Galactosemia Foundation
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Modifier Genes and Epigenetic Effects in Galactosemia

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Hereditary galactosemia is due to a deficiency of the enzyme, galactose-1-phosphate uridyltransferase (GALT), which catalyzes the conversion of galactose-1-phosphate to uridine diphosphate galactose. Over 230 naturally-occurring mutations in the GALT gene have been described and there are at least 3 major phenotypes: classic galactosemia, clinical variant galactosemia, and the apparently benign Duarte or biochemical variant form of galactosemia. Only the classic form with absent or barely detectable GALT activity is associated with a potentially lethal multi-organ disease state with E. coli sepsis in the newborn period and chronic long term diet-independent complications. Newborn screening has largely eliminated the acute lethal neonatal component, but chronic complications involving the brain and, in females, the ovary, occur even in patients treated prospectively on day one of life. The cause and treatment of these complications is now the single biggest issue in this field. None of the well-known variables such as the time treatment was started or longitudinal galactose-1-phosphate levels can predict who will suffer these complications. Given the inexplicable variation in phenotype, we hypothesize that modifier genes and/or epigenetic effects play a major role in the phenotypic expression of brain disease in classic galactosemia. We hypothesize that the discovery of modifier genes and epigenetic factors will improve our understanding of disease mechanisms and counseling of the patients and their families, and may identify new targets for improved intervention. Our aims are to identify genes that modify outcome severity in classic galactosemia using an unconventional genetic approach, in which we study neurons in culture (derived from patients' induced pluripotent stem cells) to generate transcriptome and epigenetic data in order to eliminate non-informative genomic DNA mutations/polymorphisms obtained from whole genome sequencing.

The purpose of this project is to better understand the cause(s) of long-term CNS complications that occur in individuals with galactosemia. By achieving this goal, better counseling about long-term prognosis can be provided to families whose newborn infant has been diagnosed with galactosemia. We anticipate this information may also lead to a better treatment of this rare orphan disease.