The Functional Perspective

Client: Jane Sample

Lyme Study Phase I SNPs

These are the SNPS that were found to be most prevalent for individuals with chronic Lyme for our Phase I Study, and is not a test for Lyme. Inherited genetic mutations when expressed may reduce enzyme production. This can lead to, nutrient deficiencies, an increased production of free radicals or other toxic substances, or a slow clearing of toxic substances. Any one of these or a combination of may have the potential to allow Lyme to be resistant to traditional treatment by suppressing the immune system or susceptible to creating toxic conditions

Gene Name	Variants	Metrics
HFE and Potential Hydroxyl Radical Production SNPs		
HFE C282Y (rs1800562)		GG 89.4%
HFE H63D (rs1799945)	1	CG 23.8%
CBS C699T (rs234706)	2	AA 11%
BHMT-08 (rs651852)		CC 27%
SOD2 (rs2758331)	1	CA 49.3%
SOD2 A16V (rs4880)	1	AG 49.5%
GSTP1 (rs1138272)		CC 85%
GSTP1 (rs1695)	1	AG 44.2%
CTH (rs1021737)	2	TT 8.5%
PEMT (rs4244593)		TT 17.3%
PEMT (rs7946)	1	CT 40.6%
PEMT (rs4646406)		TT 26.1%
HFE and Potential Hydroxyl Radical SNPs	+0	
Mitochondrial Function SNPs		
SLC22A5 (rs17622208)	1	GA 48.3%
SLC22A5 (rs2073643)	2	CC 28.6%
SLC22A5 (rs1045020)		CC 79.2%
ACAT-2 (rs3465)		GG 38.5%
ACAT-2 (rs3798211)	1	AC 48.5%
ACAT-2 (rs25683)	1	AG 48.8%
NDUFS7 (rs1142530)		TT 37.5%
Mitochondrial Function SNPs	+0	

The following SNPs may increase the potential of the Fenton Reaction and those with Lyme had a higher number of SNPs in each of the genes. CBS699 and BHMT-08 may increase the cysteine, while the glutathione variants may slow the conversion of cysteine into glutathione. Variants in SOD genes may slow the ability to neutralize the hydroxyl radicals.

Further research is needed to determine if iron oxidation from the Fenton Reaction is a contributing factor to those with chronic Lyme, and if nutritional interventions with nutrients that may slow iron absorption, regulate iron, support cysteine to glutathione conversion and NADH to recycle glutathione and superoxide dismutase may be an appropriate holistic support.

The following SNPs relate to mitochondrial function.

These findings may suggest that lowered energy production in the Krebs Cycle, may be a contributing factor to Chronic Lyme. Further studies of these findings are needed to confirm if these observations are clinically relevant, and if nutritional intervention with carnitine, choline, NADG, CoQ10 and pantethene may be a useful therapy when these variants are present.

Methylation Cycle SNPs		
MTHFR C677T (rs1801133)		GG 41.8%
MTHFR A1298C (rs1801131)	1	TG 42.7%
Methylation Cycle SNPs	+1	

These findings may suggest that an increased amount of SNPs in the MTHFR gene, in particular, and the entire Methylation pathway, may be a contributing factor in chronic Lyme. Further studies of these findings are needed to confirm if these observations are clinically relevant.

As a result of these observations, further analysis on a larger scale, and other lab testing may be warranted to see if these observed variants play a role in Chronic Lyme Disease and if supplementation of methyl folate, methyl B12, choline, B6, TMG and SAMe may be helpful holistic therapies.

Urea Cycle SNPs		
CPS1 (rs1509821)		CC 81.7%
CPS1 (rs6435580)		CC 46.1%
CPS1 (rs12468557)	1	CT 45.5%
CPS1 (rs7607205)	1	TG 47.6%
ASS1 (rs12375699)	1	CT 47%
ARG2 (rs3742879)	1	AG 39.9%
ARG2 (rs742869)	1	GA 47.6%
Urea Cycle SNPs	+0	

The following SNPs relate to the Urea Cycle.

As a result of these observations, larger scale testing and associated lab work may be needed to see if these variants create increased ammonia burden and are clinically significant in those with Chronic Lyme Disease, and if supporting the Urea Cycle and ammonia clearance would be an appropriate nutritional therapy. Digestive support therapies that reduce ammonia may be appropriate as well.

Detoxification SNPs		
CYP1A1*4 C2453A (rs1799814)		GG 91.2%
PON1 (rs854561)		CC 42.2%
SOD2 (rs2758331)	1	CA 49.3%
GSTP1 (rs1138272)		CC 85%
Detoxification SNPs	#N/A	

The following SNPs relate to detoxification.

As a result of these observations, larger scale testing and associated lab work may be needed to see if these variants are clinically significant in those with Chronic Lyme Disease, and if supporting the detox mechanisms controlled by CYP, PON1, SOD, and glutathione would be an appropriate nutritional therapy. Additional nutritional therapies that scavenge peroxynitrite should be investigated as well.

Glutamate SNPs		
GAD1 (rs3791850)		GG 58%
GAD1 (rs3828275)	2	TT 18.7%
GAD1 (rs12185692)	2	AA 16.8%
GAD1 (rs3791878)		GG 49.5%
Glutamate SNPs	-2	

The following SNPs relate to glutamate.

As a result of these findings, future research may be needed to see if higher glutamate levels and peroxynitrite are associated with symptoms related to Lyme Disease, or if supporting the conversion into GABA may be a part of a holistic treatment plan.

DNA Repair SNPs		
ATM (rs1801516)		GG 74.2%
DNA Repair SNPs	+1	

If those with chronic Lyme disease have higher rates of oxidative stress due to mitochondrial dysfunction, lowered ability to detox, iron oxidation, etc., higher rates of variants in the ATM genes may also play a contributing role. Further research may be warranted.

Lyme Study Phase II SNPs

These are the SNPS that were found to be most prevalent for individuals with chronic Lyme in our Phase II Study, and is not a test for Lyme. Inherited genetic mutations when expressed may reduce enzyme production. This can lead to, nutrient deficiencies, an increased production of free radicals or other toxic substances, or a slow clearing of toxic substances. Any one of these or a combination of may have the potential to allow Lyme to be resistant to traditional treatment by suppressing the immune system or susceptible to creating toxic conditions.

Gene Name	Variants	Metrics	
Allergic Response			
FCER1A (rs2251746)		TT 55.8%	The protein encoded by FCER1A represents the alpha subunit of the immunoglobulin epsilon receptor. This receptor is the initiator of an allergic response.
Allergic Response	+1		
Antioxidant Detox			
CAT (rs11032703)		CC 82.8%	The CAT gene provides instructions for making an enzyme called catalase. Catalase is a key antioxidant enzyme in the body's defense against oxidative stress. Oxidative stress is when there is an imbalance between the production of free radicals and the body's defense against the free radicals harmful effects. Studies have hypothesized that oxidative stress plays a role in the development of many chronic or late-onset conditions such as diabetes, asthma, Alzheimer's disease, and rheumatoid arthritis.
Antioxidant Detox	+0		
Beta-Carotene Metabolism			
BCMO1 (rs4889294)		TT 31%	BCMO1 or Beta-Carotene Oxygenase 1 is a protein coding gene. The protein encoded by this gene is a crucial enzyme in beta-carotene metabolism to vitamin A. It catalyzes the oxidative cleavage of beta-carotene into two retinal molecules. Vitamin A metabolism is important for vital processes such as vision, embryonic development, and skin protection. Polymorphisms in this gene can affect serum retinol concentration.
BCMO1 R267S (rs12934922)		AA 31.8%	
Beta-Carotene Metabolism	+2		
Drug Metabolization			
NAT2 (rs2410556)	1	TC 22.1%	The NAT2 gene encodes an enzyme that catalyzes the transfer of an acetyl group from acetyl-CoA to various arylamine and hydrazine substrates. This enzyme helps in the metabolization of drugs. Variations in these genes are associated with higher incidences of drug toxicity.
Drug Metabolization	-2		
Fatty Acid Desaturase			
FADS2 (rs174611)	1	TC 39.8%	The protein encoded by the FAD2 gene is a member of the fatty acid desaturase (FADS) gene family. Desaturase enzymes regulate the unsaturation of fatty acids through the introduction of a double bond between the carbons of the fatty acyl chain. Variations in these genes may affect long-chain polyunsaturated fatty acids metabolism.
Fatty Acid Desaturase	-1		
Fatty Acid Lipid Biosynthesis			
TALDO1 C749776T (rs11246300)	1	CT 32.4%	TALDO1 is a key enzyme in the synthesis of NADPH for lipid biosynthesis. This enzyme also helps to maintain glutathione in a reduced state to prevent cellular damage from oxygen radicals.
Fatty Acid Lipid Biosynthesis	-2		

Peanuts Allergy			
HLA-DQA2 (rs9275596)		TT 44.3%	Studies have shown that peanut allergies are one of the most common food allergies. Peanuts are not the same as tree nuts such as almonds, cashews, and walnuts. Peanuts grow underground and are part the legume family. Other examples of legumes include beans, peas, lentils and soybeans.
Peanuts Allergy	+1		
Gluten Intolerance/Celica's Disease			
IL2-21 (KIAA1109) (rs6822844)	1	GT 24.4%	Variants in these genes may increase the chances of Celiac Disease or gluten intolerance. Other factors that may impact gut health are FUT variants that impact probiotics, HNMT and ABP1 variants that lessen histamine degradation and consequently cause zonulin production, low folate or high peroxynitrite.
Gluten Intolerance/Celica Disease	-2		
Hydrolysis of Paroxon			
PON1 (rs854561)		CC 42.2%	PON1 (Paraoxonase) plays a large role in removing pesticides. It is also involved with supporting HDL function, crucial for healthy circulation.
Hydrolysis of Paroxon	+2		
Immune System			
HLA-DRB1 (rs35445101)	2	GG 9.4%	HLA-DRB1 belongs to the HLA class II of beta chain paralogs. It plays a central role in the immune system by presenting peptides derived from extracellular proteins.
Immune System	-3		
Histamine Inactivation			
HNMT (rs4646322)		CC 69%	HNMT produces the enzyme that uses a methyl group to degrade histamine in the body.
Histamine Inactivation	+1		
Lactose			
MCM6 (rs4988235)	2	AA 33.5%	The MCM6 gene is a protein coding gene. Single nucleotide polymorphisms in this gene can impact the neighboring LCT gene. The LCT gene provides instructions for making an enzyme called lactase. Variations in the MCM6 genes cause the LCT gene to remain active during adulthood. Because of this, individuals with increased variants are more likely able to digest the lactose found in milk and dairy products.
MCM6 (rs182549)	2	TT 34.1%	
Lactose	-2		

Mitochondria		
NDUFS4 (rs4147740)	1	TC 29.1%
UQCRC2 (rs4850)		GG 89.7%
PANK1 (rs10509577)		AA 87.9%
PANK1 (rs997456)	1	GA 34.1%
PANK4 (rs7535528)	1	GA 45.3%
Mitochondria - ATP	-2	
Total Phase II Mitochondria SNPs	-2	
Mitochondria - CoA Synthesis	-1	
Mitochondria - Complex III	+0	

Mitochondria -ATP Production

NDUFS4 encodes a protein that is part of a subunit for Complex I. Complex I is the first enzyme of the mitochondrial electron transport chain. There are over 40 subunits found in Complex I.

Mitochondria -Complex III

The protein encoded by UQCRC2 is located in the mitochondrion, where it is part complex III. This complex is part of the mitochondrial respiratory chain.

Mitochondria-CoA Synthesis

This gene encodes members of the pantothenate kinase family. Pantothenate kinase catalyzes the ATP-dependent phosphorylation of pantothenate (vitamin B5) to give 4′- phosphopantothenate. This reaction is the first and rate limiting step in the synthesis of coenzyme A (CoA). Coenzyme A (CoA) is a pantothenic acid derived metabolite that is essential for many crucial cellular processes including energy, lipid and amino acid metabolism. About 4% of all known enzymes utilize CoA as a cofactor and CoA thioesters are essential for over 100 different reactions of the intermediary metabolism, such as the Krebs Cycle. In humans, CoA synthesis requires cysteine, pantothenate, and ATP.

PANK1 encodes a member of the pantothenate kinase family.

PANK4 is most abundant in muscle but is expressed in all tissues.

Sex Hormone Binding Globulin		
SHBG (rs1799941)	1	GA 35.6%
Sex Hormone Binding Globulin	-1	

Variants in the SHBG gene may cause dysregulation in testosterone and estrogen levels and lowered progesterone. Hormone testing may be in order if hormonal symptoms exist. For Men (especially older men), SHBG variants may indicate more circulating SHBG resulting in lowered testosterone levels. For women, SHGB variants may indicate less SHBG resulting in higher androgen levels overall.

Interfero Activation		
IRF5 (rs4728142)	2	AA 19%
Interfero Activation	-2	

The IRF5 gene encodes a member of the interferon regulatory factor (IRF) family. The role of this factor includes modulation of cell growth, differentiation, apoptosis, and immune system activity.

Vitamin D Receptor		
VDR G14442A (rs3890733)	1	CT 42.9%
VDR G48288246A (rs11574026)	1	GA 18.7%
VDR G48293716T (rs11168293)	1	GT 42.9%
Vitamin D Receptor	-2	

VDR is a protein coding gene. This gene encodes the nuclear hormone receptor for vitamin D3. This receptor also functions as a receptor for the secondary bile acid lithocholic acid.

Cannabinoid Receptors		
CNR1 (rs806380)	2	GG 11%
CNR1 (rs806378)	2	TT 7%
CNR1 (rs12205430)	2	CC 4.3%
CNR1 T453T (rs1049353)		CC 55.8%
Cannabinoid Receptors	-3	

The CNR1 gene encodes one of two cannabinoid receptors. The cannabinoid receptors are members of the guanine-nucleotide-binding protein (G-protein) coupled receptor family.

Dopamine		
ANKK1 G318R (rs11604671)	2	AA 25.9%
DBH T8114C (rs2519155)	1	TC 42.5%
DBH T13150C (rs2519152)	1	TC 48.3%
DDC C166017G (rs1470750)	1	CG 47.5%
DRD2 (rs17529477)		GG 47.3%
DRD2 (rs12363125)	2	TT 34.9%
DRD3 (rs11706283)		CC 81.9%
DRD2 (rs4630328)		GG 40.5%
GCH1 (rs2878169)		GG 82.3%
DRD2 (rs2734839)	2	TT 35.1%
DRD2 (rs2734838)	2	GG 34.9%
DRD2 (rs2234690)	2	AA 34.7%
DRD2 (rs1800498)	2	AA 34.8%
DRD2 (rs1107162)	2	AA 34.8%
DRD2 (rs1076563)	2	CC 34.6%
DRD3 (rs963468)		GG 38.8%
DRD2 (rs6277)	2	AA 27.8%
Dopamine	-1	

The protein encoded by ANKK1 belongs to the Ser/Thr protein kinase family, and protein kinase superfamily involved in signal transduction pathways. This gene is closely linked to DRD2 gene.

The protein encoded by the DBH gene is an oxidoreductase belonging to the copper type II, ascorbate-dependent monooxygenase family. This protein converts dopamine to norepinephrine.

DDC is a protein coding gene. The encoded protein catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine (DOPA) to dopamine, L-5-hydroxytryptophan to serotonin and Ltryptophan to tryptamine.

DRD2 and DRD3 genes encode the D2 and D3 subtypes of the dopamine receptor. These Gprotein coupled receptors inhibit adenylyl cyclase activity.

The GCH1 gene encodes a member of the GTP cyclohydrolase family. The encoded protein is the first and rate-limiting enzyme in tetrahydrobiopterin (BH4) biosynthesis.

Glutamate		
GLS (rs3088307)		CC 33.3%
GLS (rs6758866)	2	AA 18.5%
GOT1 (rs9971274)		GG 84.4%
GOT1 (rs9971275)		GG 84.4%
GOT1 (rs11190083)		AA 84.3%
GRIA1 (rs889062)	1	TC 48.5%
GRIA1 (rs1381119)	1	GT 31.8%
GRIA1 (rs1463747)	1	GT 48.4%
GRIA1 (rs1493383)		CC 68.3%
GRIA1 (rs1864205)		TT 47.6%
GRIA1 (rs2910263)	1	GA 48.1%
GRIA1 (rs2910266)	1	GA 39.4%
GRIA1 (rs7719292)		AA 62.2%
GRIA1 (rs11746246)		CC 52.3%
GRIA1 (rs11741511)	1	TC 37.6%
GRIA1 (rs11748500)		GG 52.4%
GRIA2 (rs17243330)		GG 70.4%
GAD1 (rs3791850)		GG 58%
GAD1 (rs3791878)		GG 49.5%
Glutamate	+1	

GLS or Glutaminase encodes a protein that catalyzes the hydrolysis of glutamine to glutamate and ammonia.

Glutamic-oxaloacetic transaminase is a pyridoxal phosphate-dependent enzyme which exists in cytoplasmic and inner-membrane mitochondrial forms, GOT1 and GOT2, respectively. GOT plays a role in the conversion of glutamate to alpha-ketoglutarate.

GRIA1 and GRIA2 are Protein Coding genes and are glutamate receptors. Glutamate receptors are the predominant excitatory neurotransmitter receptors in human brains and are activated in a variety of normal neurophysiologic processes.

The GAD enzyme converts glutamate to GABA. When someone has high glutamate and a lot of variants in GAD, it creates conditions that may have high glutamate and low GABA that could increase stress and conditions related to high glutamate. It has been observed, that Homozygous variants in GAD have more impact that many Heterozygous. SER-GAB Assist and GABA Assist may be helpful if there is low GABA.

Lyme Study Phase III SNPs

These are the SNPS that were found to be most prevalent for individuals with chronic Lyme in our Phase III Study, and is not a test for Lyme. Inherited genetic mutations when expressed may reduce enzyme production. This can lead to, nutrient deficiencies, an increased production of free radicals or other toxic substances, or a slow clearing of toxic substances. Any one of these or a combination of may have the potential to allow Lyme to be resistant to traditional treatment by suppressing the immune system or susceptible to creating toxic conditions.

Gene Name	Variants	Metrics
Iron Absorption/Potential for Iron Overload		
SLC40A1 (rs1123109)	1	TC 32.6%
Iron Absorption/Potential for Iron Overload	-1	

When Iron combines with hydrogen peroxide in the Fenton Reaction, it creates hydroxyl radicals that create toxicity and depletes glutathione. Variants in SLC40A1 impact iron absorption.

The SLC40A1 gene contains the instructions for making a protein called ferroportin. Ferroprtin is found in all cells and tissues where iron is regulated and is the only cellular iron exporter. Ferroportin transports iron from the small intestine into the bloodstream. Ferroportin also plays a role in the metabolism of iron. Different variants of the SLC40A1 gene affect the ferroportin protein in different ways which in turn can alter the export and metabolism of iron.

Glutathione Production & Utilization		
GSTA1 (rs4715326)		TT 35.1%
GSTA2 (rs2608632)		GG 49.1%
GSTA5 (rs4715352)		CC 63.9%
GSTA5 (rs4715354)	1	GA 49.3%
GSTM1 (rs448934)		TT 53%
GSTM1 (rs12097277)	1	GA 17.7%
GSTM3 (rs10735234)	2	GG 17.4%
GSTM4 (rs627365)		GG 76.1%
GSTM4 (rs650985)		TT 88.9%
GSTO2 (rs2297235)	1	AG 40.3%
GSTP1 (rs762803)	1	CA 47.3%
GSTP1 (rs1871042)	1	CT 36.3%
GSTZ1 (rs4147578)	1	GA 40.3%
GSTZ1 (rs7972)	1	GA 14.6%
CTH A11886G (rs1145920)		GG 55.6%
CTH A32114G (rs515064)		AA 44.9%
CTH G25229T (rs663649)		GG 50.3%
CTH T16147C (rs12723350)		TT 86.4%
GCLC (rs502862)	2	CC 18.4%
GCLC (rs2066511)		CC 54.8%
GCLC (rs553822)	2	CC 18%
GCLC (rs617066)		GG 60%
GCLC (rs761141)		CC 60.2%
GLRX (rs4561)	1	AG 48%
GSR (rs3779647)	2	TT 29.2%
GSR (rs17557435)		TT 77.4%
GSR (rs8190893)		CC 87.6%
GSS A5997G (rs6088659)		CC 68.8%
SHMT2 (rs34095989)	1	GA 47.1%
Glutathione Production & Utilization	+0	

Glutathione is the master antioxidant that clears toxins, is anti-inflammatory and supports immunity. Those with chronic Lyme showed increased SNPs in the genes that support the creation, regeneration and utilization of Glutathione.

GSTs - Glutathione S-transferase encode enzymes that add glutathione to target electrophilic compounds such as therapeutic drugs, environmental toxins, and products of oxidative stress. This action is an important step in detoxification of these compounds.

CTH - The CTH gene catalyzes the last step in the trans-sulfuration pathway from methionine to cysteine. Cysteine is needed for glutathione. Glutathione synthesis in the liver is dependent upon the availability of cysteine. Variants in this gene may reduce Glutathione, especially when combined with Glycine issues (SMHT) and Glutathione enzymes.

CTH + Pyridoxal 5'-phosphate → Cysteine

GCLC - Glutamate-Cysteine Ligase is the first rate-limiting enzyme of glutathione synthesis.

The major determinants of GSH synthesis are the availability of cysteine, the sulfur amino acid precursor, and the activity of the rate-limiting enzyme, glutamate cysteine ligase (GCL) also known as gamma-glutamylcysteine synthetase. GCL is composed of two subunits. These subunits include catalytic GCLC and modifier GCLM.

Glutamate + Cysteine → GCLM + GCLC → y-Glu-Cys + Glycine

GLRX - GLRX catalyzes the reversible reduction of GSH to GSSG.

GSH → GLRX → GSSG

GSR - GSR is a central enzyme in cellular antioxidant defense, and reduces oxidized glutathione disulfide (GSSG) to GSH.

GSSG → GSR → GSH

GSS - The protein encoded by GSS catalyzes the second step of glutathione biosynthesis. This step is the ATP-dependent conversion of gamma-L-glutamyl-L-cysteine to glutathione.

y-Glu-Cys + Glycine → GSS + ATP → GSH

SHMT2 - Serine Hydroxymethyltransferase 2 encodes the mitochondrial form of a pyridoxal phosphate-dependent enzyme that catalyzes the reversible reaction that creates glycine and 5,10-methylene tetrahydrofolate.

Catalase		
CAT (rs1049982)	1	TC 44.4%
Catalase	+0	

Catalase is an antioxidant that reduces H2O2. This is a critical function as H2O2 combines with iron to create Hydroxyl Radicals.

Catalase gene provides instructions for making catalase.

Nrf2 and Keap1		
NFE2L2 (rs10183914)	2	TT 11.9%
NFE2L2 (rs1806649)	1	CT 36%
KEAP1 (rs8113472)	1	CA 15.7%
Nrf2 and Keap1	-2	

The NFE2L2 gene has major involvement in the defense against oxidative stress. The NFE2L2 gene encodes Nrf2. Nrf2 regulates and activates the intracellular antioxidant response element signaling pathway (ARE). The antioxidant response element signaling pathway controls the expression of genes whose protein products are involved in detoxication, inflammation, injury, elimination of reactive oxygen species, electrophilic agents, and enhanced cellular antioxidant capacity.

Under normal conditions, Nrf2 is repressed by a negative regulator KEAP1. When cells are exposed to oxidative stress, or electrophiles, Nrf2 escapes KEAP1 and activates the ARE to maintain cellular redox homeostasis.

Variants in the KEAP1 gene may impede the release of Nrf2.

MTOR		
MTOR (rs1770345)	2	AA 29.4%
MTOR (rs11121691)	1	CT 35.4%
MTOR	-3	

The mammalian target of rapamycin (mTOR) coordinates cell growth with the growth factor and nutrient and energy status of the cell. Consequently, it increases energy production, but creates junk products that need to be cleared. Autophagy contributes to clearing the cells of all irreversibly oxidized biomolecules (proteins, DNA and lipids). However, autophagy is most active when mTOR is decreased. Nrf2 regulates mTOR.

Lyme Study Phase IV SNPs

These are the SNPS that were found to be most prevalent for individuals with chronic Lyme in our Phase IV Study, and is not a test for Lyme. Inherited genetic mutations when expressed may reduce enzyme production. This can lead to, nutrient deficiencies, an increased production of free radicals or other toxic substances, or a slow clearing of toxic substances. Any one of these or a combination of may have the potential to allow Lyme to be resistant to traditional treatment by suppressing the immune system or susceptible to creating toxic conditions.

Gene Name	Variants	Metrics
HFE		
HFE H63D (rs1799945)	1	CG 23.8%
HFE C282Y (rs1800562)		GG 89.4%
HFE (Lyme Study Phase IV)	-1	

Iron deficiency has been shown to inhibit mTOR signaling. The Lyme group showed increased variation within several iron-related genes that would increase iron levels.

The HFE protein interacts with other proteins on the cell surface to detect the amount of iron in the body. The HFE protein regulates the production of another protein called hepcidin, which is considered to be the master iron regulatory hormone.

TFR2		
TFR2 (rs7385804)		AA 40.9%
TFR2 (rs4727457)		CC 71.3%
TFR2 (Lyme Study Phase IV)	+1	

The protein encoded by TFR2 mediates cellular uptake of transferrin-bound iron, and may be involved in iron metabolism, hepatocyte function and erythrocyte differentiation.

Variations in this gene have been associated with hereditary hemochromatosis type III.

HMOXs		
HMOX1 (rs2071749)	2	AA 21.6%
HMOX2 (rs2160567)	2	TT 45.3%
HMOX1 (Lyme Study Phase IV)	-2	
HMOX2 (Lyme Study Phase IV)	-1	

Heme oxygenase is an essential enzyme in heme catabolism. Heme oxygenase cleaves heme to form biliverdin. Biliverdin is then converted to bilrubin by biliverdin reductase, and carbon monoxide. Bilirubin is a compound that breaks down heme in vertebrates. This catabolism is a necessary process in the body's clearance of waste products that are produced from the breakdown of aged red blood cells. Under physiological conditions, the activity of heme oxygenase is highest in the spleen.

Variations in this gene have been associated with Heme oxygenase 1 deficiency and pulmonary disease.

SLC40A1		
SLC40A1 (rs1123109)	1	TC 32.6%
SLC40A1 (Lyme Study Phase IV)	-1	

The SLC40A1 gene contains the instructions for making a protein called ferroportin. Ferroprtin is found in all cells and tissues where iron is regulated and is the only cellular iron exporter.

Ferroportin transports iron from the small intestine into the bloodstream. Ferroportin also plays a role in the metabolism of iron.

Different variants of the SLC40A1 gene affect the ferroportin protein in different ways which in turn can alter the export and metabolism of iron.

SOD1		
SOD1 (rs1041740)	1	CT 41.4%
SOD1 (Lyme Study Phase IV)	-1	

Inflammation stimulates mTOR. An increased number of variants were found in the antioxidant production genes in the Lyme group.

SOD1 enzymes deal with the superoxide radical by alternately adding or removing an electron from the superoxide molecules it encounters.

The SOD-catalyzed dismutation of superoxide reactions with copper are as follows:

Cu2+-SOD + O2− → Cu+-SOD + O2 (reduction of copper; oxidation of superoxide)

Cu+-SOD + O2− + 2H+ → Cu2+-SOD + H2O2 (oxidation of copper; reduction of superoxide)

GCLC		
GCLC (rs2066511)		CC 54.8%
GCLC (rs502862)	2	CC 18.4%
GCLC (rs553822)	2	CC 18%
GCLC (rs617066)		GG 60%
GCLC (rs761141)		CC 60.2%
GCLC (Lyme Study Phase IV)	+0	

The major determinants of GSH synthesis are the availability of cysteine, the sulfur amino acid precursor, and the activity of the rate-limiting enzyme, glutamate cysteine ligase (GCL) also known as gamma-glutamylcysteine synthetase. GCL is composed of two subunits. One of these subunits includes catalytic GCLC.

GLRX		
GLRX (rs4561)	1	AG 48%
GLRX (Lyme Study Phase IV)	+0	

GLRX catalyzes the reversible reduction of GSH to GSSG.

GSH → GLRX → GSSG

GSS		
GSS A5997G (rs6088659)		CC 68.8%
GSS (Lyme Study Phase IV)	+1	

The protein encoded by GSS functions as a homodimer to catalyze the second step of glutathione biosynthesis. This step is the ATP-dependent conversion of gamma-L-glutamyl-L-cysteine to glutathione.

GPXs		
GPX3 (rs8177435)	2	TT 37.6%
GPX7 (rs1970951)		CC 69%
GPX7 (rs1970949)		CC 53.1%
GPX3 (Lyme Study Phase IV)	-2	
GPX7 (Lyme Study Phase IV)	+1	

Hydroxyl radicals are formed when hydrogen peroxide combines with copper or iron.

The protein encoded by GPX genes belongs to the glutathione peroxidase family. Glutathione peroxidase functions in the detoxification of hydrogen peroxide, and is one of the most important antioxidant enzymes in humans.

PRDX1		
PRDX1 (rs2356559)		CC 47.4%
PRDX1 (Lyme Study Phase IV)	+1	

The PRDX genes encode members of the peroxiredoxin family of antioxidant enzymes, which reduce hydrogen peroxides.

Peroxiredoxin can act to produce inflammatory cytokines

In some types of cancer, studies have found that PRDX1 can act as a tumor suppressor

Peroxiredoxin uses thioredoxin (Trx) to recharge after reducing hydrogen peroxide (H2O2) in the following reactions:

Prx(reduced) + H2O2 → Prx(oxidized) + 2H2O

Prx(oxidized) + Trx(reduced) → Prx(reduced) + Trx(oxidized)

TXNRD1		
TXNRD1 (rs4630362)		CC 81.9%
TXNRD1 (rs6539137)		TT 82%
TXNRD1 (Lyme Study Phase IV)	+0	

The protein encoded by this gene reduces thioredoxins and plays a role in protection against oxidative stress.

ME1		
ME1 (rs1145917)	1	TC 39.2%
ME1 (rs1180241)	1	GA 24.6%
ME1 (rs3798890)	1	GA 43.4%
ME1 (rs750385)	1	AG 27.5%
ME1 (rs767144)	1	GT 39%
ME1 (rs983087)	1	TC 43.1%
ME1 (Lyme Study Phase IV)	-1	

ME1 encodes a cytosolic, NADP-dependent enzyme that generates NADPH for fatty acid biosynthesis.

Glutamine-derived malate is transported out of the mitochondria, and is converted by ME1 into pyruvate, reducing one molecule of NADP+ to NADPH.

SLC7A11		
SLC7A11 (rs6537244)	2	GG 24.5%
SLC7A11 (rs11734488)	2	CC 24.5%
SLC7A11 (rs6854381)	2	AA 24.1%
SLC7A11 (rs4863771)		GG 33.5%
SLC7A11 (rs7674870)		AA 33%
SLC7A11 (rs4131888)		CC 63.3%
SLC7A11 (Lyme Study Phase IV)	+0	

Glutamine stimulates mTOR. More variants were found in the Lyme group impacting glutamine.

This gene encodes a member of a heteromeric, sodium-independent, anionic amino acid transport system that is highly specific for cysteine and glutamate.

Glutamine derived glutamate can also be exchanged through the SLC7A11 and SLC3A2 antiporter for cystine.

SLC1A1		
SLC1A1 (rs10491732)	2	AA 11.9%
SLC1A1 (rs10758631)	1	CA 49%
SLC1A1 (rs10974591)		GG 84.1%
SLC1A1 (rs2228622)	1	GA 47.6%
SLC1A1 (rs7022772)	1	CA 39.6%
SLC1A1 (rs10974584)		TT 44.7%
SLC1A1 (rs10974587)	1	TC 39%
SLC1A1 (rs11791930)	1	GC 47.7%
SLC1A1 (rs4742004)	1	TC 44.3%
SLC1A1 (rs6476875)	1	TC 44.9%
SLC1A1 (rs7858877)	1	TC 47.9%
SLC1A1 (rs10815004)	1	AG 48.7%
SLC1A1 (rs10815018)	1	AG 43.7%
SLC1A1 (rs16921385)	2	GG 11.9%
SLC1A1 (rs7021569)	1	CG 43.1%
SLC1A1 (rs7022369)	1	CG 49%
SLC1A1 (rs10974619)	1	CT 44.5%
SLC1A1 (Lyme Study Phase IV)	-2	

SLC1A1 encodes a member of the high-affinity glutamate transporters that play an essential role in transporting glutamate across plasma membranes. In the brain, these transporters are crucial in terminating the postsynaptic action of the neurotransmitter glutamate, and in maintaining extracellular glutamate concentrations below neurotoxic levels.

This transporter also transports aspartate.

GAD1		
GAD1 (rs12185692)	2	AA 16.8%
GAD1 (rs3791850)		GG 58%
GAD1 (rs3791878)		GG 49.5%
GAD1 (rs3828275)	2	TT 18.7%
GAD1 (Lyme Study Phase IV)	-2	

The GAD enzyme converts glutamate to GABA. When someone has high glutamate and a lot of variants in GAD, it creates conditions that may have high glutamate and low GABA that could increase stress and conditions related to high glutamate. It has been observed, that Homozygous variants in GAD have more impact that many Heterozygous. SER-GAB Assist and GABA Assist may be helpful if there is low GABA.

GOTs		
GOT1 (rs11190083)		AA 84.3%
GOT1 (rs3793935)	2	TT 69.5%
GOT1 (rs9971274)		GG 84.4%
GOT1 (rs9971275)		GG 84.4%
GOT2 (rs30838)	1	CT 42.3%
GOT2 (rs30842)	1	CA 42.2%
GOT1 (Lyme Study Phase IV)	+0	
GOT2 (Lyme Study Phase IV)	-1	

Glutamic-oxaloacetic transaminase is a pyridoxal phosphate-dependent enzyme which exists in cytoplasmic and inner-membrane mitochondrial forms, GOT1 and GOT2, respectively. GOT plays a role in the conversion of glutamate to alpha-ketoglutarate.

DAO		
DAOA (rs2391191)	2	AA 14.9%
DAO (rs3741775)	2	CC 19.1%
DAO (Lyme Study Phase IV)	-3	

The name of this gene is D-amino-acid oxidase and DAO is the gene's official symbol. Health conditions observed with this variant are: Schizophrenia, Bipolar Disorder, Primary Hyperoxaluria, ALS (Type 18) , Autism and Crohn's Disease.

Studies have found that the A allele in rs2391191 is a possible genetic feature of certain health conditions such as Schizophrenia, and Bipolar Disorder.

NFE2L2		
NFE2L2 (rs10183914)	2	TT 11.9%
NFE2L2 (rs1806649)	1	CT 36%
NFE2L2 (Lyme Study Phase IV)	-2	

In addition to supporting iron sequestration, the production, recycling and utilization of glutathione, Nrf2 also regulates both mTOR and autophagy.

The NFE2L2 gene has major involvement in the defense against oxidative stress. The NFE2L2 gene encodes Nrf2. Nrf2 regulates and activates the intracellular antioxidant response element signaling pathway (ARE). The antioxidant response element signaling pathway controls the expression of genes whose protein products are involved in detoxication, inflammation, injury, elimination of reactive oxygen species, electrophilic agents, and enhanced cellular antioxidant capacity.

In addition to this critical function, Nrf2 also regulates iron sequestration, NADPH production, the enzymes that reduce Hydrogen Peroxide, and has influence of the critical process of Autophagy (the cleaning of cellular debris).

FOXO1		
FOXO1 (rs7981045)		AA 57.4%
FOXO1 (rs10507486)		GG 64.4%
FOXO1 (rs2951787)	2	AA 15.5%
FOXO1 (rs4943794)		GG 64.4%
FOXO1 (rs7323267)		TT 65.5%
FOXO1 (Lyme Study Phase IV)	+0	

The FOXO genes are involved with the mTOR/Autophagy balance. The FOXO genes control the expression of genes involved in stress resistance, metabolism, cell-cycle arrest and apoptosis.

Inhibition of AKT following mTORC2 depletion reduces the phosphorylation of, and therefore activates, the forkhead box protein O1 (FoxO1) and FoxO3a transcription factors, which control the expression of genes involved in stress resistance, metabolism, cell-cycle arrest and apoptosis.

FOXO3		
FOXO3 (rs1935949)	2	GG 48.5%
FOXO3 (rs2802288)	2	GG 36.8%
FOXO3 (rs3800231)	2	GG 48.7%
FOXO3 (rs2764264)	2	TT 46%
FOXO3 (rs2153960)	2	AA 47.3%
FOXO3 (rs2802290)	2	AA 36.7%
FOXO3 (rs2802292)	2	TT 36.9%
FOXO3 (rs3800229)	2	TT 48.5%
FOXO3 (rs13220810)	1	TC 36.4%
FOXO3 (Lyme Study Phase IV)	-2	

Inhibition of AKT following mTORC2 depletion reduces the phosphorylation of, and therefore activates, the forkhead box protein O1 (FoxO1) and FoxO3a transcription factors, which control the expression of genes involved in stress resistance, metabolism, cell-cycle arrest and apoptosis.

ULK1		
ULK1 (rs3088051)		TT 51.8%
ULK1 (Lyme Study Phase IV)	+1	

The ULK1, ULK2 and ATG13 genes are involved with supporting autophagy.

ULK1 is an important protein in autophagy. ULK1 is an essential component for amino acid starvation-induced autophagy in HEK293 cells.

ULK2		
ULK2 (rs281357)		CC 45.4%
ULK2 (rs17794370)	2	AA 7.3%
ULK2 (rs157386)		GG 73.3%
ULK2 (Lyme Study Phase IV)	+0	

ULK2 acts upstream of phosphatidylinositol 3-kinase PIK3C3 to regulate the formation of autophagophores, the precursors of autophagosomes.

ATG13		
ATG13 (rs4606447)	1	AG 38.7%
ATG13 (rs4752926)		CC 16.6%
ATG13 (Lyme Study Phase IV)	+2	

The protein encoded by this gene is an autophagy factor and a target of the mTOR kinase signaling pathway. The encoded protein is essential for autophagosome formation and mitophagy.

AMPK		
PRKAA1 (rs12188129)		GG 72.3%
PRKAA2 (rs11206890)	1	TC 49.8%
PRKAA2 (rs1124900)	1	TG 48.4%
PRKAA1 (Lyme Study Phase IV)	+1	
PRKAA2 (Lyme Study Phase IV)	+0	

AMPK also stimulates autophagy.

The energy status of the cell is signaled to mTORC1 through AMP-activated protein kinase (AMPK), a master sensor of intracellular energy status.

In response to energy depletion (low ATP:ADP ratio), AMPK is activated and phosphorylates TSC2, which increases the GAP activity of TSC2 towards Rheb and reduces mTORC1 activation.

Additionally, AMPK can reduce mTORC1 activity in response to energy depletion by directly phosphorylating Raptor.

Lyme Study Phase V SNPs

These are the SNPS that were found to be most prevalent for individuals with chronic Lyme in our Phase V Study, and is not a test for Lyme. Inherited genetic mutations when expressed may reduce enzyme production. This can lead to, nutrient deficiencies, an increased production of free radicals or other toxic substances, or a slow clearing of toxic substances. Any one of these or a combination of may have the potential to allow Lyme to be resistant to traditional treatment by suppressing the immune system or susceptible to creating toxic conditions.

Gene Name	Variants	Metrics
ACAT		
ACAT-2 (rs3798211)	1	AC 48.5%
ACAT-2 (rs3465)		GG 38.5%
ACAT-2 (rs9347340)	1	TC 38.3%
ACAT-2 (rs25683)	1	AG 48.8%
ACAT (Lyme Study Phase V)	+1	
NAT		
NAT1 (rs4921581)	1	AG 43.3%
NAT1 (rs13253389)	1	AG 44.7%
NAT2 (rs11780272)	1	TC 47.6%
NAT2 (rs1390358)	1	TC 46.7%
NAT2 (rs2087852)		AA 51.4%
NAT2 C481T (rs1799929)	1	CT 47.5%
NAT2 R197Q (rs1799930)		GG 50.1%
NAT (Lyme Study Phase V)	+0	
PANK		
PANK1 (rs997456)	1	GA 34.1%
PANK1 (rs7921294)	1	GT 48.3%
PANK1 (rs7091402)	1	TC 48.3%
PANK1 (rs10881606)	1	TC 44%
PANK1 (rs10509577)		AA 87.9%
PANK4 (rs7535528)	1	GA 45.3%
PANK (Lyme Study Phase V)	+0	

The balance between protein acetylation and deacetylation plays a critical role in the regulation of gene expression and signal pathways and affects a large range of cellular processes with many related to detoxification of toxins.

For proper acetylation, there needs to be an adequate supply of Acetyl-CoA The ACAT enzymes are the final step of Acetyl-CoA creation.

The NAT enzymes are responsible for carrying out acetylation.

The PANK genes are responsible for coding the enzyme that creates the pantethine that plays a critical role in Acetyl-CoA creation.

Lyme Study Phase VI SNPs

These are the SNPS that were found to be most prevalent for individuals with chronic Lyme in our Phase VI Study, and is not a test for Lyme. Inherited genetic mutations when expressed may reduce enzyme production. This can lead to, nutrient deficiencies, an increased production of free radicals or other toxic substances, or a slow clearing of toxic substances. Any one of these or a combination of may have the potential to allow Lyme to be resistant to traditional treatment by suppressing the immune system or susceptible to creating toxic conditions.

Gene Name	Variants	Metrics	
ALAD			The ALAD gene provides instructions for making an enzyme known as delta-aminolevulinatedehydratase, which is responsible for the second step in the heme production process, to form a compound called porphobilinogen.
ALAD (rs818708)	1	AG 49.9%	
ALAD (Lyme Study Phase VI)	+0		
CPOX			The CPOX gene provides instructions for making an enzyme known as coproporphyrinogen oxidase which is responsible for the sixth step in the heme production process, the removal of carbon and oxygen atoms from coproporphyrinogen III to form protoporphyrinogen IX.
CPOX (Lyme Study Phase VI)	#N/A		
FECH			The FECH gene provides instructions for making an enzyme known as ferrochelatase. Ferrochelataseis responsible for the eighth and final step in this process, in which an iron atom is inserted into the center of protoporphyrin IX to form heme.
FECH (Lyme Study Phase VI)	#N/A		
HMOX			Heme oxygenase is an essential enzyme in heme catabolism. Heme oxygenase cleaves heme to form biliverdin. Biliverdin is then converted to bilrubinby biliverdin reductase, and carbon monoxide. Bilirubin is a compound that breaks down heme in vertebrates. This catabolism is a necessary process in the body's clearance of waste products that are produced from the breakdown of aged red blood cells.
HMOX1 (rs2071749)	2	AA 21.6%	
HMOX2 (rs2160567)	2	TT 45.3%	
HMOX (Lyme Study Phase VI)	-2		
KIT			The KITgene provides instructions for making the KIT protein. The KIT protein can be found in the cell membrane of certain cells where stem cell factors bind to it. This binding activates the KIT protein, which will then activate other proteins inside the cell by adding a cluster of oxygen and phosphorus atoms at specific positions. The signaling pathways stimulated by the KIT protein control many important cellular processes such as cell growth, proliferation, survival, and migration. KIT protein signaling is important for the development of mast cells.
KIT (Lyme Study Phase VI)	#N/A		
RAD50			The protein encoded by the RAD50 binds to DNA and has numerous enzymatic activities that are required for nonhomologous joining of DNA ends. This protein, cooperating with its partners, is important for DNA double-strand break repair, cell cycle checkpoint activation and telomere maintenance.
RAD50 (Lyme Study Phase VI)	#N/A		

HRH1			Histamine is a ubiquitous messenger molecule released from mast cells, enterochromaffin-like cells, and neurons. Its various actions are mediated by histamine receptors such as HRH1. HRH1 mediates the contraction of smooth muscles, the increase in capillary permeability due to contraction of terminal venules, the release of catecholamine from adrenal medulla, and neurotransmission in the central nervous system. It has been associated with multiple processes, including memory/learning, circadian rhythm, and thermoregulation. It is also known to contribute to the pathophysiology of allergic diseases such as atopic dermatitis, asthma, anaphylaxis and allergic rhinitis.
HRH1 (Lyme Study Phase VI)	#N/A		
FCER1A			The immunoglobulin epsilon receptor (IgEreceptor) is the initiator of the allergic response. When two or more high-affinity IgEreceptors are brought together by allergen-bound IgEmolecules, mediators such as histamine that are responsible for allergy symptoms are released. FcεRIis the key structure mediating immediate-type inflammation via the IgE-dependent degranulation of mast cells and basophils and, more recently, has been found to be important for IgE-mediated activation of eosinophils and IgE-mediated allergen presentation.
FCER1A (rs2251746)		TT 55.8%	
FCER1A (Lyme Study Phase VI)	#N/A		
DARC			The protein encoded by this gene is a glycosylated membrane protein and a non-specific receptor for several chemokines. The encoded protein is the receptor for the human malarial parasites Plasmodium vivax and Plasmodium knowlesi. Polymorphisms in this gene are the basis of the Duffy blood group system. When expressed on erythrocytes, DARC modulates chemokine bioavailability by acting as a chemokine “sink” and as a long-term blood reservoir of chemokines that prevents their loss into distant organs and tissues. DARC may also act as a cell-autonomous migratory rheostat for leukocytes. The primary aim of this may be to protect crucial barrier tissues from the unnecessary toxic effects of neutrophil and mast cell contents.
DARC (rs863002)	1	CT 45.4%	
DARC (Lyme Study Phase VI)	+0		