Increased Genetic Variants Found in Acetylation & Lipid Synthesis Genes in Chronic Lyme Disease Patients *(Phase V)*

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Some patients with Lyme disease do not respond well to treatment: it has been hypothesized this may be due to difficulty with detoxification and inflammation.

Xenobiotics such as plastics, industrial chemicals, drugs, pesticides, fragrances, and environmental pollutants need to be detoxified by the body [1]. Phase I CYP450 enzymes and Phase II conjugation pathways are needed to eliminate these toxins through the urine, bile, and stool [2].

The balance between protein acetylation and deacetylation plays a critical role in the regulation of gene expression, signaling pathways, and affects a large range of cellular processes, many related to detoxification. Acetylation is the Phase II Conjugation Reaction process of introducing an acetyl functional group (acetyl-CoA) onto a chemical compound by N-Acetyltransferase (NAT). Acetylation can alter gene expression epigenetically. Acetylation is an important route of metabolism for xenobiotics [3]. Deacetylation is the removal of an acetyl group.

For proper acetylation, there needs to be an adequate supply of acetyl-CoA. The PANK genes are responsible for catalyzing the ATP-dependent phosphorylation of pantothenate (vitamin B5) to create 4′-phosphopantothenate, which is needed to create adequate Acetyl-CoA [4].

The NAT enzymes are responsible for carrying out acetylation of the xenobiotics [5].

Acetyl-CoA is also needed for the expression of Nrf2 and ARE (Antioxidant Response Element), which make glutathione for the conjugation of xenobiotics [6].

The ACAT2 gene is an enzyme involved in lipid metabolism, which results in the creation of hormones, DHEA, and cortisol [7].

The purpose of this research was to evaluate whether treatment-resistant Lyme disease patients have increased levels of variants in genes involved in the creation of acetyl-CoA, acetylation and lipid synthesis. Genetic weakness in these two functions may reduce the potential to clear toxic xenobiotics and reduce the potential to create cortisol, which reduces inflammation and histamine.

421 participants with chronic Lyme disease submitted their 23andMe supplied genome for a contrast to the 1000 Genome Project [8]. We evaluated the PANK, ACAT and NAT gene polymorphisms that have the potential to be involved in acetylation.

The major and minor alleles for each of the SNPs were determined using the 1000 Genome Project. The ratio of SNPs between the Chronic Lyme Group and the Genome Project was calculated.

The genetic analysis, detailed in this poster, illustrates a 1.31 to 3.85 ratio increase in genetic variants involved with acetylation.

PANK

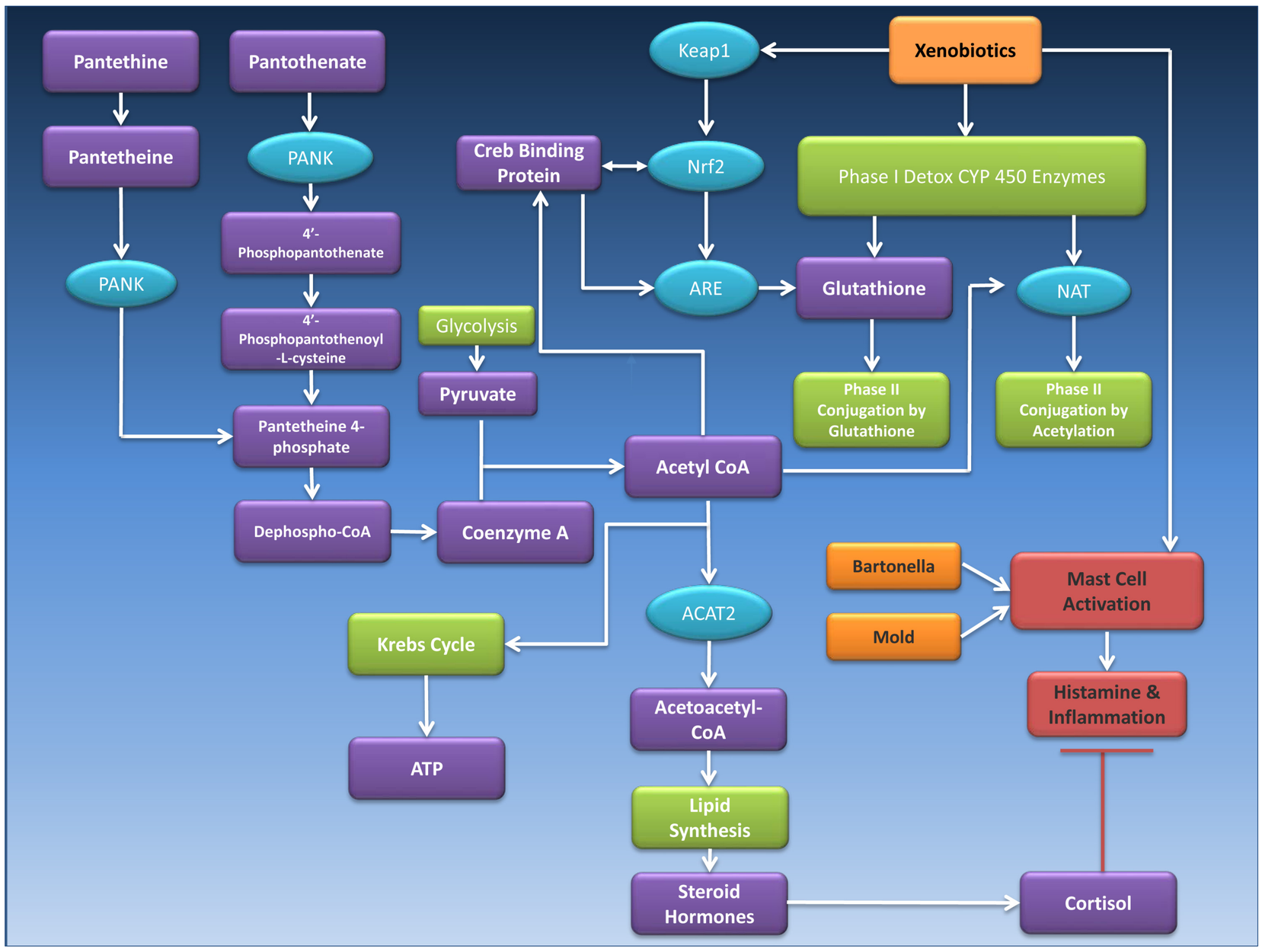
Pantothenate kinase (PANK) catalyzes the ATP-dependent phosphorylation of pantothenate (vitamin B5) to create 4′-phosphopantothenate. This reaction is the first step in the biosynthetic pathway of coenzyme A (CoA). Because CoA is a ubiquitous and essential cofactor in all organisms, the PANK genes that make up this pathway are essential for all organism survival and growth [9]. The PANK4 gene is most abundant in muscle but is expressed in all tissues [10].

Coenzyme A (CoA) is a pantothenic acid-derived metabolite essential for many crucial cellular processes including energy, lipid, and amino acid metabolism. CoA occupies a central position in the regulation of the cellular 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, lipid synthesis, oxidation, and the synthesis of some amino acids [11].

The lipid synthesis process includes the production of cortisol, an important factor in reducing inflammation and histamine [12].

Table 1: Increased ratio of PANK SNPs in the treatment-resistant Lyme disease group compared to the control group.

Gene	RS Number	Ratio Increase
PANK1	rs7091402	1.18
PANK1	rs7921294	1.18
PANK1	rs10881606	1.31
PANK4	rs7535528	1.59
PANK1	rs997456	2.17
PANK1	rs10509577	3.85



ACAT2

The ACAT2 protein is limited to only two cell types, enterocytes in the small intestine and hepatocytes. Immunofluorescence analysis of human liver has shown that ACAT2 is expressed in the endoplasmic reticulum of the hepatocytes [13].

The product of the ACAT2 gene is an enzyme involved in lipid metabolism, and it encodes cytosolic acetoacetyl-CoA thiolase. Acetoacetyl-CoA thiolase condenses two molecules of acetyl-CoA to form acetoacetyl-CoA [14].

Table 2: Increased ratio of ACAT2 SNPs in the treatment-resistant Lyme disease group compared to the control group.

Gene	RS Number	Ratio Increase
ACAT-2	rs9347340	1.11
ACAT-2	rs25683	1.58
ACAT-2	rs3798211	1.59
ACAT-2	rs3465	1.65

NAT

The enzyme encoded by the NAT1 gene catalyzes the transfer of an acetyl group from acetyl-CoA to various arylamine and hydrazine substrates. This enzyme helps metabolize drugs and other xenobiotics, and functions in folate catabolism. The NAT2 gene encodes an enzyme that functions to both activate and deactivate arylamine and hydrazine drugs. Variations in this gene are also associated with higher incidences of drug toxicity [15].

Table 3: Increased ratio of NAT SNPs in the treatment-resistant Lyme disease group compared to the control group.

Gene	RS Number	Ratio Increase
NAT2 R197Q	rs1799930	1.20
NAT2	rs2087852	1.24
NAT2	rs1390358	1.35
NAT2	rs11780272	1.45
NAT2 C481T	rs1799929	1.46
NAT1	rs13253389	1.59
NAT1	rs4921581	1.60

Conclusion

In conclusion, increased levels of genetic variants involved in lipid synthesis and proper acetylation were found in individuals with Lyme disease: potentially creating a self-perpetuating cycle of toxicity favorable to pathogens, inflammation, increased mast cell activation and treatment resistance.

Personalized supplementation, lifestyle, and dietary modifications designed to support acetyl-CoA production and acetylation may be an effective complementary treatment. Future research evaluating genetic weakness, and the effects of supporting acetyl-CoA in treatment-resistant Lyme patients is needed.

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