NIH Award through the Eunice Kennedy Shriver National Institute of Child Health and Human Development

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- **Project:** X-Linked Recessive Familial Neuro-Hypophyseal Diabetes Insipidus
- **Start Date:** September 1, 2009
- **Total Award Amount:** $76,250

**How the results of this project will benefit society:**
Normal water balance is essential for normal function of the body and includes retention of water in the kidney, which is, in part, regulated by a hormone called anti-diuretic hormone (ADH), or vasopressin (AVP). We have identified a family with several males who lack this hormone and therefore void very large volumes of urine. This proposal aims at finding the underlying genetic defect because understanding of the defect at the molecular level could provide important insights into normal and abnormal water metabolism in humans.

**How this project will work:**
We have identified a novel form of neurohypophyseal DI that is inherited in an X-linked recessive manner, and have established linkage to an ~8 centiMorgan interval on Xq28.

**The problem the project is trying to solve:**
Patients with diabetes insipidus (DI) present with persistent thirst, polydipsia, and hypotonic polyuria. The disorder is caused by several distinct etiologies and an appropriate diagnostic work-up is essential for the distinction of the various forms that include neurohypophyseal, nephrogenic, gestational, and polydipsic DI, which is also referred to as primary polydipsia. A complete, properly performed fluid deprivation/DDAVP test permits establishing the correct diagnosis. Several genetic forms of DI have been characterized at the molecular level during the last two decades.

The neurohypophyseal form is caused by mutations in the AVP-NPII gene located on chromosome 20p13, which encodes AVP, and is usually inherited in an autosomal dominant fashion. Clinically, the deficiency in AVP secretion becomes apparent several months to years after birth and progresses in severity from partial to nearly complete. The postnatal progression is explained by degeneration of the AVP producing magnocellular neurohypophyseal neurons due to intracellular retention and a cytotoxic effect of the mutated precursor. The progressive deficiency in AVP is typically accompanied by the disappearance of the posterior pituitary bright spot signal on T1- weighted magnetic resonance imaging. Rarely, the disorder is caused by biallelelic mutations in the region of the AVP-NPII gene that encodes the nonapeptide AVP.

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