Lesch-Nyhan Syndrome (LNS) is a lethal, X-linked, recessive disease that causes bizarre symptoms such as self-mutilation. For example, some patients bite off their lips, tongue, and fingers1. LNS is caused by a severe deficiency of hypoxanthine-guanine phosphoribosyltransferase (HPRT), an enzyme that recycles two purine bases, guanine and hypoxanthine, into nucleic acid precursors that are used to build DNA and RNA. The HPRT enzyme is encoded by the *hypoxanthine phosphoribosyltransferase 1* (*HPRT1*) gene. The deficiency in HPRT and purine recycling in LNS directly induces the overproduction of uric acid in the blood and urine, resulting in gouty arthritis and kidney stones, which is well-understood. However, it is not known how loss of HPRT function leads to other LNS symptoms such as muscle control problems, cognitive defects, and self-injurious behavior.

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 pharmacological rat model supported a relationship between reduction of brain dopamine during development and self-mutilative behavior4. *However, the relationship between the dopamine deficit and HPRT deficiency is still unknown.*

**Hypothesis:** Loss-of-function mutations in *HPRT1* change the development of the dopaminergic neurotransmitter system by changing protein interactions and HPRT 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 mutations in the *HPRT1* gene.

**Aim 1:** Identify proteins that interact with HPRT and that regulate cognitive development and function.

**Approach:** We will use affinity purification-mass spectrometry and STRING to identify proteins that interact with HPRT in Drosophila. We will sort these proteins by Gene Ontology (GO) terms to identify biological pathways, including the dopaminergic system, that may be disrupted by *HPRT1* mutations. We will then use mutational analysis to determine the function of proteins that act in neurological pathways. This will help to uncover the mechanism of how loss of HPRT function leads to LNS symptoms.

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

**Approach:** We will use quantitative mass spectrometry to compare protein levels in wild-type and *HPRT*-mutant mice. This will show which proteins’ expression levels are affected by the *HPRT1* mutation. We hypothesize that some of these proteins may be involved in dopaminergic pathway development. Our primary focus will be on brain tissue because this is where the neurological symptoms of LNS originate.

**Aim 3:** Establish how gene expression levels change during development as a result of mutations in *HPRT1*.

**Approach:** We will use a DNA microarray to quantify the expression levels of all genes in the brains of wild-type and *HPRT1*-mutant mice throughout development. This will indicate how loss-of-function mutations in *HPRT1* alter brain development. Analysis of the microarray expression data by GO will reveal alternative biological processes affected by *HPRT1* knockout. We hypothesize that pathways implicated in neurogenesis and dopamine metabolism will be identified.

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.

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