Researchers describe molecular 'two-step' leading to protein clumps of Huntington's disease

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In a paper published in the early online version of *Nature Structural and Molecular Biology*, researchers at the University of Pittsburgh School of Medicine deconstruct the first steps in an intricate molecular dance that might lead to the formation of pathogenic protein clumps in Huntington's disease, and possibly other movement-related neurological disorders.

Huntington's is one of 10 diseases in which a certain protein, different for each disease, contains polyglutamine, a stretch of repeating blocks of the amino acid glutamine, explained Ronald Wetzel, Ph.D., professor in the Department of Structural Biology and member of the Pittsburgh Institute for Neurodegenerative Diseases at the University of Pittsburgh School of Medicine. The affected protein in Huntington's disease is called huntingtin.

Most people have a huntingtin protein whose polyglutamine segment contains 20 or so glutamines, and even a polyglutamine with as many as 35 repeats may not cause Huntington's symptoms. But the risk of developing Huntington's disease rises sharply in individuals whose polyglutamine sequences are only slightly larger. A block of 40 repeats, for example, is associated with a very high likelihood of having the disease.

"To a protein chemist, this is a fascinating situation," Dr. Wetzel said.

"Polyglutamine doesn't seem to play a sophisticated role in these proteins, and it doesn't have a defined structure. Yet by changing its length to only a very slight extent, it takes on some new physical properties that somehow initiate diseases."

One consequence of the lengthening is protein aggregation, or clumping, a feature that consistently appears in brain cells of patients who have one of these neurodegenerative diseases. Many research groups, including Dr. Wetzel's, study how polyglutamine expansion alters the huntingtin protein's behavior.

In its most recent studies, the Pitt team worked out the details of how the aggregation behavior of huntingtin depends, in a surprisingly intricate way, on the neighboring segments of amino acid sequence flanking the polyglutamine.

They found that longer polyglutamine sequences have the ability to disrupt the structure of a neighboring region, 17 amino acids long, at the beginning of the protein known as the N-terminus. That sets the stage for new physical interactions with the rest of the huntingtin protein that drive it to aggregate.

"If the N-terminus is not there, huntingtin makes clumps very slowly, even if the polyglutamine stretch is rather long," Dr. Wetzel noted. "When the N-terminus is disrupted by its polyglutamine neighbor, it takes a lead role in the aggregation process, with the polyglutamine then following to consolidate and stabilize the clumps - a kind of 'aggregation two-step'."

The choreography might be similar in other polyglutamine diseases, meaning physical disruption of neighboring regions may influence the tendency for the protein to clump, he added. More research is needed to establish whether the aggregates cause disease or are merely a marker

for it, and to try to develop treatments that can redirect the protein dance or perhaps halt it entirely. "For those of us interested in developing therapeutics," Dr. Wetzel notes, "the strong role played by the N-terminus in initiating aggregation gives us another possible molecular target."

Huntington's disease is an inherited disease in which progressive degeneration of certain brain neurons causes uncontrolled writhing, twisting and jerking movements, and cognitive and psychiatric problems. It was once called Huntington's "chorea", from a Greek word for dance.

Source: University of Pittsburgh Schools of the Health Sciences