NIH Award from the National Institute of Environmental Health Sciences

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- **Project:** Environment-Sensitive Genes in Motoneuron Degeneration
- **Start Date:** July 16, 2009
- **Total Award Amount:** $762,500

**How the results of this project will benefit society:**
This investigation will establish genetic and environmental risks, and lead to rational treatment and prevention of the disabling fatal disorders of sporadic amyotrophic lateral sclerosis (SALS).

**The problem the project is trying to solve:**
The goal of this project is to identify functional variants of environmentally responsive genes that are biologically relevant to motor neuron degeneration of SALS. Considerable progress has been made in inherited motor neuron degeneration where genes such as SOD1 and ALSIN have been discovered and suitable animal models engineered. However, etiology of SALS and PLS remains undefined. Both are complex disorders, and it is widely accepted that susceptibility encoded in the genome interacts with environmental stressors to produce motor neuron degeneration.

**How this project will work:**
These investigators have recently identified two sets of genes of environmentally responsive enzymes that are etiologically relevant to motoneuron degeneration. The PON cluster of genes (PON1, 2 and 3) was associated with SALS, and this finding has been validated in four other studies. Mutations in the second gene, CYP7B1, are caused in corticospinal degeneration in a form of hereditary spastic paraplegia (SPG5A). PONs are antioxidant and detoxify pesticides, while CYP7B1 is inhibited by agricultural fungicides. We will examine in detail variations in these genes and in genes related to them by metabolic pathways and coexpression for association to SALS and PLS. Further, we will also examine their interactions with environmental exposure to pesticides, fungicides, and other relevant stressors. This is a novel opportunity for a comprehensive study of two etiologically relevant environmentally responsive genes in SALS. One thousand ALS cases and 1,000 matched controls will participate in this study.

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