Higher Levels of Genetic Variants (SNPs) Found in those with Chronic Lyme Disease

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Every year in the U.S. alone, more than 300,000 people contract Lyme disease according to the CDC. Those who are untreated, undertreated or misdiagnosed and treated late can develop severe lingering symptoms. The CDC estimates a range of 10-20% are diagnosed, treated and remain ill, while another study reports 36% who were diagnosed and treated upon having the EM bulls-eye rash and remained ill [**1**]. ILADS (International Lyme and Associated Diseases Society), an international organization dedicated to the treatment of Lyme's Disease published new treatment guidelines that contained a rigorous assessment of the evidence and found treatment failure rates ranging from 16% to 39% for early treatment. Estimates for patients with chronic Lyme disease are much higher, ranging from 26% to 50% [**1**]. The ILADS website quick facts page indicates that 40% of Lyme patients end up with long-term health problems, and minimal treatment approaches have resulted in an upwards of a 40% relapse rate, especially if treatment is delayed. Based on these varying statistics, there may be 30,000 to 150,000 new people each year suffering from chronic Lyme disease in the U.S., with potentially an equal amount of those in Europe and more around the world [**2**].

The concept of traditional naturopathy is that although pathogens may be creating illness, the individual dealing with it may very well have conditions in the body that allow the invading pathogen to thrive, or conditions that may weaken the immune system, thus lessening the success of medical treatment. Consequently, improving the conditions in the body, and strengthening the immune system, may result in medical care being more effective.

As a traditional naturopath my goal, while working with my clients, is not to diagnose and treat disease but to consult and educate them on how they can use nutrition and detoxification therapies to support health. Several years ago I started investigating how advances in genetic testing can give us valuable clues as to how critical functions in the body may be impaired due to what is called genetic variants. As I consulted with those with chronic Lyme, I noticed that they appeared to have genetic patterns that resulted in the creation of a molecule called peroxynitrite that is an oxidizing agent that damages the body, adds to the toxic load, depletes glutathione and weakens the immune system. This has the potential to be a factor as to why some individuals remain chronically ill, despite the best antibiotic and medical care.

Peroxynitrite is formed when a free radical called superoxide combines with an important and critical gas called nitric oxide and forms peroxynitrite. The name for this process is called NOS uncoupling.

To determine if unique genetic patterns existed that would cause higher levels of peroxynitrite and higher toxicity in those individuals suffering from chronic Lyme, I created the NutriGenetic Research Institute to further investigate. For those with chronic Lyme, we examined 350 genes from 192 participants, who voluntarily submitted their genome for a global contrast to data supplied by the 1000 Genome Phase 3 Project [**3**].

The reference and alternate alleles for each of the SNPs were determined using the HaploReg v4.1 database [**4**]. This data was then compared to data supplied by the 1000 Genome Phase 3 Project. The ratio of SNPs between the Chronic Lyme Group and the Genome Project study was then calculated.

Each of us inherit our genes from parents, 50% from mother and 50% from father. Sometimes, there are genetic mutations, technically called Single Nucleotide Polymorphisms or SNPs. These SNPs can reduce the production of much needed molecules in the body that perform critical functions and potentially interfere with the removal of toxic substances that can harm the body.

It's quite possible that these genetic mutations (SNPs) can lead to nutrient deficiencies, increased free radicals or other toxic substances that may allow Lyme to be resistant to the treatment of Lyme.

The study showed some potentially promising results. The hope is that if we can identify where the SNPs are creating deficiencies, or impeding the ability to clear toxins, then those SNPs may be compensated for with targeted nutritional support that may allow medical treatments to be more effective.

The genes with the most significant increase in the Lyme group are detailed below.

Mitochondrial Function

Inside each cell there is, what is called, the Mitochondria where fats, carbohydrates and proteins are turned into energy, known as ATP. ATP is the fuel of the body. The first step of getting fats into the mitochondria is the production of carnitine from the SLC22A5 genes. Carnitine is responsible for carrying the fats into the cell so the mitochondria can create ATP. If fats are not carried into the mitochondria, the likely result is lack of ATP production [**5**].

Then after carnitine carries fats into the mitochondria, other enzymes play vital roles. The ACAT2 gene is involved with producing Acetyl-CoA C-acetyltransferase. This enzyme participates in 10 metabolic pathways: fatty acid metabolism, synthesis and degradation of ketone bodies, valine, leucine and isoleucine degradation, lysine degradation, tryptophan metabolism, pyruvate metabolism, benzoate degradation via coa ligation, propanoate metabolism, butanoate metabolism, and two-component system - general [**6**]. The last function of the mitochondria is the electron transport chain. NDUFS7 is one of the 40 subunits that makes Complex I of the electron transport chain. Complex I translocates four protons across the inner membrane per molecule of oxidized NADH, helping to build the electrochemical potential difference used to produce ATP [**7**]. Interestingly those with chronic Lyme have higher amounts of variants in many critical portions of mitochondrial function.

Table 1 shows how the group with chronic Lyme compared to the control group. The ratio shows how many times more SNPs there were in those with chronic Lyme and the control group. With these extra genetic mutations it would seem likely that these would result in less ATP, the energy that fuels the body.

The top portion of Appendix 1 illustrates how variants in these critical steps of mitochondrial function may result in less ATP.

Table 1: Mitochondrial Function & SNPs

Gene Name	RS Number		Ratio Between Groups
SLC22A5	rs17622208		2.39
SLC22A5	rs2073643		1.56
SLC22A5	rs1045020		2.17
ACAT-2	rs3465		1.72
ACAT-2	rs3798211		1.70
ACAT-2	rs25683		1.69
NDUFS7	rs1142530		1.45

Methylation

There is a very important nutrient the body needs for many functions called methyl folate. This methyl folate is the result of folic acid being transformed into methyl folate through several reactions from enzymes. Table 2 illustrates how there are significantly more SNPs in the genes that make methyl folate in the Lyme study group.

Another process called the methylation cycle creates a very important molecule called SAMe. The methylation cycle produces SAMe, the methyl donor that is involved in at least 165 processes in the body. The Lyme group has 1.26 times the amount of SNPs in the genes involved in the entire methylation cycle.

Table 2: Methylation Cycle SNPs

Gene Name	RS Number		Ratio Between Groups
MTHFR C677T	rs1801133		1.40
MTHFR A1209C	rs1801131		1.35
Methylation Cycle SNPs	(Appendix A)		1.26

Detoxification Genes

Removing toxins from the body is critical for good function. Toxins can accumulate with in the body as a result of many external sources in the environment, as well as biochemical reactions that create toxins in the body as it goes through various processes.

The liver is a major source of detoxification and the CYP genes are responsible for phase I liver detoxification and glutathione is responsible for phase II liver detoxification. The CYP1A1 gene, encodes a member of the cytochrome P450 superfamily of enzymes which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids [**8**]. If there are SNPs in the CYP genes, toxins may remain in the body, and create an environment that is not as healthy as one where the toxins are removed.

The amount of pesticides and herbicides being used in the United States is now at record rates, and many studies are showing too high of an exposure may be harmful to our health. Fortunately, our body makes an enzyme called paroxanase that supports the removal of these toxins. The PON1 gene is responsible for making this enzyme that helps in hydrolyzing organophosphate pesticides and nerve gasses.

Unfortunately, where there are mutations or SNPs in the PON1 genes, the ability to detox pesticides may be impaired.

Table 3 illustrates how CYP and PON1 SNPs are higher in the Lyme group, and the Appendix 1 illustrates how this may increase the toxic burden.

Superoxide dismutase and glutathione are also critical antioxidants, and deficiencies in these antioxidants may lead to increased peroxynitrite and poor detoxification. The antioxidant superoxide dismutase (SOD) takes the free radical superoxide and turns it into hydrogen peroxide. Then glutathione and catalase turns hydrogen peroxide into oxygen and water. If there is higher levels of iron that can combine with hydrogen peroxide, the lack of SOD and glutathione will exacerbate the creation of damaging hydroxyl radicals.

Table 3: Detoxification SNPs

Gene Name	RS Number		Ratio Between Groups
CYP1A1*4 C2453A	rs1799814		4.09
CYP1B1 N453S	rs1800440		1.72
PON1	rs854561		1.79
SOD2	rs2758331		1.53
GSTP1 A114V	rs1138272		2.80

Excess Glutamate that Creates More Peroxynitrite

Glutamate is an amino acid that is an excitatory neurotransmitter that also makes the relaxing neurotransmitter called GABA and is also involved in making alpha ketoglutarate, which supports energy production. The enzyme encoded by GAD1 is responsible for catalyzing the production of gamma-aminobutyric acid (GABA) from L-glutamic acid. When there are SNPs in the GAD1 genes, glutamate may remain high. This not only has the potential to make the individual anxious, but also inflamed and the potential for a weakened immunity. Studies have shown that glutamate triggers the production of nitric oxide and superoxide, which can lead to the formation of peroxynitrite ($ONOO^-$). High serum levels of total NO, MDA and nitrotyrosine observed in patients with Lyme borreliosis indicate on enhancement of lipid peroxidation and protein nitration, which may enhance the inflammatory process in Lyme patients [**9**].

On average, those with Lyme disease have more SNPs in the GAD genes, thus potentially increasing the glutamate. Table 4 illustrates the increased amount of SNPs.

Additionally, ATP is a co-factor that supports the conversion of glutamate into GABA. If the individual has low ATP from mitochondria SNPs, this may further exacerbate the inability to convert glutamate into GABA, thus creating more anxiety, higher levels of peroxynitrite and more inflammation, and a higher potential for immune weakness.

Appendix 1 illustrates how lowered ATP may hinder the GABA production and filter down into more damaging peroxynitrite.

Table 4: Glutamate SNPs

Gene Name	RS Number		Ratio Between Groups
GAD1	rs3691850		1.61
GAD1	rs3828275		1.53
GAD1	rs12185692		1.55
GAD1	rs 3791878		1.53

Excess Ammonia

Ammonia can be a toxic substance that can cause brain fog, fatigue, and other health complications if it remains too high. The Urea Cycle is responsible for removing ammonia. The Urea Cycle turns the ammonia into urea for excretion. The CPS1 gene provides instructions for making the enzyme carbamoyl phosphate synthetase I, the first step of the urea cycle. The ASS1 gene provides instructions for making argininosuccinate synthase 1, which is responsible for the third step of the urea cycle. A series of additional chemical reactions uses argininosuccinic acid to form urea, which is excreted in urine [**10**].

Additionally, if ammonia is not removed from the Urea Cycle, the body uses another important substance called BH4 to neutralize it. Lowered BH4 can impact serotonin levels and increase inflammation by making more superoxide free radical and peroxynitrite.

As Table 5 illustrates, for those with a higher amount of SNPs in the Urea Cycle, there is potential for less than optimal removal of ammonia from those with chronic Lyme disease.

Appendix 1 shows the pathway of high SNPs in the Urea Cycle may lower ammonia clearance. This higher ammonia may result in more superoxide and peroxynitrite through a process called NOS uncoupling.

Table 5: Urea Cycle SNPs

Gene Name	RS Number		Ratio Between Groups
CPS1	rs15009821		2.54
CPS1	rs6435580		2.18
CPS1	rs12468557		1.54
CPS1	rs7607205		1.52
ARG2	rs3742879		2.17
ARG2	rs742869		1.74
ASS1	rs12375699		1.62

Fenton Reaction & Iron Oxidation

The gene that was the most significantly elevated in the Chronic Lyme group was the HFE C282Y which often results in higher absorption of iron. This gene is associated with a condition called Hemochromatosis, where the excess iron can damage the internal organs.

Increased body stores of iron in various clinical situations may tip the immune regulatory balance unfavorably to allow increased growth rates of infectious organisms, and complicate the clinical management of preexisting acute and chronic diseases [**11**].

A process called the Fenton reaction occurs when cysteine combines with iron, which then combines with hydrogen peroxide to make hydroxyl radicals, ultimately damaging the body. The following SNPs may increase the potential of the Fenton Reaction, thus resulting in hydroxyl radicals, toxicity and higher peroxynitrite. As noted earlier, peroxynitrite may weaken the immune system and deplete glutathione, thus adding to the toxic burden of the body.

See Appendix 1 to see the process in which these hydroxyl radicals may be made. If there is lowered glutathione and catalase, this process may be exacerbated.

Table 6: HFE and Potential Hydroxyl Radical Production SNPs

Gene Name	RS Number		Ratio Between Groups
HFE C282Y	rs1800562		5.21
HFE H63D	rs1799945		1.53
CBS C699T	rs234706		1.93
BHMT-08 -	rs651852		1.17
SOD2	rs2758331		1.53
SOD2 A16V	rs4880		1.28
GSTP1 A114V	rs1138272		2.80
GSTP1 I105V	rs1695		1.13
CTH	rs1021737		1.25
PEMT	rs4244593		1.03
PEMT	rs7946		1.71
PEMT	rs4646406		1.78
Total			1.40

Impaired DNA Repair

When our DNA is damaged from pollutants, UV radiation, or free radicals, our bodies have the ability to do repair. The ATM gene provides instructions for making a protein that is located primarily in the nucleus of cells, where it helps control the rate at which cells grow and divide. ATM assists cells in recognizing damaged or broken DNA strands and coordinates DNA repair by activating enzymes that fix the broken strands [**12**].

The ratio between groups for ATM, rs1801516 was found to be 2.33 times higher. For those with higher levels of oxidizing agents that damage the cells, and lower level of repair, this may mean their health is negatively impacted by this combination of genetic patterns.

Conclusion

As this data was analyzed, it became increasingly clear that the SNPs that are highest in those with chronic Lyme have the potential to create the very dangerous peroxynitrite and lowered ability to repair from the damage. Peroxynitrite depletes glutathione, weakens the immune system and increases the overall toxic load in the body. Here's why this could be occurring:

The lowered ATP from mitochondria SNPs, and the GAD SNPs, can increase the glutamate that can turn into peroxynitrite.

Higher levels of SNPs in glutathione and superoxide dismutase, will allow peroxynitrite to increase and not be neutralized.

The ammonia related SNPs can enhance a process called NOS uncoupling that creates more superoxide and peroxynitrite.

The PON1 and CYP SNPs may impact the toxic load.

Finally, the HFE SNPs and corresponding SNPs involved in the creation of the Fenton reaction can deplete glutathione, make dangerous hydroxyl radicals, create further toxicity and weakened immunity.

Further studies of the data will determine if there are patterns of SNPs that emerge in individuals. For example, do we see two or three of these existing simultaneously in those with chronic Lyme disease. Look for future articles that show these results.

Please watch a video found at www.nutrigeneticresearch.org that further explains the SNP findings.

This is a small study, and at this point, it's uncertain how these SNPs may impact those with chronic Lyme, however, it's a starting point for further research. The NutriGenetic Research Institute is now requesting the 23andMe files of more individuals with chronic Lyme, with a goal of studying 500 individuals and expanding the SNPs investigated. To participate, please visit www.nutrigeneticresearch.org. Participants will receive a free genetic report, and a report as to how their genome compared to the new findings. Future research may include lab measurements, to see if these SNP patterns are impacting toxic levels or immunity.

Ongoing research will be needed to see if nutritionally compensating for these SNPs improves the quality of life for those with chronic Lyme, or supports medical treatment being more effective. Any help with the research is invited.

About the author:

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Appendix

Appendix 1: Variants (SNPs) Found in those with Chronic Lyme Disease