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STUDY TIES “NEW” CELL-DEATH MECHANISM TO DEVELOPMENTAL AND DEGENERATIVE BRAIN DISORDERS

LOS ANGELES (Feb. 26, 2006) – An international research team has provided the first conclusive evidence that neurodevelopmental disorders such as mental retardation and neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease and ataxias can be caused, at least in part, by specific gene defects that interfere with the electrical impulses of rapid-firing brain nerve cells called bursting neurons.

The implicated gene, *KCNC3*, and two mutations are described in the journal *Nature Genetics*, published online Feb. 26, 2006. Until now, theories on degenerative cell death have centered on defective proteins and/or their accumulation and aggregation in the brain.

“The neurodegeneration field has been dominated by the hypothesis of misfolded proteins and their aggregation, but the identification of *KCNC3* mutations and their functional characterization represent a novel avenue for understanding cell death,” said Stefan M. Pulst, M.D., director of the Division of Neurology at Cedars-Sinai Medical Center, holder of the Carmen and Louis Warschaw Chair in Neurology, and principal investigator of this study.

KCNC3 forms a potassium channel, part of a biochemical mechanism that regulates the electrical impulses of bursting neurons. Although potassium channel mutations have previously been linked to episodic disorders such as seizures, this is the first time they have been identified as causative factors – and potentially therapeutic targets – in neurodegenerative diseases.

“Very recent neurophysiological studies of bursting neurons have led to speculation that voltage-gated potassium channels could be involved in human neurodegenerative disease, but proof has been lacking,” Pulst said. “This is the first time neurodegeneration has been directly linked to potassium channel mutations.”

In the *Nature Genetics* article, the researchers describe their analysis of two ataxia-causing mutations of the *KCNC3* gene – one present in a Filipino family and one in a French family. Although both mutations affect the firing of cerebellar neurons, they impact them in different ways and apparently lead to different disease manifestations.

The Filipino family’s ataxia is an adult-onset type with prominent motor coordination symptoms and cerebellar atrophy. The French family’s ataxia is a childhood-onset type, with mental retardation and seizures in some individuals. With mental retardation as one of the consequences, the *KCNC3* potassium channel mutations are linked to neurodevelopmental as well as neurodegenerative disorders.

Spinocerebellar ataxias (SCA) include a number of hereditary neurological disorders, some of which emerge in childhood and others in adulthood, affecting one in 17,000 people. Ataxias affect coordination and many basic functions such as walking and speaking. They also may lead to eye movement abnormalities, cognitive decline, epilepsy and other significant deficits.

(more)

Twenty-seven specific locations on human chromosomes have been identified for involvement in the development of ataxias, and 10 causative genes or mutations have been determined. The gene and mutations in this study affect the SCA13 gene.

Ataxias are characterized by degeneration of nerve cells in the cerebellum, while the cell death of Alzheimer's disease takes place in the hippocampus of the temporal lobe and that of Parkinson's disease occurs in the substantia nigra of the brain stem.

Pulst said the new findings on neurodegeneration do not necessarily supersede the prevailing hypothesis of defective proteins. In fact, the two may be linked.

"It could be that the behavior of the nerve cell is altered, making it more susceptible to the onslaught of misfolded proteins, and it could be that misfolded proteins interfere in channel functions," said Pulst, who led a team of scientists from Cedars-Sinai Medical Center, the University of California, Los Angeles, the Mayo Clinic and the Pasteur Institute in France.

Funding for the study was provided by the National Institutes of Health, the National Ataxia Foundation, Programme Hospitalier de Recherche Clinique, the Verum Foundation, and the EuroSCA Integrated Project.

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