Development of a New Mouse Model for Lesch-Nyhan Disease

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Field of Research: Genetics and Psychology

Project summary:

Lesch-Nyhan Disease (LND) is an X-linked disorder caused by mutations in *HPRT1*, the gene that encodes the purine salvage enzyme hypoxanthine phosphoribosyltransferase (HPRT). It affects both the central nervous and renal systems. Symptoms become apparent within the first few months of life and include severe motor dysfunction, self-injurious behavior, cognitive impairment, and uric acid over-production, which may lead to crystalluria or urate stone formation in the kidney. There is extensive phenotypic variability but, in general, the severity of the phenotype correlates with the level of residual enzyme activity. LND is the most severe form of the disease, with null HPRT activity. The mildest form of the disease is characterized by overproduction of uric acid but affected patients do not have overt neurological or behavioral abnormalities. Between these two extremes is a range of phenotypes that include variable neurological and behavioral abnormalities, but no self-injurious behavior. The estimated incidence is 1/380,000 live births per year and the disease has been reported in all population groups. The renal symptoms can be controlled by allopurinol but there is no effective treatment for managing the neurobehavioral aspects of the disease. How HPRT deficiency leads to the profound neurobehavioral problems remains unknown. Because of the rarity of the disease and the difficulty of obtaining human brain tissue for analysis, much of our current understanding of LND has been derived from studies in model systems, especially mouse models generated by homologous recombination in embryonic stem cells. These models capture some of the features of the corresponding human disease, including accelerated purine biosynthesis *de novo* and decreased dopamine levels in the basal ganglia, but they do not have overproduction of uric acid and they do not display any neurological symptoms. One possible explanation for this disparity may be due to differences in purine degradation between humans and mice. Humans lack urate oxidase (UOX), the enzyme that degrades uric acid to the soluble allantoin. Mice have this enzyme, so they do not accumulate uric acid. Thus, to make a mouse model for LND, it is imperative to ablate *Uox* in addition to *Hprt1*. Mouse knockouts for *Hprt1* and *Uox* are available from Jackson Labs. The aims of this proposal are to: (i) cross the single knockouts to make an *Hprt1/Uox* double knockout; and (ii) conduct neurobehavioral, cognitive, and biochemical studies in these mice to determine if they are a more pertinent model for LND.

Applicant GPA and other requirement(s): GPA-not applicable. Introductory course in genetics (desired).

Applicant responsibilities: please discuss with researcher if invited for interview