Increased Genetic Variants in the Genes related to the Production and Utilization of NAD+ and NADPH in Lyme Patients *(Phase VII)*

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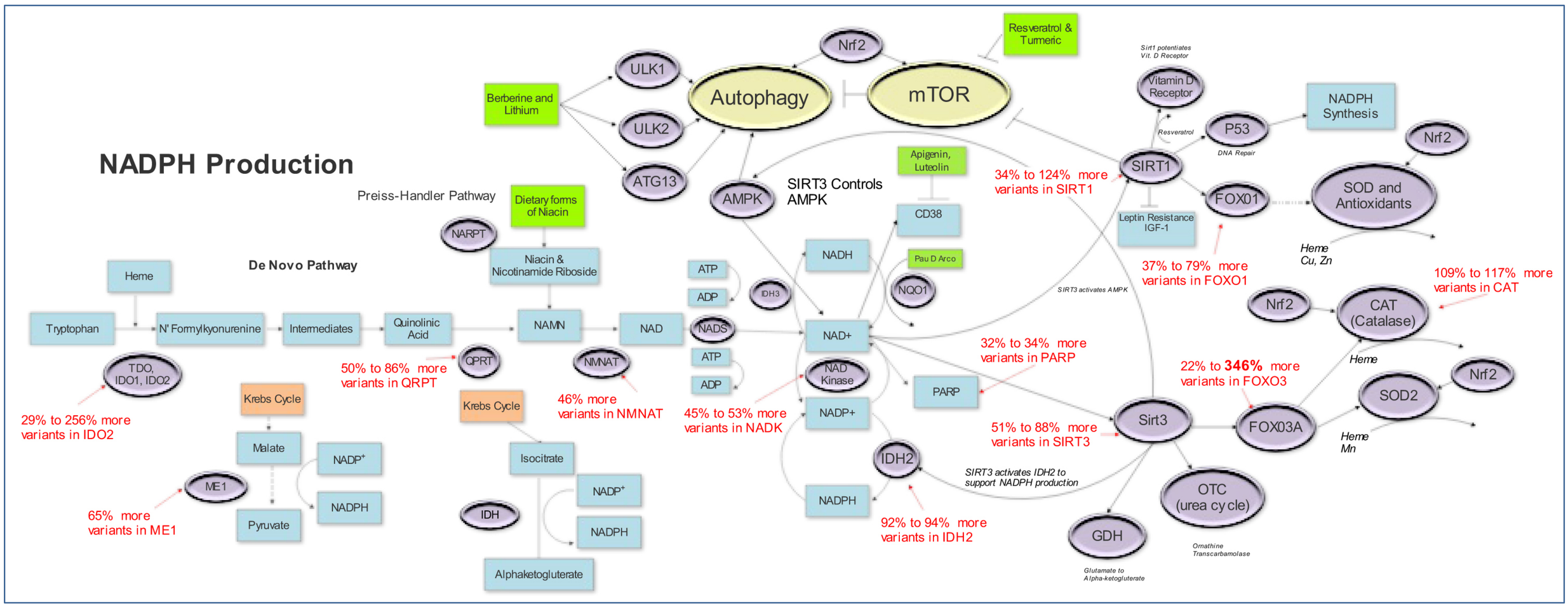

Environmental toxicity has increasingly become the focus of research as more evidence points to the cumulative effects on homeostasis, and the ability to clear toxins. NAD+ and NADPH play an integral role in the removal of environmental toxins. NAD+ plays a critical role in supporting:

- The PARP enzymes which support DNA repair [1].
- The SIRT3 enzyme and subsequently the longevity-related FOXO3A gene, superoxide dismutase (SOD), catalase, autophagy, Urea Cycle, NADPH, and oxidative phosphorylation [2,3,4].
- The SIRT1 enzyme which supports Vitamin D receptors, SOD, and regulates mTOR [5,6,7].
- NADPH synthesis which is responsible for reducing oxidized glutathione, and thioredoxin [8,9]. Lack of NADPH will impede Phase II detoxification, glutathione conjugation, and enable the potential for oxidized glutathione to create the free radicals superoxide and peroxynitrite [10,11].

To determine if unique genetic patterns within NAD+ and NADPH pathways exist in chronic Lyme patients, we compared 421 participants genome to data supplied by the 1000 Genome Project Phase 3. The reference and alternate alleles for each of the SNPs were determined using the HaploReg v4.1 database.

The following enzymes are related to the production of NAD+:

IDH2

As part of the Krebs cycle, isocitrate dehydrogenase 2 (IDH2) oxidizes isocitrate to 2-oxoglutarate, and utilizes NADP+ as a cofactor. This reaction results in the production of NADPH which is critical for the regeneration of the glutathione and peroxiredoxin systems [12][13].

Gene	RSID	Increased SNPs/100	Percentage Increase
IDH2	rs11630814	56.70	94%
IDH2	rs10520685	47.25	92%

QRPT

Quinolinate phosphoribosyltransferase (QPRT) is responsible for the catabolism of quinolinate: the product of the kynurenine pathway, and critical to the de novo NAD-pathway [14]. Quinolinate is also a potent excitotoxin, and has been reported to be associated with neurodegenerative conditions [15].

Gene	RSID	Increased SNPs/100	Percentage Increase
QPRT	rs6565169	30.40	86%
QPRT	rs12596308	48.67	50%

The following enzymes are related to the production of NADPH:

NADK

NADK catalyzes the production of NADP from ATP and NAD which is critical for the regeneration of glutathione and thioredoxin [8,9,16].

Gene	RSID	Increased SNPs/100	Percentage Increase
NADK	rs7407	36.25	53%
NADK	rs35672141	30.61	45%

ME1

Malic Enzyme 1 (ME1) is a NADP-dependent enzyme that catalyzes the oxidation of malate to pyruvate, and thus produces NADPH. [17]

Gene	RSID	Increased SNPs/100	Percentage Increase
ME1	rs3798890	24.90	65%

The following enzymes are NAD+ dependent:

PARP1

PARP1 is a major NAD + consumer in the nucleus, and also responds to DNA strand breaks and facilitates the DNA repair process [18].

Gene	RSID	Increased SNPs/100	Percentage Increase
PARP1	rs3219090	33.31	34%
PARP1	rs1805414	31.88	33%
PARP1	rs747657	31.64	32%

SIRT1

SIRT1, a NAD-dependent deacetylase, removes acetyl groups from numerous proteins, including histones. Sirt1 has also been reported to be involved in aging, and regulating various FOXO genes [19].

Gene	RSID	Increased SNPs/100	Percentage Increase
SIRT1	rs2236318	59.53	124%
SIRT1	rs7896005	63.60	98%
SIRT1	rs1885472	33.53	34%

SIRT3

SIRT3 is a NAD-dependent mitochondrial histone deacetylase (HDAC), but also deacetylates and activates SOD2. Reactive oxygen species can stimulate SIRT3 transcription, and thus the production of SOD via FOXO gene expression [20].

Gene	RSID	Increased SNPs/100	Percentage Increase
SIRT3	rs12365010	20.17	88%
SIRT3	rs4758633	30.86	51%

FOXO1

The FOXO1 gene is part of the forkhead family of transcription factors. The specific function of the FOXO1 gene is still being investigated; however, it appears to play a critical role in growth and cellular differentiation, autophagy, and the transcription of antioxidant proteins [21,24,25].

Gene	RSID	Increased SNPs/100	Percentage Increase
FOXO1	rs2951787	35.17	79%
FOXO1	rs2721068	46.90	48%
FOXO1	rs9549244	39.64	42%
FOXO1	rs1923249	37.55	39%
FOXO1	rs2721069	36.63	38%
FOXO1	rs2755209	31.74	37%

FOXO3A

The FOXO3A gene is also part of the forkhead family of transcription factors. The FOXO3A gene appears to signal for apoptosis by regulating the expression of various genes [22]. FOXO3A is further involved in the regulation of FOXO1, autophagy, and antioxidant proteins, such as SOD [23,24,25,26].

Gene	RSID	Increased SNPs/100	Percentage Increase
FOXO3	rs3800231	101.94	346%
FOXO3	rs2764264	33.39	35%
FOXO3	rs2153960	33.39	35%
FOXO3	rs3800229	33.99	35%
FOXO3	rs1935949	34.05	35%
FOXO3	rs2802292	21.48	23%
FOXO3	rs2802290	20.82	22%
FOXO3	rs2802288	20.76	22%

CAT

The CAT gene encodes for catalase, a heme enzyme. Catalase catalyzes hydrogen peroxide into water and oxygen, and thus plays a significant role in protecting against oxidative stress [27].

Gene	RSID	Increased SNPs/100	Percentage Increase
CAT	rs494024	43.64	117%
CAT	rs511895	42.24	109%

Identifying and supporting/compensating for weakness in NAD+ and NADPH production and utilization may be an effective complementary therapy in addition to medical care for those with chronic Lyme disease.

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