Researchers Locate Gene That Triggers Huntington's Illness

By Natalie Angier

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After 10 backbreaking years in a research purgatory of false leads, failed experiments and long stretches of mordant despair, an international team of scientists says it has discovered the most coveted treasure in molecular biology, the gene behind Huntington's disease.

Now that they have the gene in hand, researchers say they can begin making headway in understanding the disorder, a neurodegenerative illness that usually strikes a person in the 30's or 40's, insidiously destroys body and sanity alike, and kills within 10 to 20 years.

Huntington's disease afflicts about 30,000 Americans, and as many as 150,000 are at risk of developing it. The best-known victim was the folk singer Woody Guthrie. Holy Grail of Genetics

The first clues to the gene's location came in the early 1980's, at the dawn of the contemporary era of molecular genetics. But researchers soon ran into a succession of snags that transformed the search into an irresistible if irritating quest that seduced some of the biggest names in biology.

Of particular interest to scientists, the mutation that causes the disease is one they have lately seen in genes that cause other illnesses, a sort of molecular accordion effect in which a tiny segment of the gene is abnormally expanded and repeated over and over. Key to the Puzzle

Researchers emphasized today that much work needed to be done before they could use the mutation as any sort of precise prognostic tool. Nor does the finding the gene mean that a treatment for the disease is imminent. But the discovery is essential to cracking the puzzle of Huntington's.

The finding will be reported Friday in the journal Cell, crediting as its author the Huntington's Disease Collaborative Research Group. This reflects a rare instance of sustained scientific cooperation in which six laboratories in the United States, England and Wales shared their data and ideas.

Biologists everywhere, even those who were competing against the victorious consortium, greeted the news with uninhibited joy and deep relief.

"This is a landmark event," said Dr. Rick Myers of the University of California at San Francisco, who had independently been seeking to isolate the gene. "I can hardly believe that it's finally here after all these years. This is a very important, a very significant discovery."

Dr. David L. Nelson, a molecular geneticist at Baylor College of Medicine in Houston, said: "I think this is fantastic. It's taken so long to find this gene, and there's been such bizarre speculation about why people couldn't get it, that I'm relieved and thrilled to see the search has ended." Dr. Nelson has worked on another disorder, called fragile X syndrome, which is caused by a similar abnormal gene expansion.

Dr. Nancy S. Wexler of the Hereditary Disease Foundation in Santa Monica, Calif., and Columbia University in New York, helped hold the consortium together over the years and often traveled to towns in Venezuela where many of the villagers suffer from Huntington's. She said she had just been about to walk out the door to leave for South America when she heard the news that her group had isolated the gene.

"I felt like I'd walked into a brick wall," she said. "I was stunned. I was ecstatic. I was wandering around like a zombie after that." Researcher at Risk

Dr. Wexler, whose mother died of Huntington's disease, has a 50-50 chance of having inherited the gene. A test has been available for about a decade that predicts with high accuracy who is likely to be at risk, but Dr. Wexler declines to discuss whether she has taken the test.

The next step in research is to find out how the protein produced by the normal version of the Huntington's gene works in the body, and why the expanding mutation within the gene has such catastrophic consequences.

"From what we've seen so far, the protein doesn't look like anything else we're familiar with," said Dr. Francis S. Collins of the University of Michigan in Ann Arbor, another participant in the collaboration.

The disorder sometimes begins in childhood or adolescence but more often is silent until well into adulthood, at which point the symptoms begin: random, uncontrollable movements in every part of the body, psychiatric disorders, mental deterioration and death. Huntington's victims can be mistaken for drunks, so careening is their walking and so slurred is their speech. Researchers now suspect that some of the Salem witches may have suffered from Huntington's. Odyssey Through Chromosome

The disease results from the extensive death of neurons in the basal ganglia, a region of the brain that controls movement and possibly cognition.

Rare as the disorder is, it has remained much in the public eye over the years, partly because the search for the gene has been so widely publicized.

Through a stroke of great luck 10 years ago, Dr. James F. Gusella of Massachusetts General Hospital and the leader of the collaboration, came up with a so-called marker for Huntington's, a piece of DNA that indicated roughly where the gene must be, somewhere on the upper arm of chromosome 4, one of 23 pairs of chromosomes packed in every human cell.

Dr. Gusella and his collaborators assumed it would be a relatively straightforward task to

find the specific gene, but instead scientists floundered for years as other genes -- including those for cystic fibrosis, muscular dystrophy and neurofibromatosis -- were plucked out to much fanfare.

The scientists repeatedly were led astray by unusual inheritance patterns of the Huntington's gene and by the complexity of working near the tip of a chromosome. The end regions of chromosomes are thought to be dense with genes and to be subject to a lot of so-called recombination, or chromosomal-exchange events, making them very difficult to sift through.

Scientists said the detection of the Huntington's gene marks the closure of the era of laboriously tracking down individual genes for diseases. From now on, biologists plan to put most of their enterprise into the Human Genome Project, the vast Federal effort to systematically lay out all 100,000 genes found in the human blueprint.

At last the scientists identified a gene with all the hallmarks of being unstable and subject to dangerous expansion, exactly as they had seen in fragile X syndrome and two other hereditary disorders. A Molecular Stutter

In the Huntington's gene, the mutation affects a triplet of genetic subunits, or bases, represented by the chemical initials CAG. In normal people, the gene has from 11 to 34 of these triplets. But Huntington's patients possess anywhere from 35 to 100 or more of them. This molecular stutter either disrupts the gene's ability to make a protein at all or results in a misshapen and malfunctioning protein. In either case, the defect results in the death of brain cells.

Examining 75 families with a history of Huntington's, the researchers have seen the abnormal expansion in every case of an afflicted patient. They now are firming up the evidence suggesting that the exact number of excess triplets predicts when in life a person will fall prey to the illness.

Should the correlation hold, enabling researchers to tell people that they are going to get an incurable disease and when it will strike, Dr. Collins said the knowledge could strain genetic counseling to its limits.

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