Nearly 10 years after scientists isolated the gene responsible for Huntington’s, they are still searching for how it wreaks its devastation

OF HUNTINGTON’S DISEASE

By Elena Cattaneo, Dorotea Rigamonti and Chiara Zuccato

U
nusual grimaces are normally the first sign that something is wrong. Next, affected people become more and more absentminded and begin to display involuntary gestures, especially when under psychological or physical stress.

As the disease progresses, the dancelike movements—which may be confused with drunkenness—occur more frequently and become disabling. People lose their capacity to perform simple, everyday tasks and show impairments in intellectual abilities such as planning. In the later stages, depression and aggressiveness—and, in the most severe cases, dementia and psychosis—take over, reducing a formerly healthy, vital family member, friend or co-worker to a miserable, bedridden shadow.

This is the grim picture of Huntington’s disease, a heritable disorder that commonly strikes people who have the predisposing gene during the prime of life, the 30s or 40s. No effective treatment exists, so the disease advances slowly but inexorably, generally leading to total disability and death after 15 or 20 years. Although Huntington’s primarily affects the central nervous system, most individuals suffering from it eventually die from heart or respiratory complications, as a result of their being confined to bed, or from having sustained head injuries caused by frequent falls.

The gene that causes Huntington’s disease was identified in 1993 by a coalition of 58 scientists from around the world, including James F. Gusella of Massachusetts General Hospital and Francis S. Collins, who was then at the University of Michigan at Ann Arbor. Shortly thereafter, genetic tests became available that enable people who have family members with Huntington’s disease to determine whether they have inherited the mutant gene. Because the gene is dominant, those who inherit the mutant form are destined to acquire the disease and have a 50 percent chance of passing the gene on to each child they conceive. Some people choose to take the test to allow them to plan their lives better; others decide they would rather not know.

Scientists such as ourselves are trying to offer hope to families with Huntington’s by working to understand more fully how the mutant gene causes the disease and how it might be circumvented to provide a treatment. We are finding evidence that the mutation underlying
Huntington’s is double-barreled: it not only encodes an abnormal protein that appears to be toxic to nerve cells, but the faulty protein can no longer prompt production of a key growth factor, starving a particular part of the brain. Animal studies—and early clinical trials involving humans—suggest that therapies involving growth factors might counter these effects. But the recent findings explain the pathology of Huntington’s only partially, so continued research is needed to discern its complexities.

**From Huntington’s to huntingtin**

*Huntington’s disease* is named for George Huntington, a physician from Ohio. In 1872 Huntington reported extensively about a peculiar hereditary disease that he and his father—who was also a doctor—had observed in a family on Long Island, N.Y. Noting the grotesque and uncoordinated movements of the patients, he termed the disease “chorea,” from the Greek word *choros*, for “dance.” Today doctors recognize Huntington’s as one of the most common hereditary disorders of the brain, affecting roughly one person in every 10,000.

The symptoms of Huntington’s are caused by the degeneration of cells, or neurons, located in the striatum, a region deep within the brain that is part of a structure called the basal ganglia [see illustration at right]. These neurons normally work to shut off excitatory signals from the motor cortex, the part of the brain that dictates movement. When they die, the motor cortex becomes hyperactive, resulting in involuntary movements (also called chorea). It is less clear how the death of striatal neurons causes the disorder’s psychological symptoms.

The gene that is mutated in Huntington’s disease is dubbed *huntingtin*, and it lies at one end of chromosome 4. Genes are segments of the DNA double helix that encode the information for making proteins. The code consists of combinations of four simple units, called bases, named adenine (A), thymine (T), cytosine (C) and guanine (G). The bases pair with one another to form the rungs of the DNA helix’s ladder: A pairs with T, and C pairs with G. When a cell needs to make new proteins, the helix untwists and the rungs split apart so the cell’s machinery can read the code. A triplet of three bases codes for one of the 20 amino acids that are strung together in various combinations to make all the body’s millions of distinct proteins.

When researchers pinpointed the *huntingtin* gene, they noted that even in normal people it contains a kind of molecular stutter in which the triplet CAG is repeated between nine and 35 times. (Such expanded repeats can occur in different genes as well and are associated with several other neurodegenerative diseases.) But in people with Huntington’s, the stutter becomes especially prolonged—in some rare cases stretching to up to 250 repeats. Intriguingly, scientists have found that people with the most CAG repeats tend to develop the disease at an earlier age than those with a shorter stutter. And for unknown reasons, the number of CAG repeats can increase from generation to generation in families with Huntington’s (this appears to happen more frequently when the mutated gene is inherited from the father).

**The Theories**

The triplet CAG codes for the amino acid glutamine, which researchers denote with the letter Q. People with mutant forms of the *huntingtin* gene have huntingtin proteins that contain so-called polyglutamine sections consisting of 36 or more Qs. But why should extra glutamines in a protein cause disease?

The simplest explanation is that an extended stretch of polyglutamines destroys the huntingtin protein’s ability to carry out its usual job in the brain. This loss of function hypothesis was initially dismissed because early studies found that huntingtin is made not only in the striatum—the region that shrinks in response to the disease—but in the rest of the brain as well and in other brain regions that do not appear to be affected during the course of Huntington’s. In addition, humans have two copies of every gene—one from the mother and one from the father—so people with Huntington’s should still have one good copy of *huntingtin* and thus should make a decent amount of the healthy protein. Similarly, people with Wolf-Hirschorn syndrome, a rare

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**Overview/Huntington’s Disease**

- Huntington’s disease—which cripples and causes dementia in people in midlife—is a genetic disease that results from a mutation in a gene called *huntingtin* found on chromosome 4.
- Genetic tests for the disorder exist, but there is no cure.
- People destined to acquire Huntington’s have a molecular stutter in *huntingtin* that causes them to make a mutant form of huntingtin protein in which the same amino acid, glutamine, repeats dozens of times.
- Mutant huntingtin appears to be toxic to key nerve cells in the brain. It also lacks the ability to turn on a necessary growth factor gene.
BRAIN DEVASTATION of Huntington’s occurs predominantly in the striatum, a region deep within the brain that is part of a structure called the basal ganglia. The striatum is full and healthy in a brain from someone who died of causes other than Huntington’s (left); it is shrunken in a brain from a person who had the disorder (right).

disease in which a large region of chromosome 4—including one copy of the huntingtin gene—is deleted, do not show any symptoms of chorea.

An alternative, gain of function hypothesis holds that the huntingtin mutation yields a toxic form of the huntingtin protein. According to this view, the long polyglutamine stretch resulting from the huntingtin mutation transforms the shape of the mutant protein, enabling it to stick to several other proteins—notably normal huntingtin, which it disables. The binding could explain why the disease is inherited in a dominant fashion. In fact, the late Max F. Perutz of the Medical Research Council’s Laboratory of Molecular Biology in Cambridge, England, and his co-workers determined that the polyglutamine stretches of mutant huntingtin fold into a form called a beta sheet, which is known to act as a glue between proteins. Erich E. Wanker of the Max Delbrück Center for Molecular Medicine in Berlin, Gillian P. Bates of Guy’s Hospital in London and Marian DiFiglia of Massachusetts General Hospital and their colleagues have observed aggregates of mutant huntingtin in the brains of mouse models of the disease and in striatal and cortical neurons from people who died with Huntington’s.

How these aggregates cause the neuronal damage observed in Huntington’s remains strongly debated, however. One hypothesis is that proteasomes—cell structures that destroy worn-out or toxic proteins—are unable to dispose of the mutant huntingtin proteins because of their aberrant conformation. As a result, the mutated huntingtin accumulates unrestrained, killing cells. But the gain of function hypothesis cannot easily explain why brain regions besides the striatum are not affected.

Conversely, other hypotheses suggest that instead of being responsible for the disease, the aggregates might represent a defense mechanism to protect cells from the toxic effects of polyglutamine. Studying the role of these aggregates remains crucial to understanding Huntington’s, and finding ways to prevent their formation or break them apart might lead to new drugs for the disease. Wanker and his colleagues have recently devised a laboratory test for identifying potential drugs that can prevent mutant huntingtin from forming aggregates.

Another line of research is based on identifying molecules that are specifically expressed in the striatum and that can interact with huntingtin. If such molecules become trapped in the aggregates, they could contribute to the toxicity. Researchers have so far identified three groups of proteins that interact with huntingtin, but none seems to account for the toxic nature of mutated huntingtin or to explain why only striatal neurons die in Huntington’s disease.

A Lifesaver

TO SOLVE THIS PUZZLE, we and others—including Scott Zeitlin of Columbia University—have sought to determine the function of normal huntingtin in the brain. We started by examining the effects of using genetic engineering to insert either extra copies of normal huntingtin or mutant forms of the gene into neurons grown in culture dishes in the laboratory. In 2000 we reported that cells that overproduce normal huntingtin can persist when deprived of growth medium or under other conditions that would generally cause them to die. What is more, we found that normal huntingtin appears to keep neurons alive by halting the cascade of molecular events that usually leads to apoptosis, or programmed cell death. We concluded that normal huntingtin works as a lifesaving protein for neurons.

Zeitlin and his colleagues have extended these findings by generating so-called conditional knockout mice, in which both copies of the huntingtin gene can be switched off once the animals are mature. When the gene is inactivated, the mice stop making huntingtin protein and develop severe brain damage.

Zeitlin’s group has also demonstrated that interrupting huntingtin production at various points in a mouse’s life leads to the death of brain neurons by apoptosis. In addition, the researchers have shown that mice lacking the normal form of huntingtin

THE AUTHORS

ELENA CATTANEO, DOROTEA RIGAMONTI AND CHIARA ZUCCATO are in the department of pharmacological sciences and at the Center of Excellence on Neurodegenerative Diseases at the University of Milan in Italy, where Cattaneo is a professor of pharmaceutical biotechnology. Cattaneo’s research also involves the study of stem cells and their use for the treatment of neurodegenerative disorders such as Huntington’s disease. Since 1995 she has collaborated on the Coalition for the Cure, an international research consortium promoted by the Huntington’s Disease Society of America, and on the Cure HD Initiative, sponsored by the Hereditary Disease Foundation. She has been an investigator of the Italian Telethon Foundation since 1996. Among her awards and honors is a medal from the president of Italy, Carlo Azeglio Ciampi, for her work on stem cells and Huntington’s. Rigamonti and Zuccato are postdoctoral associates in Cattaneo’s laboratory. Both received their Ph.D.s in 1998: Rigamonti from the University of Milan and Zuccato from the University of Insubria in Varese.
have very similar neurological symptoms to mice that express the mutant form of the protein. This observation suggests that the absence of normal huntingtin and the presence of mutant huntingtin might be different sides of the same coin.

But the mouse studies cannot explain why striatal neurons are targeted preferentially in Huntington’s. To unravel this mystery, we and others have turned to studies of brain-derived neurotrophic factor (BDNF), a growth factor that is known to be crucial for the development and survival of neurons in the striatum. BDNF is typically produced in the cell bodies of neurons in the cortex and then travels to the striatum along fibers that span the two brain regions. Accordingly, we began to look for a connection between huntingtin and BDNF.

Intriguingly, we discovered that normal huntingtin stimu-
lates the production of BDNF in neurons grown in laboratory cultures. In particular, huntingtin appears to activate the “on” switch, or promoter, of the gene that encodes BDNF. This turns on the BDNF gene, prompting neurons to make more of the growth factor. In contrast, mutant huntingtin does not stimulate the BDNF promoter, resulting in a decrease in BDNF production. We also observed a link between huntingtin and BDNF in experiments involving mice genetically engineered by Michael R. Hayden and his colleagues at the University of British Columbia. We found that these mice, which overproduce normal huntingtin, have elevated amounts of BDNF in their brains, whereas those with mutant huntingtin do not.

Based on this information, we now speculate that Huntington’s is a very complex disorder that does not conform neatly to our earlier hypotheses. Not only does the Huntington’s mutation generate toxic aggregates that can kill brain cells directly, it also deprives the brain of normal huntingtin—which would otherwise turn on the gene for the growth factor BDNF. Indeed, these two aspects might be related. In 1999 Robert M. Friedlander of Brigham and Women’s Hospital and his co-workers observed in genetically engineered mice that the mutant form of huntingtin can destroy the normal version.

**Brain Rescue?**

**As a better understanding of the complexities of Huntington’s disease, we can now turn to devising better treatments for the disease. The drugs that are currently available alleviate just some of the symptoms of the disorder and can have serious side effects. Indeed, the drugs often ameliorate one symptom only to make another worse. Although doctors commonly prescribe sedatives to people with Huntington’s to control their involuntary movements, these drugs also lower levels in the brain of the neurotransmitter dopamine, worsening the person’s depressive symptoms. Antidepressant drugs lift the depression, but some types can exacerbate the chorea. Physicians use so-called neuroleptic drugs to treat patients with hallucinations and psychosis, but the doses must be kept low because these medications can also induce spastic movements. For several years, researchers in the U.S. and Europe have been conducting tests of riluzole, a drug whose specific mode of action is unknown but that is already in use for the neurological disorder amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease). Still, the drug appears to have limited success against either disorder.

More innovative trials for the treatment of Huntington’s are aimed at replacing the damaged neurons with transplants of fetal tissue or at injecting or infusing neurotrophic factors such as BDNF. The first approach has yielded encouraging, though preliminary, results in patients in the early stages of Huntington’s, but its use remains controversial in light of ethical questions concerning tissue derived from aborted fetuses. Marc Peschanski and his collaborators at INSERM in Creteil, France, for instance, have transplanted fetal neurons into the striata of five patients with Huntington’s, and three have experienced appreciable improvements in their motor and intellectual function. New clinical trials are now being conducted in a larger number of patients. Meanwhile, to overcome the limited availability of fetal cells and the controversy surrounding them, researchers are now trying to grow neural stem cells in the laboratory for use in transplantation. But stem cells are less mature than fetal cells, and it is an open question whether stem cells will be able to develop and integrate fully into a patient’s damaged brain. It is also unclear whether mutant huntingtin made by a patient’s other neurons would disrupt the normal huntingtin made by engrafted fetal or stem cells.

The second approach is based on animal studies showing that ciliary neurotrophic factor (CNTF) can protect striatal cells from death. But it has been difficult to deliver the growth factor to the brain in sufficient amounts and in active form. Proteins such as BDNF and CNTF are broken down in the stomach when given orally; when administered by injection or infusion, they sometimes cannot cross the barrier of cells that protects the brain from substances circulating in the blood. Accordingly, Patrick Aebischer of the Swiss Federal Institute of Technology in Lausanne has designed a gene therapy protocol in which he and his co-workers implant semipermeable capsules containing cells genetically modified to deliver CNTF into the right ventricle of the brain. Having found in chimpanzees that the capsules release CNTF continuously, Aebischer’s group has teamed up with Peschanski’s to evaluate the strategy in a small number of patients. CNTF is being tried in people before BDNF because its effects in protecting striatal cells were discovered several years before the benefits of BDNF were known. Various research groups are now planning to test BDNF in animals and, depending on the results, in Huntington’s sufferers.

The BDNF promoter might also offer a target for developing drugs against Huntington’s disease. Drugs that mimic the normal function of huntingtin in turning on the BDNF gene might circumvent the huntingtin mutation. Because such drugs would act “downstream” of the huntingtin protein, it might not matter if a patient’s normal huntingtin became tied up into aggregates with the mutant form of the protein. Indeed, we predict that the future of pharmacological therapy for Huntington’s rests on drugs that can interfere with the toxicity of mutant huntingtin while restoring normal huntingtin’s beneficial effects. Perhaps by unravelling the mechanics of Huntingtin’s, we will be able to provide hope for the next generation.

**More to Explore**


The Web sites of the Huntington’s Disease Society of America [www.hdsa.org] and the Hereditary Disease Foundation [www.hdfoundation.org] are useful resources on genetic testing for the disease and contain information for families with Huntington’s.