Top 5 Topics to Investigate:
Created for Graham

Below is a summary of the genetic variants that may impact your overall health. Most genetic variants only increase (or decrease) your probability of getting a disease statistically. Your genetic susceptibility then combines with environmental factors, such as food, toxins, light, stress, pathogens, etc.

How can you use this information?

- *Focusing on the best ways to prevent a chronic condition by knowing where your genetic susceptibility lies.*
- *Guiding you towards the most effective ways to manage or heal a condition you already have by understanding the genes involved.*

Keep in mind that everything written here is for informational and educational purposes. It is not intended to be medical advice and should not be used as a substitute for professional medical advice, diagnosis, or treatment. Please talk with your doctor if you have any medical questions.

Please read through the recommended articles for more details and for links to scientific peer-reviewed references. Keep in mind that your genetic data may not be clinically accurate, and that it may not cover all genes related to the topic.

Topic #1: Optimizing the Methylation Cycle

The methylation cycle is a fundamental biological pathway that affects many aspects of your well-being. In a nutshell, methylation is the addition of a methyl group, which is needed for a variety of reactions such as DNA synthesis, neurotransmitter synthesis, and detoxification of some toxins. A methyl group is one carbon plus three hydrogens, and this is easily used in biological reactions. Many of the molecules that make up your body have a backbone of carbons and hydrogens, so adding another carbon plus three hydrogens (methyl group) can modify the compound. I picture methyl groups as Lego blocks, and the changes to a molecule are like adding another Lego block or two to turn your Lego car into a Lego truck.

Problems within the methylation cycle often cause high homocysteine levels, which is a marker that doctors test for heart disease risk and other problems that researchers have linked to methylation cycle problems include an increased risk of depression, anxiety, miscarriage, stroke, and certain cancers. Doctors often find that methylation cycle problems cause brain fog and mood problems. They can also lead to fatigue.

One source of methyl groups in the methylation cycle is folate (vitamin B9), and your genetic variants decrease the key enzyme needed in the folate pathway. The MTHFR gene codes for the enzyme that is

the limiting factor in the formation of methylfolate in the folate cycle. The methylfolate molecule is then used as a methyl donor in the methylation cycle.

Your genetic data shows that you have two copies of the MTHFR C677T variant. This reduces the function of the enzyme by about 70%. You also have variants (MTRR and TCN1 gene) that make it important to get enough vitamin B12.

In addition to folate, there are other sources of methyl groups in the body, such as the choline pathway. However, you have several genetic variants that interfere with your choline pathway.

Optimizing your methylation cycle is something that can help your overall wellness at a basic level.

Ways to improve methylation include:

- Eat folate-rich foods, including liver, legumes, broccoli, and leafy greens.
- Make sure you eat enough choline-rich foods (eggs, liver, sunflower lecithin).
- While the methylation cycle has a lot to do with DNA synthesis, neurotransmitters, etc., about 40% of the methyl groups are actually used to make creatine in the body. So supplementing with creatine can free up methyl groups for other uses.
- Many people supplement with methylfolate when they learn about the MTHFR variant. Along with methyl folate, the folate cycle requires B12, riboflavin (B2), and B6, so a B-complex that includes methyl folate may be a good option if you don't eat enough folate-rich foods. The RDA for folate is 400 mcg/day, so be sure to check the amount included in methylfolate supplements. Many supplements on the market now are really high doses.
- Your data also shows two copies of a COMT variant that clinicians associate with sensitivity to supplements containing methyl groups. If you decide to take a supplement, you may want to avoid high doses of methylfolate (eat more folate-rich foods instead). Also, choose adenosylB12 or hydroxyB12 instead of methylB12 (methylcobalamin).

Note that folic acid is not the same as methyl folate. Folic acid is a synthetic, stable form of folate that is often used in multivitamins and fortified foods, but it requires the MTHFR enzyme to convert it to the active form. Methyl folate is the active form of folate that bypasses the need for the MTHFR enzyme. Your data shows a DHFR gene variant that limit the amount of folate your body can use at one time. If you are looking at vitamins and supplements, I would suggest choosing methylfolate instead of folic acid.

Blood Pressure and Heart Health: Both folate (vitamin B9) and riboflavin (vitamin B2) are important for heart health and blood pressure. The MTHFR gene codes for a key enzyme needed to convert folate into the active form used by cells (methylfolate). This may mean that getting enough folate in your diet could help reduce your risk of heart disease. Alternatively, supplementing with low-dose methylfolate may also help. In addition, research studies show that in people with low riboflavin intake, the combination of folate plus riboflavin lowers blood pressure. Read the article for details on the clinical trials.

If you are wondering how much folate, choline, and B12 you are already getting in your diet, the best way to find out is to track what you eat for a few days. Again, the RDA for folate is 400 mcg/day. The

website www.cronometer.com has an easy way to track your nutrient intake (and it's free). This can show you if you need to add more folate-rich foods, supplement with B12, etc.

Articles: MTHFR Mutation: How to check your genetic data
Blood pressure, MTHFR, and riboflavin
Recipes for MTHFR: Folate-rich foods
How to check your genetic data for COMT
COMT: Interactions with Supplements
Should you take folic acid or methylfolate?
Your genes:

MTHFR C677T	rs1801133	A	AA	Decreased MTHFR enzyme, which affects the methylation cycle

COMT	rs4680	A	AA	GG= higher activity AA= lower activity
COMT	rs4633	T	TT	CC = higher activity TT= lower COMT activity
COMT	rs165599	A	AA	Incr. risk of anxiety in combination with rs4680

MTRR	rs1801394	G	GG	Decreased MTRR, affects B12
FUT2	rs601338	A	AA	AA only: non-secretor, serum B12 tests may be inaccurate
TCN1	rs526934	G	AG	B12 transporter, lower circulating B12

Topic #2: Possible Problems with Biogenic Amines

Biogenic amines include histamine and tyramine, which are formed in the body as well as being found in foods and drinks. Your data shows that you may be susceptible to problems breaking down histamine and tyramine.

Histamine Intolerance:

Your genetic data shows that you have several genetic variants that impair your ability to break down histamine. Histamine is a biogenic amine that is produced by your body and it is found in certain foods.

Too much histamine can lead to:

- Headaches/Migraines
- Digestive issues or nausea
- Problems with appetite
- Anxiety, Mood issues
- Brain fog
- Hives, Itchiness
- Sinus drainage
- Overproduction of stomach acid (heartburn)
- Problems sleeping, early waking

People often think of histamine in relation to allergic reactions, which is when your body produces a bunch of histamine at once in response to an allergen. In addition to allergic reactions, histamine is constantly used by the body in a number of ways: as a neurotransmitter (wakes you up in the morning, regulates appetite), to signal for the release of stomach acid, and within the immune system to fight off pathogens.

Histamine is a signal that works by docking with receptors to create an action within a cell. There are four different types of histamine receptors in the body, and the different functions of the receptors illustrate the many ways that high histamine levels could cause problems.

- H1 receptors are responsible for your typical allergy-type symptoms (runny nose, watery eyes) and also are involved in the sleep/wake cycle. The older types of antihistamines (e.g. Benadryl) block the H1 receptors, taking away allergy symptoms and making you sleepy.
- H2 receptors are located in the gastrointestinal tract and are responsible for the release of stomach acid (thus tied to acid reflux). Tagamet and Pepcid are medications that stop heartburn by blocking the H2 receptor.
- H3 receptors are located in the central nervous system and are responsible for regulating histamine release there.
- H4 receptors are involved in the immune system response

Your body makes and uses histamine all the time, and it regulates the levels by breaking down histamine with the HNMT enzyme. Your genetic data shows that you may not break down histamine as well as some people do.

In addition to the histamine made in your body, the foods that you eat may contain histamine. Diamine oxidase (DAO) is the enzyme needed to break down histamine from foods, and thus, decreased DAO

production can lead to higher histamine levels in the body. Your genetic variants in the AOC1 gene, which encodes the DAO enzyme, may decrease the amount of diamine oxidase that your body makes.

Foods that are high in histamine include fermented foods (salami, sauerkraut, aged cheeses, wine), spinach, avocado, chocolate, tomatoes, strawberries, shellfish and fish (if not extremely fresh), and many more. If you think you have problems related to histamine, cutting out foods containing histamine for a week or so will usually let you know if that is the problem. Here is a detailed foods list showing which foods contain histamine or cause the release of histamine. You can also google "*low histamine diet*" for a lot more information.

In addition to genetic susceptibility, your gut microbiome makes a big difference as to whether histamine intolerance is actually a problem for you. Certain types of gut bacteria can produce histamine, and an overabundance of them can tip the scales toward too much histamine in the body. While fermented foods may be great for gut health for some people, they often cause higher histamine levels. Additionally, some probiotics also contain histamine-producing bacteria.

Note: if you don't have symptoms of histamine intolerance, there is no need to avoid high histamine foods. A lot of them are really healthy!
Article: How to check for histamine intolerance genes
Your genes:

AOC1	rs10156191	T	TT	Reduced production of DAO, which is needed to break down histamine in the intestines.
AOC1	rs2052129	T	TT	
HMNT	rs1050891	A	AA	Reduced breakdown of histamine in tissues throughout the body
HMNT	rs2071048	T	CT	
HRH1	rs901865	T	CT	Increased H1 receptor

Tyramine metabolism (impaired break down of tyramine, a biogenic amine):
You may also have problems with another biogenic amine, tyramine. I've included tyramine here with histamine because a lot of the foods that are high in histamine are also high in tyramine.

There are three ways that your body breaks down tyramine -- and you have genetic variants that slow down all three pathways. Your genetic variants impacting tyramine are in the FMO3, MAOA, and CYP2D6 genes.

Eating foods containing tyramine is likely not a problem for you most of the time, but a sudden increase in tyramine levels (higher than what your body can handle) can cause a sudden jump in blood pressure. People who are on a type of antidepressant called an MAOA inhibitor also may have problems with tyramines. It is referred to as the 'cheese effect' because people on MAOA inhibitors realized they had

problems after eating aged cheeses, which are really high in tyramine. Your genetic variants make it possible for a similar reaction to happen.

Theoretically, eating a meal heavy in aged cheese, pepperoni, salami, and fermented foods, along with a lot of dark chocolate could cause a reaction with symptoms that include a severe headache, chest pain, nausea, blurred vision, and stroke-like symptoms.
Article: Tyramine Intolerance
Your genes:

MAOA	rs6323	T	TT	Decreased MAOA
FMO3	rs2266780	G	AG	Milder decrease in FMO3
FMO3	rs2266782	A	AA	
FMO3	rs909530	T	CT	
FMO3	rs909531	C	CT	
CYP2D6	rs3892097	T	CT	Decreased or non-functioning CYP2D6 enzyme
CYP2D6	rs1065852	A	AG	

Topic #3: Heart-related genetic susceptibility

Fibrinogen and increased clotting:

Your genetic data shows a number of genetic variants related to fibrinogen levels. Fibrinogen is a component of blood clots, and elevated levels of fibrinogen are associated with an increased risk of cardiovascular disease.

There are a number of lifestyle changes that affect fibrinogen. First, stress has been shown in studies to increase fibrinogen levels, so it is important to manage your stress levels as best you can. Other inflammation-related lifestyle factors such as smoking, physical inactivity, and poor diet can also raise fibrinogen levels.

People with genetic variants that increase fibrinogen can take proactive steps to keep it at normal levels. Exercise, a healthy diet, and reducing stress should help.

In addition, nattokinase supplements have been shown in studies to help lower fibrinogen levels. Talk to your doctor before starting supplements if you are taking any other medications.

For more details, background information, and references:

Elevated Fibrinogen: Risk factor for blood clots

Your genes:

FGA	rs6050	C	CT	Increased risk of stroke, DVT, heart disease
FGB	rs1800787	T	CT	Increased fibrinogen, Increased stroke risk
FGB	rs1800789	A	AG	
FGB	rs1800790	A	AG	
FGG	rs2066865	A	AG	Increased fibrinogen, Increased risk of DVT

High homocysteine:

Homocysteine is a sulfur-containing amino acid that is a byproduct of the metabolism of methionine. Methionine is used by cells to supply methyl groups, which are required in many different cellular reactions. In the methionine pathway, homocysteine is formed and then recycled back to methionine. When the pathway isn't working optimally, homocysteine levels can be elevated.

Research shows that high homocysteine levels can cause excess oxidative stress and endoplasmic reticulum stress. Epidemiologic studies show that high homocysteine levels are strongly linked to an increased relative risk of cardiovascular diseases.

Genetic variants in several pathways interact with what you eat (or don't eat) to increase homocysteine levels. Your genetic data indicates that you have several variants that are linked to higher homocysteine levels. You may want to get a blood test done at some point, perhaps the next time you go to the doctor, to see what your homocysteine levels are. If homocysteine is high, increasing dietary folate or supplementing with B vitamins (riboflavin, B6, and folate) may help to reduce your homocysteine.
Article: Homocysteine: Genetics and Solutions
Your genes:

MTHFR	rs1801133	A	AA	MTHFR C677T, higher homocysteine levels, especially if folate is lacking
MTR	rs1805087	G	AG	increased risk of cognitive impairment due to higher homocysteine
MTR	rs2275565	T	GT	associated with higher homocysteine levels
MTRR	rs1801394	G	GG	somewhat increased homocysteine levels, especially if riboflavin is low
PEMT	rs7946	T	TT	TT: homocysteine increases with low folate diet
BHMT	rs3733890	A	AG	reduced conversion of choline to betaine

Topic #4: Inflammation & Autoimmune Risk Factors

Heightened inflammatory response and propensity for chronic inflammation:

I'm going to tie together several genetic variants that affect your body's inflammatory response. These variants are covered in different Genetic Lifehacks articles (I'll list them below), but together they paint a picture of an increased inflammatory response.

Your body's inflammatory response is vital for fighting off infection, but you carry several variants that can lead to an increased inflammatory response. While this may have been great for surviving malaria or leprosy, in our modern world it often leads to an overactive inflammatory response and an increased risk of autoimmune disease.

The variants your genetic data shows you carry are in the IL17A, NLRP3, IL6, IL1A, and IL1B genes, which code for important parts of your immune system. These variants put you at increased risk for chronic inflammation-related diseases and autoimmune disorders.

Many chronic diseases, including diabetes, heart disease, NAFLD, gum disease, depression, asthma, and neurodegenerative diseases, have persistent low-grade inflammation at their root.

Carrying the genetic variant doesn't mean you'll develop any of these conditions - it just statistically increases your risk. Environmental and lifestyle factors also play a role.

The key is that if you have an inflammation-related disease, you can look at your inflammation-related genetic variants and see how they affect the disease. The related articles all list "lifehacks" that can be used specifically to counteract the genetic variants. For example, curcumin and rosmarinic acid have been shown in studies to moderate inflammatory TNF-alpha levels. Vitamin D can help reduce high levels of IL-17. Special pro-resolving mediators derived from DHA and EPA (in fish oil) are essential for resolving inflammation.

Genetic Lifehacks Articles:

Inflammation: Causes and Natural Solutions
TNF-alpha: Inflammation Genes
Gingivitis and Your Genes
Chronic Inflammation & Autoimmune Risk - IL17
Emulsifiers and Your Microbiome
Genetics and back pain
Specialized Pro-resolving Mediators: Getting Rid of Chronic Inflammation
NLRP3 Inflammasome, Genetics, and Chronic Inflammation

Your genes:

IL17A	rs2275913	A	AG	Increased risk of autoimmune, periodontal, and bowel disease

IL10	rs1800896	C	CT	Increased risk of intestinal inflammation (Crohn's, IBD, etc) due to the emulsifiers and surfactants commonly found in processed foods, supplements and medications.
IL10	rs1800871	G	AG	

IL1A	rs1800587	A	AG	Increased risk of pain from degenerative disc disease

IL1A	rs1800587	A	AG	Increased risk of periodontitis or gingivitis
IL1B	rs1143634	A	AG	
IL6	rs1800795	C	CG	
IL8	rs4073	A	AA	
IL10	rs1800896	C	CT	

CIAS1	rs1539019	A	AC	AA only: Increased NLRP3
CIAS1	rs10754558	C	CC	Somewhat increased NLRP3 activation

IL8	rs4073	A	AA	A/A: Increased IL8; increased risk of periodontitis, gastritis, Alzheimers, diabetic nephropathy
IL6	rs1800795	C	CG	C/C: lower risk of gingivitis
IL1B	rs16944	G	GG	G - Typical risk of septic shock; A/A: Increased risk of septic shock
IL1B	rs1143634	A	AG	Increased risk of gingivitis
IL1A	rs1800587	A	AG	Increased IL1A, increased risk of gum disease, tinnitus, acne, hearing loss
IL10	rs1800896	C	CT	CC: higher IL-10 (usually good!)
INFG	rs2430561	A	AT	Increased interferon-gamma
MTHFR	rs1801133	A	AA	Decreased MTHFR; decreased detoxification of mercury and arsenic

Inflammation as a cause of depression and/or anxiety

Researchers now think that one cause of depression or anxiety is chronically elevated inflammatory cytokines which cause changes in the brain. Inflammatory cytokines cause changes in the blood-brain barrier and elevate inflammation in the brain. This causes alterations to the way that neurotransmitters are made and broken down.

There are a number of causes of chronic low levels of inflammation in the body including stress, autoimmune diseases, poor diet, obesity, and gut dysbiosis.

Combined with the lifestyle factors above, some people are genetically prone to higher levels of inflammatory cytokines. Your genetic data shows that you carry several of the genetic variants linked to higher inflammation and depression or anxiety.

If you have problems with depression or anxiety, possible ways to combat chronic inflammation -- in addition to addressing the source of your inflammation -- include supplements such as curcumin, quercetin, and Andrographis. Regular exercise has also been shown to help with depression, specifically in people with higher inflammation. Read through the article for more personalized lifehacks.

Article: Is inflammation causing your depression and anxiety? Inflammation genes and mood

Your genes:

IL6	rs1800796	G	GG	GG only: incr. depression with inflammation
IL6	rs1800795	C	CG	CC only: increased risk of depression with stress
IL6	rs1800797	A	AG	Incr. depression risk
IL1B	rs16944	G	GG	GG only: Incr. IL1B, incr. risk depression
IDO1	rs9657182	C	CC	CC only: more likely to have depr. with inflammation
KMO	rs1053230	C	CC	CC only: higher depression risk

General Autoimmune Risk:

The CTLA-4 gene codes for a part of the immune system that is important in preventing autoimmune diseases. Your immune system has a kind of checks and balances system. You need to have a powerful response against a virus or bacteria, but you also have to shut off the response so that your own cells aren't attacked. The CTLA-4 gene codes for a checkpoint that regulates the immune response.

You carry two CTLA4 genetic variants that increase the risk of several different autoimmune diseases including celiac disease, Hashimoto's (autoimmune hypothyroidism), Grave's disease (autoimmune hyperthyroidism), rheumatoid arthritis, type 1 diabetes, lupus, vitiligo, multiple sclerosis, and myasthenia gravis. The CTLA4 variants don't usually cause any of those diseases on their own - rather, it is a combination of the variants, other genes, and environmental factors.

Article: Autoimmune Disease Genetic Risk Factors: CTLA-4 Gene

Your genes:

CTLA4	rs231775	G	AG	Increased risk of autoimmune conditions including Hashimoto's, Graves, type-1 diabetes
CTLA4	rs3087243	G	GG	

Topic #5: Cognitive Function and Mood

Mitochondrial dysfunction and depressive disorders

Your cells' mitochondria are responsible for making most of the ATP (energy molecule) for the body. Recently, research has pointed to dysfunctional mitochondria as one root cause of major depressive disorder. The brain uses a ton of energy, produced mainly in the mitochondria.

Essentially, various environmental factors can combine with genetic susceptibility to increase oxidative stress and decrease mitochondrial function in a cell. Longer term mitochondrial dysfunction affects brain plasticity - the way the brain is wired. Research shows that for longer-term depression and bipolar disorder, there are structural changes that occur in the brain.

Chronic, mild stress inhibits mitochondrial function. This can lead to an increase in oxidative stress in the cell and changes to the mitochondria. The body is made to handle short-term stress - like running from a tiger - really well. But the low-level stress that doesn't go away (mental or physical stress) can cause physical changes in the cells. Constantly elevated cortisol levels can negatively affect mitochondrial function.

In addition to cortisol and chronic stress, other causes of mitochondrial dysfunction can include excessive alcohol consumption, leaky gut, exposure to toxicants, and excess iron.

Genetic variants linked to mitochondrial dysfunction and major depressive disorder include genes involved in mitochondrial function, oxidative stress, and cortisol.

Glutathione is one of the main intracellular antioxidants produced to combat oxidative stress in the cells. For the cell to make glutathione, it needs glutamate, cysteine, and glycine. N-acetyl cysteine is a supplement that has been shown to increase cysteine, and glycine is available as a supplement or in collagen and gelatin.

Melatonin, which is produced overnight in darkness, is also an intracellular antioxidant and mitochondrial protectant. Try blocking out the blue light from electronics or bright overhead lights for a couple of hours before bedtime. This has been shown in studies to increase melatonin levels by about 50% on average.

If you are dealing with depression, please talk with your doctor before adding any supplements or making major changes.

Read through the article on mitochondrial dysfunction for more information and more on supplements and lifestyle changes. Depression, genetics, and mitochondrial function

Your genes:

SOD2	rs4880	A	AG	AA only: higher chronic inflammation, increased relative risk of depression and psychological stress
GSTA1	rs3957357	A	AG	Low/ non-functioning enzyme; increased relative risk of psychiatric illness
BDNF	rs6265	T	TT	TT: decreased BDNF; decreased hippocampus volume if exposed to early life stress
FKBP5	rs1360780	T	CT	Increased relative risk for depression, incomplete cortisol recovery, and increased anxiety after psychosocial stress
FKBP5	rs3800373	C	AC	Increased relative risk of major depressive disorder
CRHR1	rs110402	G	GG	GG: elevated cortisol in people exposed to childhood trauma
CRHR1	rs242924	G	GG	GG: elevated cortisol in people exposed to childhood trauma
CRHR1	rs242941	A	AA	slightly increased relative risk of depression
TOMM40	rs2075650	G	AG	increased susceptibility to depression (mitochondrial membrane protein)

Susceptibility to Anxiety Issues:

Genetics plays a role in anxiety disorders, with heritability estimated to be up to 50%. The other half of the picture here is environmental and lifestyle factors. The genetic component can cause a physical alteration in the way the brain works or in the physiological response to stress.

Learning about the genetic pathways involved can help if you have issues with anxiety.

- The ACCN2 gene encodes an acid-sensing ion channel that is active in the brain. Breathing in more CO2 or holding your breath causes a shift in pH which is detected in the brain. This can trigger panic, which is really an appropriate response when you have too much CO2 and not enough oxygen. The genetic variant in the ACCN2 gene causes heightened sensitivity to slightly higher CO2 levels. Elevated CO2 levels could occur in someone prone to holding their breath or not breathing normally when nervous, and the elevated CO2 then increases the physiological aspects of feeling panic.
- The SLC6A4 gene encodes a serotonin receptor. The variant in this gene is associated with an increased risk of social anxiety disorder.
- BDNF variants interact with the other variants to exacerbate the risk of anxiety.

Read through the article for specific solutions related to these variants.

Article: Anxiety: Genetic connections and personalized solutions

Your genes:

ADORA2A	rs5751876	T	CT	TT: Increased risk panic disorder; Increased anxiety with high caffeine

SLC6A4	rs140701	T	CT	Increased risk panic disorder; social anxiety disorder
BDNF	rs6265	T	TT	Decreased BDNF; Increased risk anxiety disorders
FKBP5	rs1360780	T	CT	TT only: incomplete cortisol recovery; Increased anxiety after psychosocial stress
CHCR1	rs110402	G	GG	Increased cortisol in childhood trauma
ACCN2	rs10875995	C	CT	Heightened reactivity to high CO2 levels; Increased risk panic disorders
ACCN2	rs685012	C	CT	Heightened reactivity to high CO2 levels; Increased risk panic disorders

Decreased BDNF levels:

Your genetic data shows that you carry two different BDNF genetic variants that are linked with decreased BDNF (brain-derived neurotrophic factor) levels. Lower levels of BDNF are linked to learning difficulties (working memory), increased risk of depression, and cognitive decline in aging.

BDNF acts in the brain to encourage neuronal growth and improve neuronal function. The decreased BDNF from the genetic variant (rs6265) is linked in studies to increased anxiety and depression. It is also linked with slight alterations in the way people learn.

Not all agree, though, and this may be because there are lifestyle factors that impact BDNF levels.

If you think that lower BDNF levels are having a negative impact on you, here are a few things that research has shown to help:

- Sleep and circadian rhythm impact BDNF, and sleeping well is really important for higher BDNF levels.
- Getting outside in the sunlight every day increases BDNF.
- Fish oil (specifically DHA) boosts BDNF as well.
- One big way to increase BDNF is to exercise regularly.

Often, variants in one gene will interact with other genes to impact the risk of various disorders.

Your genetic data shows that you also have a serotonin receptor variant that interacts with the BDNF variant to increase the risk of depression, anxiety disorder, and bipolar disorder.

This doesn't mean that you are destined to have depression or anxiety - just that you carry the genetic variants that are statistically linked to them. But… if you do have problems with a mood disorder, read through the article for more details and talk with your doctor about ways to boost BDNF.

Article: The Interaction Between BDNF and Serotonin

BDNF variants: introversion, stress resilience, cognition, and depression

Your genes:

BDNF	rs6265	T	TT	Decreased BDNF levels
HTR1A	rs6295	G	CG	Increased risk of depression when combined with BDNF

BDNF	rs7103411	C	CC	Minor decrease in BDNF; Increased impulsivity children

Topic #6: Circadian Rhythm, Melatonin, Sleep, and Mood

Your circadian rhythm genetic variants indicate that you may be susceptible to sleep and mood problems. Let me give you some background on melatonin and circadian rhythms, and then I'll explain how your genetic variants come into play here.

There has been a lot of research in the last decade that shows how important your circadian rhythm is to your overall health. The body's circadian clock is set by the rising and falling levels of a few core circadian proteins over the course of 24 hours. During the day, the genes CLOCK and BMAL1 increase the production of their proteins, and during the night, there is an increase in the levels of PER and CRY proteins. This is a transcription/translation feedback loop that gets a little complicated -- but at a simple level, these four genes, rising and falling in pairs, make up the core of the circadian clock.

Researchers have now determined that this central circadian clock controls many of the processes that take place in the body. For example, the enzymes your liver produces to break down food, drugs, and toxins are mostly controlled by circadian rhythms. Your body expects you to eat food (or take medicine) at the same time each day. The liver gears up to produce the enzymes needed for metabolism and detoxification at the time you normally eat. Researchers have now found that this timing mechanism plays a big role in how well drugs (especially chemotherapy) work.

Numerous studies have linked circadian disruption to weight gain, depression, anxiety, bipolar disorder, ADHD, Alzheimer's disease, heart disease, diabetes, and breast and prostate cancer.

Most people think of circadian rhythms in terms of the sleep/wake cycle—and sleep is a big part of it! But your circadian rhythm also controls your changes in body temperature throughout the day, the rise and fall of cortisol and other hormones, the release of insulin at night, the timing of enzyme production, and (literally) about a thousand other processes going on in your body!

The core circadian clock mechanism is located in the suprachiasmatic nucleus, which is part of the hypothalamus in the brain. This "clock" is reset each day by light hitting specific receptors in the retina of your eye. These receptors are called non-image-forming photoreceptors.

Specifically, light in the blue wavelengths (~480 nm) excites a photoreceptor called melanopsin, which sends a signal that it is daytime. This turns off melatonin production in the brain. Thus, blue-wavelength light at night (from televisions, cell phones, computers, and bright overhead lights) has been found to cause chronic modern health problems by reducing melatonin production at night and altering circadian rhythms.

Melatonin acts as a signaling molecule in the brain to set circadian rhythm. It also does other things, though, such as acting as an intracellular antioxidant, which is important in cancer prevention. Melatonin is a signaling molecule in the pancreas, controlling insulin release overnight. While melatonin is often called the 'sleep hormone', it is more of a circadian regulator that rises while you sleep rather than something that makes people fall asleep.

Circadian rhythm and ADHD: While dopamine is integrally related to ADHD symptoms, such as focus and working memory, ADHD patients often also have circadian rhythm abnormalities, including sleep problems. Studies on circadian rhythm genes show that they can be part of the cause of ADHD for some people. The studies show that people with ADHD often have altered core circadian gene expression. Additionally, dopamine levels may interact with and change circadian gene expression.

Circadian rhythm and Alzheimer's prevention: Melatonin and circadian rhythms are important in the prevention of Alzheimer's disease. Animal studies also show that exposure to artificial light at night increases tau fibrils and decreases clearance of amyloid-beta plaque, two factors that are hallmarks of Alzheimer's disease pathology. Several recent, high-quality human studies show that melatonin specifically clears amyloid-beta proteins from the brain at night. Alzheimer's patients often have an altered circadian rhythm, and researchers are finding that it is a two-way street: an altered circadian rhythm is likely part of the cause of Alzheimer's, and then the Alzheimer's pathology further disrupts the circadian rhythm.

Circadian rhythm impacts mood: Circadian disruption is also linked to mood and mood disorders. If you've ever traveled and experienced jet lag, you may have noticed how circadian disruption affects mood, cognition, and overall well-being. Similar to jet lag on a smaller scale, changes in sleep timing (e.g., staying up late on weekends) and mismatches between lighting, meal timing, etc., can cause your body to be chronically a bit jet-lagged. Research has shown for decades (perhaps centuries) that altered circadian rhythms are associated with mood disorders. One way researchers can now determine whether this "link" is causal is to look at genetics. In this case, to prove that circadian disruption can cause mood disorders, researchers have examined whether genetic variants that disrupt circadian rhythms are also associated with mood disorders.

A number of genetic variants in the genes that code for the circadian clock system have been linked to depression, anxiety, and bipolar disorder. Interestingly, several commonly used antidepressants (SSRIs) actually interfere with the body's circadian rhythm, altering the rhythm or response to daylight. Getting your circadian rhythm on track and in sync can be a powerful way to change your mood.

Let's talk about how **your genes** fit into this topic, specifically:

- Your genetic data shows that you carry an OPN4 variant that may make you more susceptible to light levels at night. The OPN4 gene codes for the melanopsin receptor that detects light in the blue wavelengths. This variant is also linked to an increased risk of seasonal affective disorder (seasonal depression).
- Your genetic data shows a CLOCK (core circadian rhythm gene) variant that is linked to being more active in the evening. This translates into staying up later for some people. The variant is linked to weight gain and high ghrelin levels (the hunger hormone).
- Additionally, your genetic data shows a second CLOCK variant linked to an increased risk of sleep disturbances.

- You carry a PER2 (core circadian rhythm gene) variant linked to increased sleep difficulty and increased risk for sleep disturbances.
- Melatonin is derived from serotonin, which is made using the essential amino acid tryptophan. Your data shows two copies of a variant in the TPH2 gene, which codes for a key enzyme in the conversion of tryptophan to serotonin/melatonin. This is linked to a possible decrease in melatonin production.
- You have a GABRA6 variant that is linked to insomnia, especially when stressed or worried.
- Your data shows a GSK3B variant that is linked to insomnia, especially if depressed.
- You carry a couple of variants in the ARNTL1 (BMAL1, core circadian clock gene) that are linked to an increased risk of diabetes and heart disease.
- You carry a CRY2 (core circadian rhythm gene) variant linked to an increased risk of depression.
- Additionally, your data show an NR1D1 circadian gene variant also linked to an increased risk of depression.
- Your data shows an NPAS2 (core circadian clock gene) variant that is linked to an increased risk of depression and bipolar disorder.

None of these variants are big risk factors on their own, but they all come together to paint a picture of it being important to keep your circadian rhythm on track.

Solutions here:

First and foremost, blocking blue light at night - either by turning off light sources or wearing 100% blue-blocking glasses - will help to increase melatonin production overnight and keep your circadian rhythm in sync. Light in the blue wavelengths has a big impact on circadian rhythm at night. Exposure to sunlight in the morning is also important for your circadian rhythm. This has been shown to increase serotonin during the day and melatonin the next night. Going to bed at a consistent time is also important. Studies show that there is a negative health effect from staying up late on weekends and going to bed early on weekdays (called social jet lag).

For most people, blocking blue light at night to increase melatonin production is enough to produce better sleep and better overall mental health. (Studies show that wearing blue light blocking glasses increases melatonin production by 50% in about two weeks). However, melatonin production declines with age. Depending on your age, you may want to consider a low-dose, time-released melatonin supplement. More is not always better with melatonin; a low dose is often enough. The key is that it must be timed release. Supplemental melatonin is metabolized pretty quickly by the body, so the regular melatonin supplements give you a big dose that is then cleared out too quickly.

There are also a number of studies that show that dim light from streetlights at night has a negative effect on people. Blackout curtains or blinds are great for making a bedroom really dark at night. I've also found it helps to cover all the little glowing indicator lights on electronics with black tape. Eating on a regular schedule also helps to keep your circadian rhythm in sync, and your body expects you to stop eating several hours before bedtime.

Genetic Lifehacks Articles: Depression, Genetics, and Circadian Rhythm

[Alzheimer's and Light at Night: Taking action to prevent this disease]
[Melatonin: Key to Health and Longevity]
[Color TV has made us fat: melatonin, genetics, and light at night]
[Blue-blocking Glasses:]
[Using your genetic data to solve sleep problems]
[Supplemental Melatonin]
[ADHD Genes: Exploring the Role of Genetics, Environment, and Neurochemistry in ADHD]

Your genes:

OPN4	rs1079610	C	CT	Attenuated response to light; earlier sleep/wake timing

CLOCK	rs1801260	G	AG	Higher activity level in the evening, often leading to delayed sleep
CLOCK	rs11932595	G	AG	Increased risk of sleep difficulty or sleep disturbances
PER2	rs35333999	T	CT	Likely to stay up later with evening chronotype; this variant is linked to a longer circadian period
GSK3B	rs334558	G	AG	Increased risk of insomnia in depression
PER2	rs7602358	G	GT	Increased risk of insomnia, especially when stressed
GABRA6	rs3219151	T	CT	Increased risk of insomnia with adverse life events, increased risk of panic disorder

BDNF	rs6265	T	TT	Decreased BDNF, averages over 20 minutes less of deep sleep

CRY2	rs10838524	G	AG	Increased risk of depression
NR1D1	rs2314339	T	CT	Increased risk of depression

NPAS2	rs13025524	A	AG	Increased risk for bipolar, depression

ADHD and Circadian Rhythm:

ANKK1	rs1800497	A	AG	increased risk of ADHD

CLOCK	rs1801260	G	AG	delayed sleep; increased risk of ADHD
ARNTL2	rs2306074	T	TT	higher risk of ADHD (common genotype)
PER1	rs2518023	G	GT	higher risk of ADHD (common genotype)
TPH2	rs1843809	G	GG	decreased risk of ADHD

Topic #7: Foods / Nutrients and Your Genes

Genetics can often help point the way to specific nutrients and foods that you may want to either increase or decrease in your diet. Below are some genetic variants that may affect certain nutrients for you.

DHA and EPA: Impaired conversion of plant omega-3s

The body converts dietary fats into different lengths of fatty acids that the body needs. It uses an enzyme called fatty acid desaturase 1, which is encoded by the FADS1 gene. This allows us to eat different types of fats, such as shorter chain fatty acids, and convert them into the longer chain forms that the body also needs. For example, when people eat plants that contain omega-3 fatty acids, the body can convert some of these fatty acids into DHA or EPA, which are important for brain health.

This conversion mechanism for plant omega-3s to DHA probably doesn't work as well for you as it does for most people. You carry genetic variants of FADS1 and FADS2 that reduce the function of the enzymes. Instead of relying on flax or chia seeds for DHA, people with this genotype may be better off eating fish on a regular basis or supplementing with DHA and EPA (fish oil, krill oil, or algae oil).

Article: Ancestral Diet: Omega-3 and Omega-6 Fatty Acids

Your genes:

FADS1	rs174546	T	CT	The FADS variants decrease conversion of linoleic acid to arachidonic acid, and alpha-linolenic acid to EPA and DHA.
FADS2	rs1535	G	AG	

Vitamin D:

Your genetic data shows that you may be prone to low vitamin D levels. You can increase your vitamin D levels by spending time in the sun or by eating certain foods. Currently, vitamin D is added to milk in the U.S. and Canada. Fatty fish such as salmon, tuna, and mackerel are also food sources of vitamin D. Some types of mushrooms, when exposed to UV light, also contain vitamin D (as D2). Testing your vitamin D levels will tell you if you are deficient and can help you understand if you need more folate.

Article: Shining Genetic Light on Your Vitamin D Levels

Your genes:

CYP2R1	rs2060793	A	AG	Lower vitamin D levels
CYP2R1	rs1562902	T	CT	Higher vitamin D levels
CYP27B1	rs10877012	T	GT	Increased fracture risk (elderly)

CYP2R1	rs10741657	G	AG	More likely to have vitamin D insufficiency or deficiency
GC	rs7041	A	AA	Lower vitamin D levels
VDR-TaqI	rs731236	A	AG	
VDR-BsmI	rs1544410	T	CT	
VDR FokI	rs2228570	G	AG	

Getting enough choline:

Choline is an essential nutrient used in the methylation cycle and in the formation of cell membranes. Choline is also a precursor to acetylcholine, an important neurotransmitter. You carry several genetic variants that affect your need for choline, so it is important to get plenty of choline-rich foods. Good sources of choline include liver, eggs, beef, chicken, fish, and mushrooms.

Article: How your genes influence your need for choline

Which type of choline works best with your genes?

Your genes:

PEMT	rs7946	T	TT	Decreased PEMT activity, phosphatidylcholine
PEMT	rs12325817	G	GG	Increased risk of organ dysfunction with low choline diet
CHKA	rs10791957	A	AA	Decr. turnover of methionine to phosphatidylcholine
BHMT	rs3733890	A	AG	Decreased conversion of choline to betaine
FMO3	rs2266782	A	AA	Choline used less as a methyl donor
MTHFD1	rs2236225	A	AG	More likely to have choline deficiency (check diet)

Riboflavin:

Your genetic data shows that you carry several FMO3 genetic variants and the MTHFR C677T variant that may increase your need for riboflavin (vitamin B2). Riboflavin is an essential cofactor in energy production in the mitochondria. Foods high in riboflavin include fortified wheat products, cheese, eggs, milk, fish, chicken, beef, and some vegetables. It is also available as a supplement. Studies have shown that for people with the MTHFR variant and high homocysteine levels, riboflavin supplementation may help to reduce homocysteine and reduce the risk of heart problems.

Your need for riboflavin (B2): MTHFR and other genetic variants

Your genes:

MTHFR	rs1801133	A	AA	Riboflavin may help lower homocysteine
FMO3	rs2266782	A	AA	Decreased FMO3, which breaks down nitrogen containing amines. Some people helped with riboflavin.
FMO3	rs909531	C	CT	
FMO3	rs2266780	G	AG	
FMO3	rs909530	T	CT	

Vitamin B6:

Vitamin B6 is an important cofactor in hundreds of different enzymatic reactions. For example, low levels of B6 are linked to an increased risk of diabetes, cardiovascular disease, neurodegenerative diseases, and cancer. B6 is also important for reducing oxidative stress and inflammation.

Your genetic data indicates that you may be more susceptible than normal to having low vitamin B6 levels if you don't get plenty in your diet. Foods high in vitamin B6 include fish (salmon, tuna, mackerel), chicken, beef, avocados, sweet potatoes, and more.

Genetic Variants that Decrease Vitamin B6

Your genes:

ALPL	rs1256335	G	AG	Decreased vit. B6 levels
ALPL	rs1697421	T	CT	Slightly decreased vitamin B6 levels
ALPL	rs1780316	T	CT	
ALPL	rs4654748	C	CT	

Topic #8: Detoxification pathways and metabolism of medications

Metabolizing (breaking down) medications:
Our bodies are all different in the way we respond to medications and detoxify foreign substances. The genes in the CYP450 family code for the enzymes that initially break down toxic substances (drugs, pollutants, pesticides, etc.). Some people have genetic variants in these genes that affect the metabolism or breakdown of drugs, changing the way they react to the medication. This is why doctors often tell you to "try this medicine and see how it works.

Your genetic data shows that you have several CYP genetic variants that affect the speed at which these drug-metabolizing enzymes are likely to work. You have variants in the CYP2D6 and CYP2B6 genes that slow down their function. This may affect the way certain prescription and over-the-counter medicines work for you.

For example, some medications must be metabolized by a CYP enzyme before they begin to work because the metabolite is actually the drug. This type of medicine is called a pro-drug because the active drug is formed when your body breaks down the pro-drug. With other medications, the tablet you take is the actual drug, and the rate at which it is broken down affects how long it stays in your system. Thus, these CYP genetic variants can affect either the amount of medication needed - or - the speed at which it is eliminated (which affects how often it should be taken).

Wikipedia has a good list of the CYP enzymes and which drugs are metabolized by them. The 'substrates' column lists the medications that you may react to differently than normal.
CYP2D6: https://en.wikipedia.org/wiki/CYP2D6#Ligands
CYP2B6: https://en.wikipedia.org/wiki/CYP2B6#CYP2B6_ligands

Just like genetic variants can slow down the metabolism of certain drugs, other variants can speed it up. You carry one copy of a CYP2C19 variant that increases the speed at which the enzyme works.
CYP2C19: https://en.wikipedia.org/wiki/CYP2C19#Ligands

What can you do with this information? Drug metabolism is a complex issue that can involve multiple genetic variants, combination with other medications or supplements, as well as interactions with your age or diet. Take this as a "heads up" that certain medications may work differently for you.
Your doctor or pharmacist can give you more detailed information about how this may affect your specific situation.

Genetic Lifehacks Articles: Detoxification: Phase I and Phase II Detox Genes
CYP2D6: Metabolism of many OTC and prescription medicines
CYP2C19 Gene: Fast and Slow Medication Metabolism (Plavix)
CYP2B6: Genetic Variants That Interact with Medications

Your genes:

CYP2B6	rs3745274	T	TT	CYP2B6*6, decreased activity
CYP2B6	rs2279343	G	GG	CYP2B6, decreased activity

CYP2C19	rs12248560	T	CT	Ultrafast metabolizer

CYP2D6	rs3892097	T	CT	CYP2D6*4 decreased function
CYP2D6	rs1065852	A	AG	CYP2D6*10 decreased function

Detoxifying Phthalates:

You carry several genetic variants that are associated with not breaking down and getting rid of phthalates very well. Phthalates are a class of chemicals that are found in plastics, synthetic fragrances (like air fresheners), laundry detergents, and some personal care products. Research shows that they can act as an endocrine disruptor within the body.

Most people can break down and get rid of phthalates, but your pathways for doing so are somewhat impaired. Phthalates can be absorbed via ingestion, through the skin, or through the lungs. To avoid excessive exposure, check your ingredient labels on personal care products and try to avoid synthetic fragrances (like air fresheners, laundry products, and fake candle scents).

Article: Detoxifying Phthalates: Genes and Diet

Your genes:

CYP2B6	rs3745274	T	TT	TT: decreased CYP2B6 enzyme needed for eliminating phthalates
GSTM1	rs366631	A	AA	AA: GSTM1 null' women with high phthalates exposure at 5-fold increased risk of fibroids
HSPA1L	rs2227956	A	AG	Common genotype; more likely to develop insulin resistance with phthalate exposure

Topic #9: Gut microbiome and Vitamin B12 (Non-secretor of blood type)

Your genetic data shows that you are a non-secretor of your blood type due to a genetic variant in the FUT2 gene. This means that the oligosaccharides that make up your ABO blood type are not found in your saliva or mucosa. About 20% of people with Caucasian or African ancestry are 'non-secretors'.

Being a non-secretor can impact your gut microbiome, altering the type of bacteria that naturally inhabit your intestines. A mucous membrane lines the intestines, forming a barrier to keep the gut bacteria away from the epithelial cells of your intestines. In people who secrete their blood type, certain bacteria will colonize the top layer of the gut mucosa. On the other hand, non-secretors end up having a different balance of gut bacteria.

Specifically, you are likely to have low *Bifidobacteria* in your gut microbiome. *Bifidobacteria* are considered 'good guys' and are often included in probiotics. If you have any digestive problems (especially with gluten), a probiotic that contains *Bifidobacteria* may help you out.

The good news here is that you are likely to be immune to the norovirus and rotavirus due to being a non-secretor! These two viruses cause what is commonly called the 'stomach flu'. Research shows that there is about a 99% chance you won't get the norovirus or rotavirus.

Non-secretors have another quirk when it comes to measuring their vitamin B12 levels. People who carry this FUT2 variant usually show about a 25% increase in serum B12 levels, but that increase in serum B12 levels doesn't always mean that cells can use the B12. Thus, non-secretors may have a B12 deficiency that goes undetected by regular serum tests.

Article: Non-secretor, FUT2 gene
Your genes:

FUT2	rs601338	A	AA	AA only: non-secretor of blood type; resistant to norovirus

Topic #10: Increased Alzheimer's Risk

Your genetic data shows that your APOE genotype is APOE E4/E4, which significantly increases your risk for Alzheimer's disease.

Prevention is key. Currently, there aren't many treatments for Alzheimer's disease (hopefully that will change soon!), so the best course of action is to do everything you can to prevent it.

Studies show that lifestyle factors play a role in Alzheimer's risk, along with genetic susceptibility. Research shows that the time to work on preventing Alzheimer's is decades before symptoms appear.

- To prevent Alzheimer's, research shows that staying active, eating a healthy diet, and having good social and family relationships are important.

- Studies also show the importance of insulin sensitivity in preventing Alzheimer's, so keeping blood sugar levels stable should also be a focus of prevention.

- Melatonin, quality sleep, and circadian rhythms are very important in Alzheimer's prevention (article linked below).

- Some research suggests that low doses (microdoses) of the mineral lithium orotate may prevent Alzheimer's disease. (Article linked below)

With the APOE E4 allele, you may want to watch the amount of saturated fat in your diet. APOE is an apolipoprotein that transports fats and especially cholesterol in the lymph and blood. There are some studies that link the E4 allele to cholesterol problems when eating a diet that is high in saturated fat, and there are a few studies linking high saturated fat intake to an increased risk of Alzheimer's in people with the E4 allele. The research isn't completely clear here, but it may be something to take into consideration with your diet.

Article: Alzheimer's and APOE genotype
Alzheimer's and Light at Night: Taking action to prevent this disease
Melatonin receptor gene: Alzheimer's risk and night shift work
Lithium Orotate: Mood, Alzheimer's, and Aging
Fibronectin, Genetics, and Alzheimer's Prevention

Downloadable .pdf of Alzheimer's Prevention Research

Good things not to miss!

It is easy to get caught up in the negatives of your genetic variants and miss the good things! So I wanted to point out a couple of the 'good' variants:

Lower Lp(a) levels:

Lipoprotein (a) is a particle made in the liver that consists of Apo(a) and LDL particles. Basically, it is a cholesterol carrier that often carries oxidized cholesterol. It is involved in atherosclerosis, which is the buildup of plaque in the arteries. Your genetic data shows that you carry a genetic variant that should lead to naturally lower Lp(a) levels and is linked to a decreased risk of heart disease.

Article: Lipoprotein(a): A big genetic risk for heart disease

Longevity:

Your genetic data shows that you have a FOXO3A variant that is associated with greater longevity. This is a variant that is often found in centenarians.

Article: Living to 100: Longevity and Genetics

Decreased CRP:

CRP levels are commonly tested to determine overall inflammation level, and high CRP is linked with an increased risk of heart disease. You have a CRP gene variant linked to lower CRP levels and a decreased risk of heart disease.

Article: C-Reactive Protein Gene: Marker of Inflammation CRP

Flu fighter:

You may be genetically at a decreased risk of getting the strain of flu that circulates in some years (H3N2 strain). This doesn't mean that you can't get the flu at all, just that you are at a decreased risk and may have a somewhat milder case if you do get it.

Article: Viral Susceptibility - Coronavirus, flu, and more