Increased Genetic Variants in Heme Pathway and Mast Cell Genes in Chronic Lyme Disease Patients *(Phase VI)*

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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.

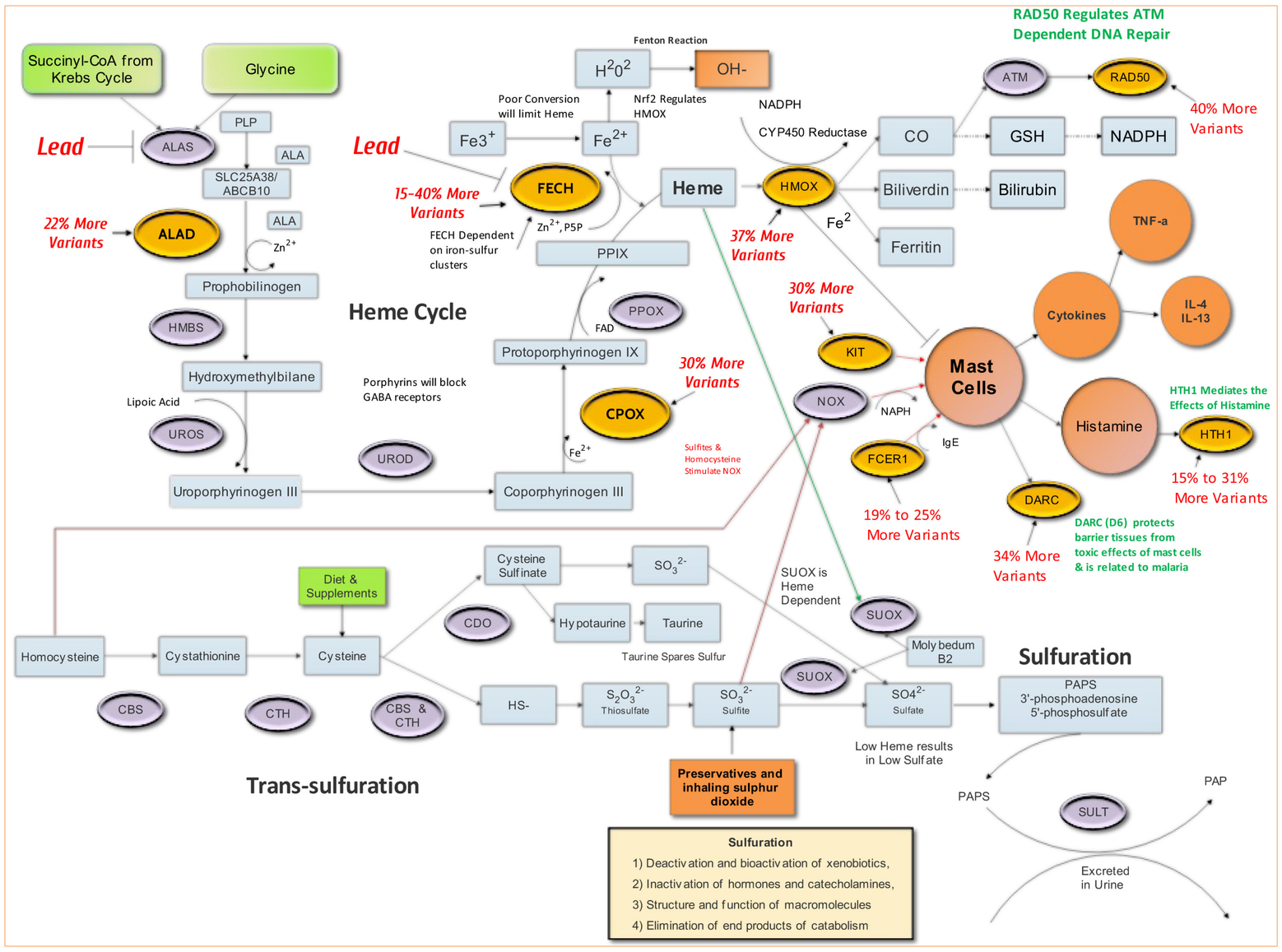
Heme proteins play a significant role not only in hemoglobin production, but also play a significant role in antioxidant protection by contributing to the production of bilirubin, supporting SUOX (sulfite to sulfate.), NOS (Nitric Oxide Synthase), NADPH (supports antioxidant recycling), and GSH (Glutathione).

For proper heme production, there are seven steps, each regulated by an enzyme and various cofactors. The ALAD, CPOX and FECH enzymes are critical to heme synthesis while HMOX catalyzes heme degradation, responsible for multiple critical processes related to controlling inflammation. Mast cells play an important role in the body, but can be detrimental when overactive. The KIT, RAD50, HRH1, FCER1A and DARC genes are related to mast cell activity and responses to mast cell activation.

The purpose of this research was to evaluate whether treatment-resistant Lyme disease patients have increased levels of variants in genes involved in heme production, utilization, and mast cell activation.

421 participants with Lyme disease submitted their 23andMe supplied genome for a contrast to the 1000 Genome Project.

The major and minor alleles for each of the SNPs were determined using the 1000 Genome Project [1]. The ratio of SNPs between the Chronic Lyme Group and the Genome Project was calculated.



ALAD

The ALAD gene provides instructions for making an enzyme known as delta-aminolevulinate dehydratase, which is responsible for the second step in the heme production process, to form a compound called porphobilinogen [2].

Table 1: ALAD SNPs

Gene	RSID	Ratio Higher
ALAD	rs818708	21.84

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 [3].

Table 2: CPOX SNPs

Gene	RSID	Ratio Higher
CPOX	rs4857405	29.95
CPOX	rs7103	15.17

FECH

The FECH gene provides instructions for making an enzyme known as ferrochelatase. Ferrochelatase is 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 [4].

Table 3: FECH SNPs

Gene	RSID	Ratio Higher
FECH	rs12957538	40.89
FECH	rs7238897	28.69
FECH	rs8099511	25.34
FECH	rs317806	21.57
FECH	rs1646594	18.77
FECH	rs1041951	18.42
FECH	rs536560	15.28

HMOX

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. [5].

Table 4: HMOX SNPs

Gene	RSID	Ratio Higher
HMOX1	rs2071749	35.32
HMOX2	rs2160567	37.15

KIT

The KIT gene 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, [**6**].

Table 5: KIT SNPs

Gene	RSID	Ratio Higher
KIT	rs13135792	29.29
KIT	rs2237023	14.95

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. [7].

Table 6: RAD50 SNPs

Gene	RSID	Ratio Higher
RAD50	rs2237060	40.29

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 [8].

Table 7: HRH1 SNPs

Gene	RSID	Ratio Higher
HRH1	rs168333	31.03
HRH1	rs443137	20.5
HRH1	rs9822871	19.14
HRH1	rs17602269	17.55
HRH1	rs2171544	15.06

FCER1A

The immunoglobulin epsilon receptor (IgE receptor) is the initiator of the allergic response. When two or more high-affinity IgE receptors are brought together by allergen-bound IgE molecules, mediators such as histamine that are responsible for allergy symptoms are released. [9].

FcεRI is 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 [10].

Table 8: FCER1A SNPs

Gene	RSID	Ratio Higher
FCER1A	rs2251746	25.67
FCER1A	rs2252226	19.15

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 [11].

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. [12].

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 [13].

Table 9: DARC SNPs

Gene	RSID	Ratio Higher
DARC	rs863002	34.1

Conclusion

In conclusion, increased levels of genetic variants involved in heme production and degradation, mast cell activity, and responses to mast cell activation were found in individuals with Lyme disease: potentially creating a self-perpetuating cycle of inflammation, and mast cell activation.

Personalized supplementation, lifestyle and dietary modifications designed to support heme formation and degradation, and mast cell activity may be an effective complementary treatment.

References

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