Fatal brain disease at work well before symptoms appear

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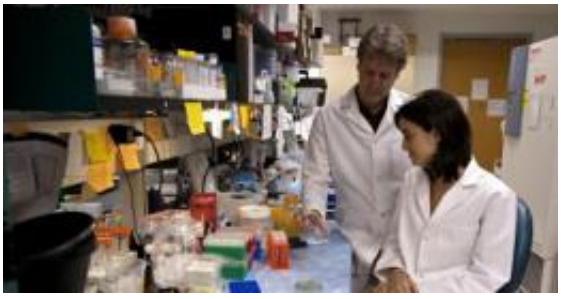

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University of Florida scientists have discovered why a paralyzing brain disorder speeds along more rapidly in some patients than others — a finding that may finally give researchers an entry point toward an effective treatment for amyotrophic lateral sclerosis, often referred to as ALS or Lou Gehrig's disease.

Of more than 100 possible mutations of a single gene inherited by people with familial ALS, the mutations most inclined to produce clumps of problematic cellular debris known as "protein aggregates" appear to be associated with quicker progress of the disease, according to researchers with the University of Florida's McKnight Brain Institute

writing online this week in *Human Molecular Genetics*.

Meanwhile, in a separate study recently online in the *Proceedings of the National Academy of Sciences,* scientists describe how these protein clumps — long considered a defining characteristic of ALS — do not cause the disease, but appear later on, increasing in number between onset of weakness and paralysis in patients.

Together, these findings suggest that the deadly course of the disease is linked to the formation of these protein clumps, even though the sickness may have been well under way.

"Blocking aggregation of these proteins could be a therapeutic target for individuals with this genetic mutation," said David Borchelt, Ph.D., a professor of neuroscience and director of the SantaFe HealthCare Alzheimer's Disease Research Center at UF's McKnight Brain Institute. "Right now, there is little that can be done to help these patients."

ALS involves the death of nerve cells that stretch from the brain to the spinal cord, and from the spinal cord to muscles. It strikes people between the ages of 40 and 70, according to the ALS Association. An estimated 30,000 Americans have the disease at any given time.

Patients usually have a life expectancy of two to five years, with some notable exceptions, such as Cambridge University scientist and author Stephen Hawking, who has survived for more than 40 years since his diagnosis.

The cause of ALS is unknown in about 80 percent of cases, but 10 percent to 20 percent of ALS cases can be traced to an inherited genetic defect. No matter the cause, scientists believe that a basic cellular process in which amino acids are folded into proteins goes wrong in ALS. The misfolded proteins cannot perform their intended function.

Instead, they form the troublesome protein aggregates.

UF's research centered around one gene that produces an enzyme called superoxide dismutase 1, or SOD1. Although SOD1 performs an important role in cell maintenance by warding off dangerous molecules known as free radicals, 146 different mutations in the SOD1 gene have been identified in patients with inherited ALS.

UF scientists, including doctoral student Mercedes Prudencio with Dr. Peter Andersen of Umea University in Sweden, analyzed data from ALS patients to correlate the disease features with more than 30 different variants of SOD1. They found that the mutations most associated with protein aggregation are generally predictive of a more rapid disease progression.

In the PNAS study, UF researchers with investigators from the University of Texas Health Science Center in San Antonio pinpointed when the protein clumping begins and how long the disease has been at work before symptoms actually appear.

By studying SOD1 in mice genetically engineered with a form of ALS, UF doctoral student Celeste Karch demonstrated that the protein clumps appear in spinal cord tissues later in the disease, about the same time that symptoms appear, but well after cell damage occurs from nerve loss and the formation of fluid-filled pockets called vacuoles.

The finding suggests the aggregated proteins may elude normal cellular "housecleaning" methods, or their formation is heightened by stress conditions in the cell.

"As the disease enters the symptomatic stage in mice, the buildup of protein is rapid and dramatic," Borchelt said. "However, the formation of these aggregates is not the whole story. It is well established that

significant damage to the nervous system occurs well before the symptoms appear. The uncontrolled misfolding of SOD1 seems to be confined to the late stage of disease, which is when symptoms first appear, giving hope that treatments targeting this process could be beneficial."

Furthermore, the findings suggest that there is a larger therapeutic window to treat ALS, if scientists can find a way to diagnose the disease before the hallmark protein clumping begins.

"Many scientists had accepted that protein aggregation was tied to the causation of ALS," said Joan Selverstone Valentine, Ph.D., a UCLA professor of chemistry and biochemistry who did not participate in the study. "But this research shows these aggregates form during disease progression, not initiation. It is important to know what to look for as an early cause of the disease and what causes it to get more severe. That means we have to look for something upstream of aggregation as a cause, as well as understand the steps in the progress. If you can prevent or halt the aggregation, you can stop the disease in its tracks. That's as good as a cure if it can be done early enough."

Source: University of Florida (news : web)