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## Pinpointing the Cause of a Neurodegenerative Disorder

Researchers have discovered how the abnormal repetition of a genetic sequence can have disastrous consequences that lead to the death of neurons that govern balance and motor coordination. The studies bolster the emerging theory that neurodegenerative disorders can be caused by having extra copies of a normal protein, not just a mutated one.

People who are afflicted with the rare neurodegenerative disorder spinocerebellar ataxia type 1 (SCA1) suffer damage to cerebellar Purkinje cells caused by a toxic buildup of the protein Ataxin-1. Researchers knew that SCA1, Huntington's disease and other related disorders arise because of a "genetic stutter," in which a mutation causes a particular gene sequence to repeat itself. These abnormal genetic repeats cause the resulting proteins to contain unusually long repetitive stretches of the amino acid glutamine.

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The new findings, which are published in the August 26, 2005, issue of the journal *Cell*, provide a molecular explanation for Ataxin-1's assault on cerebellar Purkinje cells.

The findings should help to understand a range of diseases, including Huntington's disease, which are caused by an abnormal number of repetitive gene sequences. The discovery may also offer a new conceptual approach to understanding the pathology of Parkinson's disease and Alzheimer's disease, according to Huda Y. Zoghbi, a Howard Hughes Medical Institute investigator at the Baylor College of Medicine.

People with polyglutamine repeat disorders suffer severe degeneration in particular groups of neurons that vary depending on the type of disease. In SCA1, for example, the buildup of Ataxin-1 damages the cerebellar Purkinje cells. As a result of the damage, people with SCA1 lose balance and motor coordination. Loss of muscle control worsens until patients can no longer eat or breathe.

"We had known that the expansion of the glutamine tract within Ataxin-1 probably interfered with normal clearance of Ataxin-1, meaning that it accumulated in cells," said Zoghbi. She noted that earlier studies yielded hints that the glutamine repeats somehow caused Ataxin-1 function to be altered in a way that damaged or killed Purkinje cells.

"We had been accumulating clues that the glutamine tract expansion is clearly what is important for disease because that's the mutation," said Zoghbi. "But we also concluded that there was something else beyond the glutamine that's really mediating the toxicity of the protein." Those conclusions were based, in part, on experiments in mice that showed that increased levels of normal Ataxin-1 can cause the pathology of SCA1.

Turning to the fruit fly, *Drosophila*, a favorite of geneticists, Zoghbi and her colleagues showed that a particular domain of Ataxin-1 was responsible for causing the flies to lose sensory neurons, but the domain's function remained unknown. Then, a finding by co-author Hugo Bellen, an HHMI investigator at Baylor, set the researchers off in a more fruitful direction. Bellen's team was doing experiments designed to identify proteins that interact with the *Drosophila* protein, Senseless. His group discovered serendipitously that Senseless interacts with the Ataxin-1 domain and is important for nervous system development.

In further experiments in flies, Zoghbi and her colleagues showed that increases in Ataxin-1 reduced levels of Senseless during peripheral nervous system development, causing developmental abnormalities. Additional experiments demonstrated that enhanced levels of normal and abnormal human Ataxin-1 produced even more serious pathology in the flies.

The researchers then showed that the same interaction and pathological effects occurred in mice — in which Ataxin-1 affected the mammalian version of Senseless, which is called GFi-1. And, they found that mice lacking GFi-1 showed Purkinje cell degeneration, just like humans with SCA1.

"The overall picture we have now is that glutamine expansion causes some aspects of the pathology of SCA1 in part by enhancing the activity of the domain that is outside the glutamine repeat," said Zoghbi.

The finding offers insight into the molecular mechanisms that cause SCA1, Huntington's disease and other glutamine repeat disorders, said Zoghbi. "It seems to be a recurring theme in neurodegenerative disorders that having extra copies of a normal protein, not just a mutated one, can cause pathology. There have been observations that having extra copies of the normal alpha synuclein protein that causes Parkinson's disease, or of the amyloid precursor protein that causes Alzheimer's disease, can cause pathology," she said. "So, this raises the question of whether mutations in the genes for these proteins enhance their normal action.

"Importantly, such insights can now guide studies that focus on the normal function and interactions of these proteins and how they might be enhanced

by disease-causing mutations," said Zoghbi. "These studies could give better understanding of how the proteins cause disease."