Lesch-Nyhan Syndrome (LNS) is a lethal, X-linked recessive disease that causes bizarre symptoms such as self-mutilation, where patients bite off their lips, tongue, and fingers1. This disease is caused by a severe deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT), an enzyme that recycles two purine bases, guanine and hypoxanthine, into precursors that act as building blocks for DNA and RNA. The HPRT enzyme is encoded by the *hypoxanthine phosphoribosyltransferase 1* (*HPRT1*) gene. The deficiency in HPRT and purine recycling directly causes the overproduction of uric acid in the blood and urine, which is well-understood. However, it is not known how the loss of HPRT function leads to other LNS symptoms such as muscle control problems, lower cognition, and self-injurious behavior. The severity of LNS patients’ symptoms also varies depending on the type of mutation in the *HPRT1* gene. It is unknown how these different mutations cause differences in disease phenotype.

Studies of human brains have suggested that the neurological symptoms of LNS could be related to dysfunction of the dopaminergic neurotransmitter system2,3. Dopamine is a neurotransmitter that controls reward and pleasure in the brain. One rat model supported the relationship between a deficit of dopamine and self-mutilative behavior4. *However, the relationship between the dopamine deficit and HPRT deficiency is still unknown.* The most direct effect of the deficiency of HPRT is the buildup of uric acid. Therefore, excessive levels of uric acid may disrupt the dopaminergic neurotransmitter system in the brain.

**Hypothesis:** The buildup of uric acid in *HPRT1*-mutant mice changes the development of the dopaminergic neurotransmitter system by changing protein interactions and expression levels in the brain.

**Primary Goal:** Characterize the genomic and proteomic changes that contribute to Lesch-Nyhan Syndrome neurological dysfunction as a result of mutation in the *HPRT1* gene.

**Aim 1:** Establish how gene expression levels change in the purine salvage pathway as a result of mutations in *HPRT1*.

**Approach:** We will use a DNA microarray to quantify the expression levels of all genes in the HPRT salvage pathway in wild-type and *HPRT1*-mutant mice. This will indicate how mutations in *HPRT1* alter the purine salvage pathway.

**Aim 2:** Identify proteins that are over- or under-expressed in ­*HPRT1*-mutant mice.

**Approach:** We will use a protein microarray to compare protein levels in wild-type and *HPRT*-mutant mice. This will show which proteins are affected by the *HPRT1* mutation. Our primary focus will be on brain tissue because this is where the neurological symptoms of LNS originate.

**Aim 3:** Determine which proteins interact with HPRT in wild-type and *HPRT1*-mutant mice.

**Approach:** We will use affinity purification to identify proteins that interact with wildtype and mutant HPRT. This will indicate how protein interactions change as a result of *HPRT1* mutations.

The experiments in this proposal are expected to indicate how gene expression and protein interactions change as a result of mutations in the *HPRT1* gene. This may give us insight into how mutations in *HPRT1* change the dopaminergic neurotransmitter pathway and cause the neurological phenotypes and self-mutilative behaviors associated with Lesch-Nyhan Syndrome. This work will also likely lead to potential targets for therapeutic intervention of LNS while also advancing our understanding of purine biosynthesis and salvage pathways.

1. Torres RJ and Puig JG. (2007). Hypoxanthine-guanine phosophoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome. *Orphanet Journal of Rare Diseases, 2*, 48. doi:10.1186/1750-1172-2-48
2. Ernst M, Zametkin AJ, Matochik JA, Pascualvaca D, Jons PH, Hardy C, Hankerson JG, Doudet DJ, and Cohen RM. (1996). Presynaptic dopaminergic deficits in Lesch-Nyhan disease. *New Engl J Med, 334*, 1568-1572.
3. Wong DF, Harris JC, Naidu S, Yokoi F, Marenco S, Dannals RF, Ravert HT, Yaster M, Evans A, Rousset O, Bryan RN, Gjedde A, Kuhar MJ, and Breese GR. (1996). Dopamine transporters are markedly reduced in Lesch-Nyhan disease in vivo. *Proc Natl Acad Sci USA, 93*, 5539-5543. doi: 10.1056/NEJM199606133342403
4. Breese GR, Criswell HE, Duncan GE, and Mueller RA. (1990). A dopamine deficiency model of Lesch-Nyhan disease – the neonatal-6-OHDA-lesioned rat. *Brain Res Bull, 25*, 477-484. doi:10.1016/0361-9230(90)90240-Z