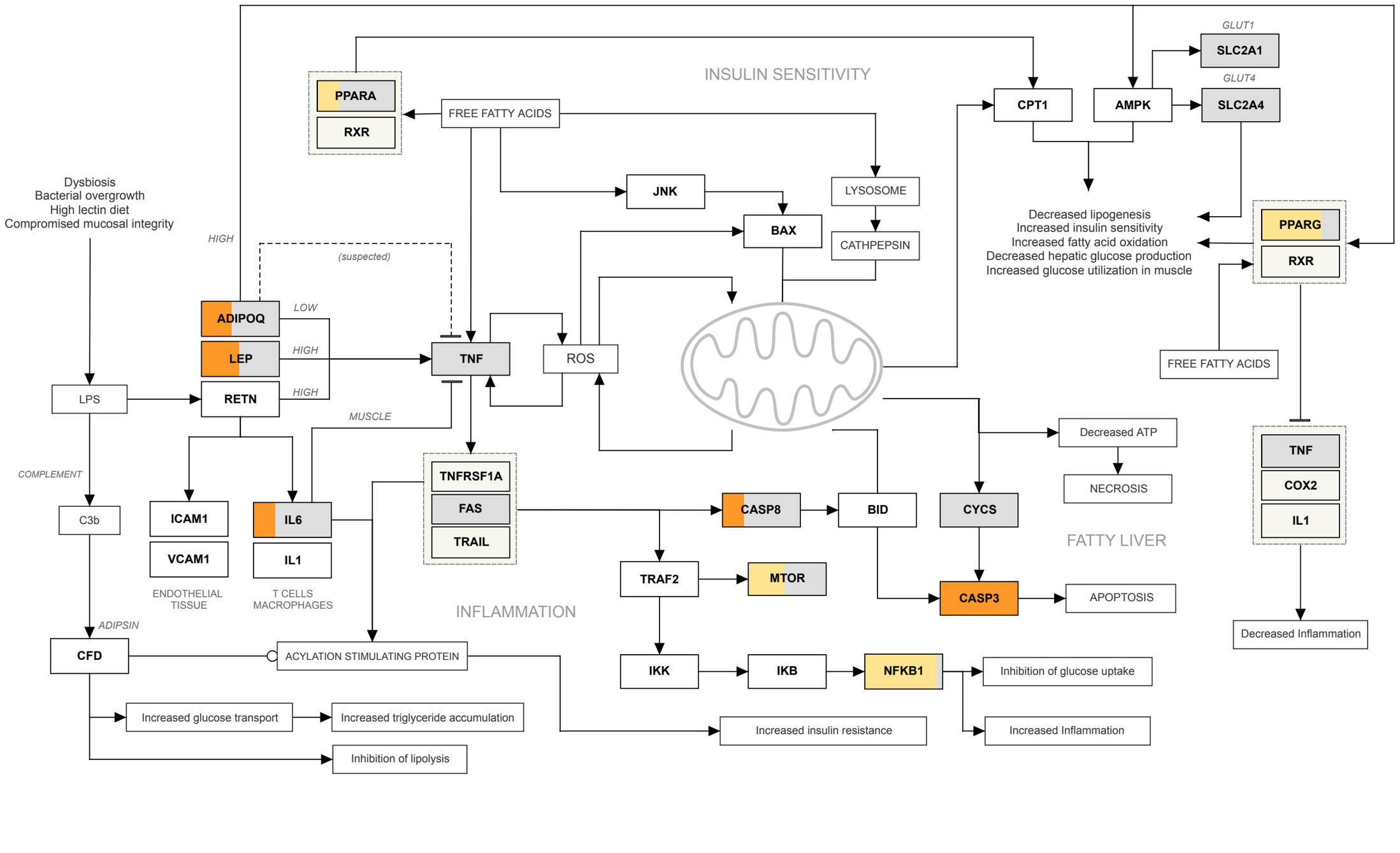
ENERGY/ METABOLISM

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).

Adipocytokine Signaling

Adipocytokine, or adipokine, is a general term for a bioactive product produced by adipose tissue. Adipocytokines mediate inflammation, drive the growth of blood vessels, and regulate metabolism. Adipose (fat)tissue secretes an array of hormones (adipokines) that signal key organs to maintain metabolic homeostasis, and their dysfunction has been causally linked to a wide range of metabolic diseases. In addition, obesity induces production of inflammatory cytokines and infiltration of immune cells into adipose tissue, which creates a state of chronic low-grade inflammation. Metabolic inflammation has been increasingly recognized as a unifying mechanism linking obesity to a broad spectrum of pathological conditions.



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.	High Fat Diet	
2.	Low Methionine Diet	
3.	Mediterranean diet	
4.	Exercise	
5.	trans-10,cis-12 conjugated linoleic acid	
6.	Ophiopogon tuber	
7.	Poria sclerotium	
8.	Polygonatum rhizome	
9.	Angelica sinensis	
10.	Resveratrol	
11.	Yerba Mate Tea	
12.	Allium fistulosum	
13.	Chronic psychological stress	
14.	Loganate	
15.	Lotus Seed n-butanol extract (LBE)	
16.	Astragalus (Astragalus membranaceus)	
17.	Omega 3 Fatty Acids	
18.	Chokeberry	
19.	Limonene ((+), D, R, citrus, orange)	
20.	Phyllodulcin	
21.	Magnolia (Magnolia officinalis)	
22.	Honokiol	
23.	Lithium orotate	
24.	Acai Berries	
25.	Rotenone exposure	

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