



LOU GEHRIG'S DISEASE

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VARIATIONS IN DETOXIFYING GENES LINKED TO ALS

CHICAGO --- Genetic variations in three enzymes that detoxify insecticides and nerve gas agents as well as metabolize cholesterol-lowering statin drugs may be a risk factor for developing sporadic amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), and possibly responsible for a reported twofold increased risk of ALS in Gulf War veterans.

These findings, from a study led Teepu Siddique, M.D., and colleagues at Northwestern University, open the door to investigating gene-environment interactions as a cause of ALS and other illnesses and to the development of molecular targets for specific treatments. The study was published in the August 22 online issue (available now) of the journal *Neurology*.

Siddique is Les Turner ALS Foundation/Herbert C. Wenske Professor, Davee Department of Neurology and Clinical Neurosciences, professor of cell and molecular biology and director of the Neuromuscular Disorders Program at Northwestern University Feinberg School of Medicine.

ALS is a complex neurodegenerative disorder of the motor neurons that results in muscle weakness, difficulty speaking, swallowing and breathing and eventual total paralysis and death generally within five years.

In 1993 Siddique and collaborators determined that mutations in a gene known as SOD1 account for 20 percent of familial, or inherited, ALS (2 percent of all cases of ALS). However, the cause of sporadic ALS is still unknown.

In earlier research Siddique and other researchers hypothesized that sporadic ALS is modulated by variations in multiple genes interacting with each other and environmental exposures.

The genes for human paraoxanases (PON 1, PON 2 and PON 3), which are located on chromosome 7q21.3, code for the production of detoxifying enzymes involved in the metabolism of a variety of drugs, organophosphate insecticides, such as parathion, diazinon and chlorpyrifos, and nerve gas agents such as sarin.

Previous research described a possible twofold increased risk for developing ALS in veterans of the Gulf War, indicating a war-related environmental exposure to organophosphates and sarin in genetically susceptible individuals as a possible cause.

PON gene cluster variants have previously been associated with other neurodegenerative and vascular disorders, including Alzheimer's disease, Parkinson's disease, coronary artery disease and stroke.

Although the Northwestern DNA study samples were not analyzed for inclusion of Gulf War veterans, Siddique and co-researchers found significant evidence that gene variations (polymorphisms) on the chromosome region encompassing PON2-PON3 were strongly associated with sporadic ALS.

“Thus, single nucleotide polymorphism genotyping in the intergenic regions of the PON gene cluster, and replication, gene expression, gene-gene interaction and PON serum/enzymatic studies may help elucidate the complexity of PON cluster association with ALS,” Siddique said.

Siddique hopes to study DNA samples from Gulf War veterans with increased incidence of sporadic ALS and has applied for their DNA from the Veterans Administration collection.

Collaborating with Siddique on this research were Mohammad Saeed, M.D.; Nailah Siddique; Wu-Yen Hung; Elena Usacheva; Erdong Liu, M.D.; Robert L. Sufit, M.D.; Scott L. Heller, M.D., Northwestern University Feinberg School of Medicine; Jonathan L. Haines, Vanderbilt University Medical Center; and Margaret Pericak-Vance, Duke University Medical Center.

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