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

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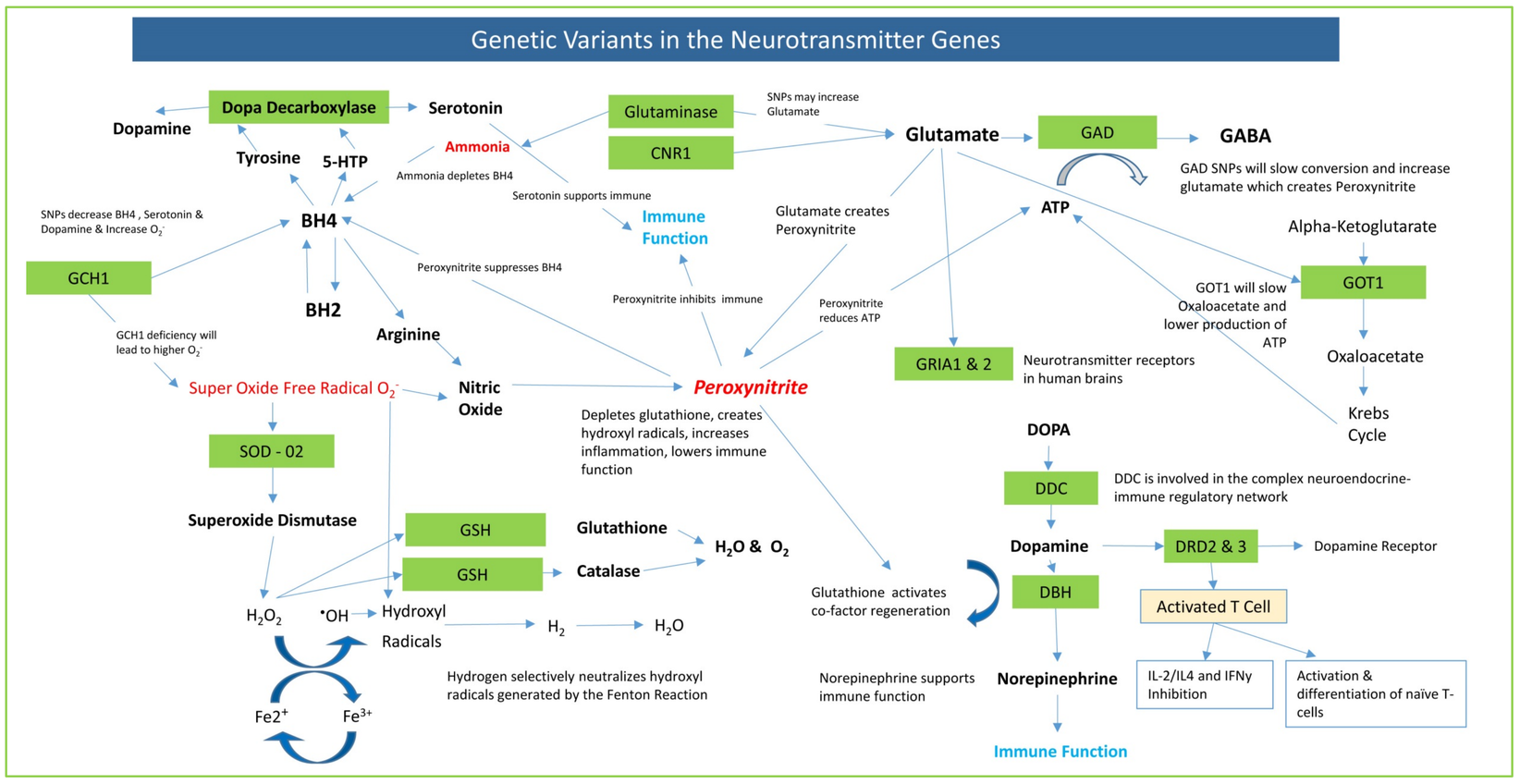
To determine if those with Chronic Lyme Disease may have a unique genetic pattern that may create excess inflammation or suppress the immune system, the NutriGenetic Research Institute compared 1,298 genes of a group of 360 individuals who identified as having chronic Lyme to the data supplied by the 1000 Genome Phase 3 Project [**1**].

The reference and alternate alleles for each of the SNPs (Single Nucleotide Polymorphisms) were determined using the HaploReg v4.1 database [**2**]. Formulas determined the top 65 genes with more variants in those with chronic Lyme than the control group. Neurotransmitter genes represented 40 of the top 65 genes with the most variants. This analysis will focus on glutamate, dopamine and cannabinoid SNPs.



Glutamate

Studies have shown that glutamate triggers the production of nitric oxide and superoxide, which creates peroxynitrite ($ONOO^-$). High serum levels of total NO, MDA and nitrotyrosine observed in patients with Lyme borreliosis indicate an enhancement of lipid peroxidation and protein nitration, which may enhance the inflammatory process in Lyme patients [**3**]. The following glutamate related genes were higher in the Lyme group than the 1000 Genome Project.

Table 1: Glutamate SNPs

Gene	Position	Ratio
GLS	6758866	1.76
GLS	3088307	1.55
GOT1	9971275	2.42
GOT1	11190083	2.42
GOT1	9971274	2.42
GRIA1	1864205	2.18
GRIA1	2910266	2.11
GRIA1	1493383	2.04
GRIA1	1463747	2.00
GRIA1	2910263	1.98
GRIA1	11746246	1.88
GRIA1	11748500	1.87
GRIA1	7719292	1.70
GRIA1	11741511	1.65
GRIA1	889062	1.58
GRIA1	1381119	1.53
GRIA2	17243330	2.04
GAD1	3791850	1.71
GAD1	3791878	1.60

GLS, glutaminase, catalyzes the hydrolysis of glutamine to glutamate and ammonia [**4**]. This protein synthesizes the brain neurotransmitter glutamate [**5**].

A study has shown that the most neurotoxic factor from activated microglia is glutamate that is produced by glutaminase utilizing extracellular glutamine as a substrate. Drugs that inhibit glutaminase were effective in reducing neurotoxic activity of microglia [**6**]. Research is being conducted on how Glutaminase GLS1 Inhibitors are being considered as potential cancer treatment [**7**].

GOT1, glutamic-oxaloacetic transaminase, plays a role in the conversion of glutamate to alpha-ketoglutarate. GOT1 is also an important regulator of glutamate and acts as a scavenger in brain neuroprotection [**8**].

GRIA1 and GRIA2, Glutamate Ionotropic Receptor AMPA Type Subunit 1 and 2, glutamate receptors are the predominant excitatory neurotransmitter receptors in human brains and are activated in a variety of normal neurophysiologic processes. [**9, 10**].

GAD1, glutamate decarboxylase 1 is a protein coding gene responsible for catalyzing the production of gamma-aminobutyric acid from L-glutamic acid (GABA) [**11**].

Dopamine

The neurotransmitter dopamine plays a modulatory role in cognition. [**12**]. Several studies have shown that immune system cells can be regulated by dopamine acting on immune cells expressing dopamine receptors present on the surface of T cells, dendritic cells, B cells, NK cells, neutrophils, eosinophils, and monocytes [**13**]. Dopamine inhibits the release of IFNγ, IL-2, and IL-4 and production of IL-12p40 in immune cells. Administration of dopamine or dopaminergic agonists in vivo reduces the TNFα response to endotoxin and the activation of leukocytes in experimental sepsis. Conversely, treatment with a dopaminergic antagonist stimulates constitutive and inducible gene expression of IL-1β, IL-6, and TNFα in macrophages [**14**]. Previous studies have identified IL-6 as a candidate for inflammation of the CNS in patients with Lyme [**15**]. Studies suggest that dopamine operates as a bidirectional mediator between nervous cells and immune cells [**13**]. The following genes were higher in the Lyme group than the 1000 Genome Project.

Table 2: Dopamine SNPs

Gene	Position	Ratio
ANKK1 G318R	11604671	2.11
DBH T13150C	2519152	1.63
DBH T8114C	2519155	1.82
DDC C166017G	1470750	1.86
DRD2	4630328	2.24
DRD2	12363125	2.17
DRD2	6277	2.14
DRD2	1800498	2.06
DRD2	2734838	2.05
DRD2	2234690	2.05
DRD2	1107162	2.04
DRD2	17529477	1.98
DRD2	1076563	1.92
DRD2	2734839	1.74
DRD3	11706283	3.35
DRD3	963468	1.55
GCH1	2878169	2.92

ANKK1, Ankyrin Repeat and Kinase Domain Containing 1, is involved in signal transduction pathways. This gene is closely linked to DRD2 gene [**16**]**.**

DBH, dopamine beta-hydroxylase**,** converts dopamine to norepinephrine. [**17**]. Genetic variants in DBH will lower norepinephrine and evidence over the past 30 years suggests that norepinephrine may also regulate the function of immune cells that protect the body against pathogens [**20**]. Studies have shown glutathione activates the co-factor regeneration for this gene [**19**].

DDC, dopa decarboxylase**,** catalyzes the decarboxylation of DOPA to dopamine, 5-HTP to serotonin, and tryptophan to tryptamine [**19**], and is involved in the complex neuroendocrine-immune regulatory network which has a crucial role in the immune system [**21**]. DDCs are also implicated to modulate the immune response against various pathogenic microorganisms [**21**].

DRD2, dopamine receptor D2, encodes the D2 subtype of the dopamine receptor. Variations in this gene have been associated with schizophrenia and hypertension [**14, 22**].

DRD3, dopamine receptor D3**,** encodes the D3 subtype of the dopamine receptor. This receptor is localized to the limbic areas of the brain, which are associated with cognitive, emotional, and endocrine functions [**23**].

GCH1, GTP cyclohydrolase 1, makes an enzyme called GTP cyclohydrolase. GTPCH is part of the folate and biopterin biosynthesis pathways [**24**]. It is involved in the production of tetrahydrobiopterin (BH4). Tetrahydrobiopterin works with the enzyme phenylalanine hydroxylase to convert phenylalanine into tyrosine and the production of dopamine and serotonin. BH4 also combines with NOS enzyme and arginine to make nitric oxide. Insufficient BH4 will lead to the creation of superoxide [**24**] and peroxynitrite resulting in inflammation and reduced immunity [**28**].

Cannabinoid Receptors

The endocannabinoid system consists of the endogenous cannabinoids, cannabinoid receptors and the enzymes that synthesize and degrade endocannabinoids. Studies show that cannabinoid receptors are involved in the regulation of dopamine [**25**]. The following four CNR1 genes were higher in the Lyme group than the 1000 Genome Project.

Table 3: Cannabinoid Receptors SNPs

Gene	Position	Ratio
CNR1	806380	1.89
CNR1	12205430	1.85
CNR1	806378	1.80
CNR1 T453T	1049353	1.95

CNR1 (CB_1), Cannabinoid Receptor 1, modulates neurotransmitter release when activated. The CB_1 receptor is activated by endocannabinoids [**27**]. The CB_1 receptor acts as a neuromodulator to inhibit release of glutamate and GABA [**26**]. The expression of these receptors modulates neurotransmitter release in a manner that reduces pain and other inflammatory symptoms [**27**].

Conclusion

The analysis appears to display an elevated rate of single nucleotide polymorphisms in the chronic Lyme group in comparison to the data provided by the 1000 Genome Phase 3 Project; however, further analysis is needed to confirm these observations. These observations suggest that genetic variants in neurotransmitters may play a role in creating conditions more favorable to Lyme infection, and medical treatment of chronic Lyme more difficult. More research is needed to determine how these SNPs impact the immune system and inflammation, and how therapies to support the SNPs may make medical treatment more effective.

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