Fenton Reaction Related Genetic Variants, Nrf2 & MTOR Variants Higher in Chronic Lyme Disease

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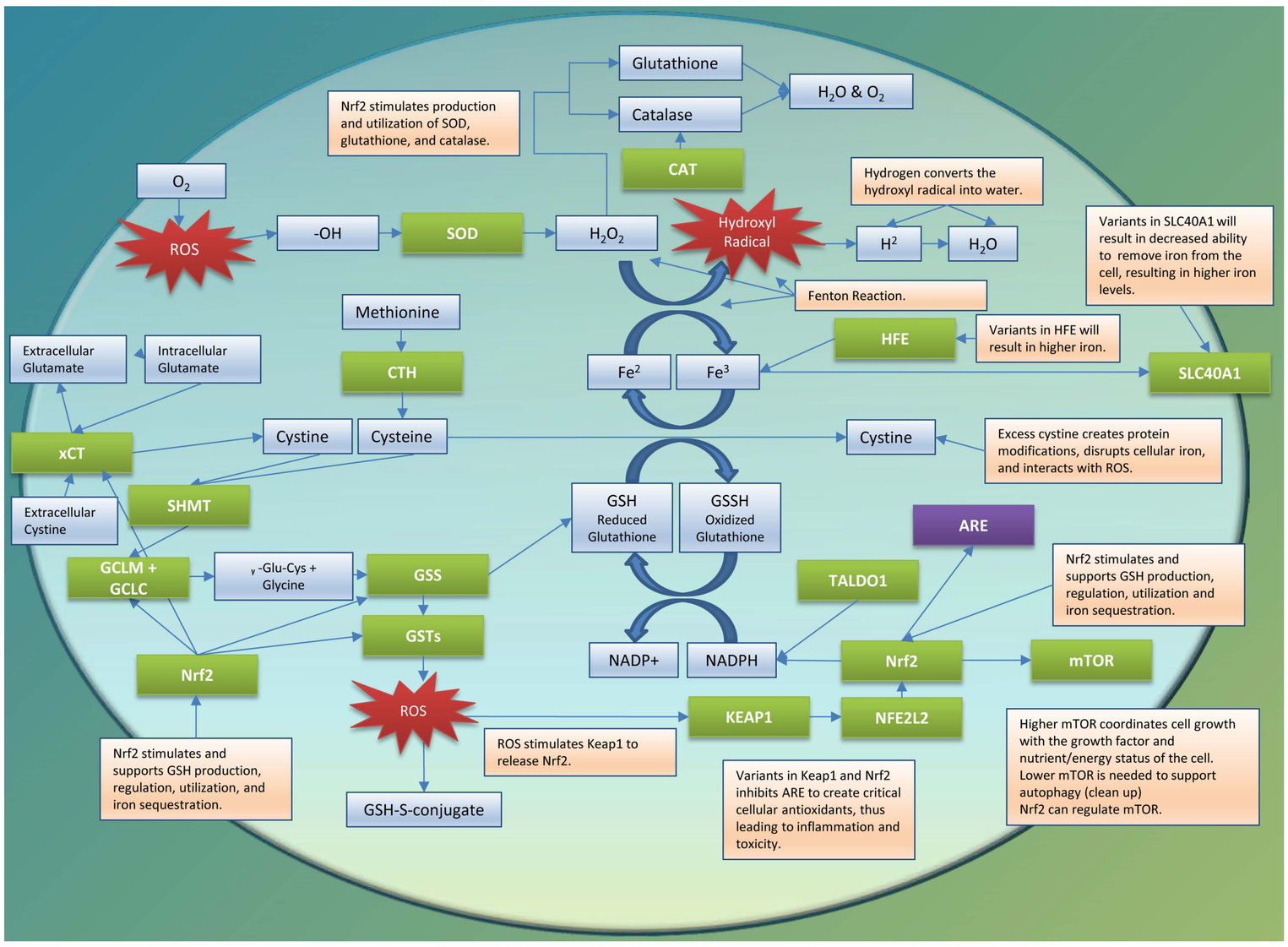
Genetic mutations (SNPs) can lead to increased free radicals, increased toxic substances, and reduced antioxidant protection causing difficulty detoxing and a weakened immune system that may allow chronic Lyme disease to be resistant to traditional treatment.

To evaluate this hypothesis, 391 participants reporting chronic Lyme disease from around the world voluntarily submitted their 23andMe® supplied analysis genome for a global contrast to data supplied by the 1000 Genome Project [**1**]. We evaluated genes that when variated would increase iron levels, and decrease the antioxidant capacity of the body.

The reference and alternate alleles for each of the SNPs were determined using the HaploReg v4.1 database [**2**]. 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.

The genes with the most significant increase in the Lyme group were as follows.



Iron Absorption/Potential for Iron Overload

When Iron combines with hydrogen peroxide in the Fenton Reaction, it creates hydroxyl radicals that create toxicity and depletes glutathione [**3**]. The following variants impact iron absorption (Table 1).

Table 1: Iron Absorption Related Genes

Gene name	RS Number	Ratio Higher
SLC40A1	1123109	2.13
HFE C282Y	1800562	5.03
HFE H63D	1799945	1.74

SLC40A1 – The Solute carrier family 40 member 1 encodes a protein called Ferroportin that may cause hereditary haemochromatosis [**4**].

HFE - The protein encoded by the HFE gene regulates iron absorption and may cause hereditary haemochromatosis [**5**].

Increased body stores of iron in various clinical situations may allow increased growth rates of infectious organisms, and complicate the management of acute and chronic diseases [**6**].

Glutathione Production & Utilization

Glutathione is the master antioxidant that clears toxins, is anti-inflammatory and supports immunity [**7**]. Those with chronic Lyme disease showed increased SNPs in the genes that support the creation, regeneration and utilization of Glutathione (Table 2).

Table 2: Glutathione Production & Utilization SNPs

Gene name	RS Number	Ratio Higher	Gene name	RS Number	Ratio Higher
GSTA1	4715326	1.33	**CTH**	1021737	1.45
GSTA2	2608632	2.38	**CTH A11886G**	1145920	1.27
GSTA5	4715352	1.58	**CTH A32114G**	515064	1.13
GSTA5	4715354	1.15	**CTH G25229T**	663649	1.50
GSTM1	448934	29.93	**CTH T16147C**	12723350	2.82
GSTM1	12097277	3.15	**GCLC**	502862	1.30
GSTM3	10735234	1.72	**GCLC**	2066511	1.52
GSTM4	627365	2.88	**GCLC**	553822	1.29
GSTM4	650985	4.08	**GCLC**	617066	1.62
GSTO2	2297235	1.59	**GCLC**	761141	1.61
GSTP1	762803	1.42	**GLRX**	4561	1.37
GSTP1	1871042	1.30	**GSR**	3779647	1.30
GSTP1 A114V	1138272	2.33	**GSR**	17557435	1.50
GSTZ1	4147578	1.29	**GSR**	8190893	3.53
GSTZ1	7972	2.52	**GSS A5997G**	6088659	2.53
			SHMT2	34095989	1.52

GSTs - Glutathione S-transferase encodes genes that are critical for detoxification through conjugation with reduced glutathione (GSH) and xenobiotics [**8**].

CTH - Cystathionine Gamma-Lyase encodes a cytoplasmic enzyme in the transsulfuration pathway that catalyzes the conversion of cystathione derived from methionine into cysteine [**9**].

GCLC and GLRX - Glutamate-Cysteine Ligase is the first rate-limiting enzyme of glutathione synthesis [**10**].

GSR - Glutathione-disulfide reductase encodes an enzyme that reduces oxidized glutathione disulfide (GSSG) to the sulfhydryl form GSH [**11**].

GSS - Glutathione Synthetase provides instructions for the enzyme that catalyzes the second step of glutathione biosynthesis [**12**].

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 [**13**].

Catalase

Catalase is an antioxidant that reduces H_2O_2. This is a critical function as H_2O_2 combines with iron to create hydroxyl radicals [**14**]. The following variants impact catalase (Table 3).

Table 3: Catalase Genes

Gene name	RS Number	Ratio Higher
CAT	1049982	1.25
CAT	11032703	2.57

CAT – Catalase gene provides instructions for making catalase, a key antioxidant in the body's defense against oxidative stress that converts the reactive oxygen species H_2O_2 to water and oxygen [**14**].

TALDO1 Genes for NADPH

Oxidized glutathione (GSSG) is reduced by the NADPH that is generated in the pentose phosphate pathway [**15**, Table 4].

Table 4: TALDO1

Gene name	RS Number	Ratio Higher
TALDO1 C749776T	11246300	1.86

TALDO1 - Transaldolase 1 encodes a key enzyme of the pentose phosphate pathway that provides ribose-5-phosphate for NADPH. The encoded protein is important for structure/function of mitochondria [**16**].

Nrf2 and Keap1

When Keap1 senses oxidative stress, it releases Nrf2 to stimulate the ARE (Antioxidant Response Element) to support the creation of, recycling of and utilization of glutathione, SOD, and catalase and is also involved in iron sequestration [**17**]. Nrf2 is also involved in mitochondrial biogenesis [**18**]. The following variants impact Nrf2 and Keap1 (Table 5).

Table 5: Nrf2 and Keap1

Gene name	RS Number	Ratio Higher
NFE2L2	10183914	1.61
NFE2L2	1806649	2.52
KEAP1	8113472	1.40

NFE2L2 – The nuclear factor, erythroid 2 like 2 gene has major involvement in the defense against oxidative stress as it encodes a transcription factor that regulates and activates the intracellular antioxidant response element signaling pathway (ARE) [**19**].

KEAP1 - Under normal conditions, Nrf2-dependent transcription is repressed by a negative regulator Keap1. When cells are exposed to oxidative stress, or electrophiles, Nrf2 escapes Keap1-mediated repression and activates ARE to maintain cellular redox homeostasis [**20**].

Variants in the NFE2L2 and KEAP1 genes contribute to toxicity and immune function.

mTOR

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 [**21**]. Nrf2 regulates mTOR [**22**]. The following are variants that impact mTOR (Table 6).

Table 6: mTOR

Gene name	RS Number	Ratio Higher
MTOR	1770345	1.44
MTOR	11121691	1.67

MTOR – The Mammalian Target of Rapamycin belongs to a family of phosphatidylinositol kinase-related kinases that facilitate cellular responses to stresses such as DNA damage, and nutrient deprivation [**23**].

Conclusion

Unique genetic variations have been found in individuals with chronic Lyme disease that have the potential to cause higher levels of iron that create hydroxyl radicals by the Fenton reaction, along with variants in multiple antioxidant pathways and metabolism genes (mTOR). This combination of increased oxidative stress and decreased antioxidant capacity has the potential to create toxic conditions and lowered immunity. Targeted nutritional therapy to compensate for these SNPs (regulate iron, improve antioxidant production and utilization, support Nrf2, Keap1 and mTOR) may be helpful for those with chronic Lyme.

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