Huntington Disease: The Orphan Enigma

By Ricki Lewis, PhD

Huntington disease, neurogenetics, George Sumner Huntington, Systematic Evaluation of Treatments for Huntington's Disease, Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis

Rigidity and dystonia in Huntington disease (HD) are associated with atrophy of the caudate nucleus and putamen (B). Extensive neuronal loss and gliosis in the cerebral cortex (A,C) in both HD and Alzheimer disease (AD) are responsible for varying degrees of cognitive impairment (however, neurofibrillary tangles and senile plaques are seen only in AD).

Understanding a rare genetic disorder can lead to treatments for more common conditions. The one-in-a-million children with familial hypercholesterolemia, for example, spearheaded development of the blockbuster statins. In neurology, study of rare familial variants of Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis (ALS), and even prion disorders revealed molecular targets for drug discovery.

For HD, however, the genes-as-a-guidepost strategy fails, because HD has no common counterpart. It is a disorder of information overload--a gene too long, a complex cellular derangement with many entangled and interacting components. "Parkinson disease is a deficiency of 1 chemical that can be replaced--we can increase availability of dopamine or mimic its effects. HD isn't that simple," said Kathleen M. Shannon, MD, director of the Huntington's Disease Center of Excellence at Rush University Medical Center in Chicago.

HD stands out even among the single-gene disorders in its strangeness. Unlike the others, homozygotes for the HD mutation are no worse off than the more common heterozygotes. Also highly unusual, penetrance approaches 100%--if you inherit the gene and live long enough, you get the disease. Yet its rarity stymies progress.

"There's no easy answer, at least for now, to the question of why HD has been so difficult to understand and treat," said Allan J. Tobin, PhD, professor of neurology at University of California, Los Angeles, and senior scientific advisor to the High Q Foundation, a New York City-based private philanthropic organization that coordinates academic, industrial, government, and private efforts to develop treatments for HD. "High Q" refers to the high numbers of glutamine (symbolized as "Q") repeats in the abnormal huntingtin (htt) protein in HD (Table 1 lists polyQ diseases.) "The question is whether there's a single pathogenic cascade, or many parallel, interacting ones," Tobin added.

CURRENT MANAGEMENT APPROACHES

The goal of disentangling the mechanistic threads that weave the fabric of HD is to identify drug targets--and that's already happening. Two drugs are in clinical trials: tetrabenazine (marketed in Canada and Europe as Nitoman by Prestwick Pharmaceuticals) and ethyl-eicosapentaenoate (ethyl-EPA; Miraxon, Amarin Neuroscience). Two are commonly used to manage symptoms: haloperidol and clonazepam.

A project called Systematic Evaluation of Treatments for Huntington's Disease (SET-HD) has identified 40 initial candidates from the existing pharmacopeia and has evaluated 24 (see www.huntingtonproject.org and Table 2). And the European Rare Diseases Therapeutic Initiative (ERDITI; www.erditi.org) is seeking new treatments among drug candidates for common disorders that never made it to market. With 10 research institutions and 4 large pharmaceutical companies on board, ERDITI is matching basic researchers with big pharma's stockpile.

Meanwhile, the role of the neurologist in treating HD isn't restricted to the prescription pad. A neurologist can do "a lot," said Karl Kieburtz, MD, MPH, professor of neurology and community and preventive medicine at the University of Rochester in New York. Information can help, such as stressing the variability of the disease. "Some people see their parents and think that they will suffer in the same exact way. Explain that, between members of a family, the disease can look very different," he added. In one family, age at onset across 3 generations varied by 50 years. Also within
families, motor, cognitive, and behavioral symptoms can occur in different orders and to different degrees.

Other specialists can help too. Genetic counseling is critical in presymptomatic testing. A speech pathologist can teach caregivers to recognize the distinct limitations in mechanical speech and cognitive processing in HD and provide practical ways for patients to communicate, even past when the patient would otherwise be able to do so, suggested Jeff Searle, MS, of the Department of Hearing and Speech at Kansas State University Medical Center. Caregivers can find creative ways to ease suffering (see accompanying article, "HD and Music").

The Huntington's Disease Society of America has designated 21 Centers of Excellence, where patients and their families can receive multidisciplinary care and support. "The center is a place where HD patients and families can go for one-stop shopping--a neurologist, psychiatrist, psychologist, social worker, speech therapist, physical therapist. A lot of different services in 1 place is valuable because it is difficult to move people with HD around," said Shannon.

The Curious Biology of HD
Shannon calls HD "a triple barrel disease," with its motor, behavioral, and cognitive components. In the 1970s, "disease" replaced "chorea" in recognition of the more subtle nonmotor symptoms. HD often begins gradually, and almost imperceptibly, as fidgeting becomes more frequent and progresses to larger movements. Hands wave, feet tap, in endless, apparently purposeless patterns. As the person loses the sense of the body in space, clumsiness sets in, with frequent bumping into things. The symptoms change as neurons die. At first, a person may drop items as the brain cuts short a grasping movement. Later on, such a movement can't be willfully stopped and a sudden kick may inflict damage. The paradox continues when movement ceases in the final months.

Joe Klein vividly captured the motor decline of HD in his biography, *Woody Guthrie, A Life*. The famed folksinger died in 1967. Wrote Klein, "The little twitches and shakes had become gross, unpredictable lurches of his arms and legs and torso. Despite heavy medication, he was in constant motion. The worst of it seemed to be his right arm, which would fly up and strike his forehead with such force that sometimes, when they hadn't clipped his nails at the hospital, he'd gash himself with his thumb and blood would pour down his face."

Behavioral and emotional changes are highly individual. They may include mood swings, depression, anxiety, antisocial behavior, or aggression or abusiveness. Perhaps the frustration about waning cognitive skills catalyzes the emotional changes. Before and if dementia occurs, the intellect is intact, but mentation is compromised. Multitasking is nearly impossible. Organizing thoughts well enough to initiate or sustain conversations becomes difficult. For example, changing the topic during conversation can provoke utter confusion. Also, short-term memories fade fast.

HD and A COUNTRY DOCTOR
"Horse and buggy doctor" George Sumner Huntington first described the disorder that would take his name in 1872. As a boy in eastern Long Island, George accompanied his father and grandfather, both physicians, as they visited patients, including 2 skinny women who were contorted grotesquely and various men who walked as if drunk.

After moving to Ohio, Huntington presented his thoughts and observations about these patients at a medical meeting, calling the condition "hereditary chorea" and noting the late onset and associated mental disturbance. In stating that the "thread is broken" after a generation thrives without the manifestation of the disease, Huntington displayed an intuitive grasp of autosomal dominant inheritance 3 decades before Mendel's laws were rediscovered.

His report drew attention, and others continued to study the extended families of Huntington's affected patients from Long Island. Eventually, more than 1000 cases over 12 generations were identified, and the hereditary disease was traced back to 2 brothers from Suffolk, England. Studies of other large families would prove crucial to current understanding of HD. In 1979, Columbia University psychologist and Hereditary Disease Foundation president Nancy Wexler, PhD, began yearly treks to the shores of Lake Maracaibo, Venezuela, where HD affected so many members of a 10-generation family of 18,149 that HD-HD marriages occurred. Offspring of these pairings provided the clue that the mutation caused a "gain-of-function" rather than disrupted function, because individuals with 2 copies of the mutant gene were no worse off than those with 1 copy. Plus, the mutant gene was altered, not absent. Wexler regularly exchanged blue jeans and M&M candies for blood samples from members of this family, who grew to love her, and these samples led directly to discovery of a genetic marker. A large family from Iowa added key data.

The marker was a tightly linked single nucleotide polymorphism that within certain families traveled exclusively with the sick individuals. The test required the participation of several family members.
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WHAT'S NEW

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A disease pathology is usually clarified by the discovery of a protein, the absence or aberration of

which underlies the disease, but HD presents a more complicated picture. The HD mutation is an

expanding triplet repeat. At one end of the gene, the DNA sequence CAG repeats fewer than 34 to 37 times in persons without HD and more than 37 to 40 times in those with the disease. Individuals

in the gray area have mild symptoms. In general, the longer the repeat, the earlier the onset, but it

isn't yet possible to predict age at onset based on repeat number.

Normal-length htt binds brain-derived neurotrophic factor (BDNF) by interacting with htt-associated protein (HAP-1) and dynactin, a motor molecule. When BDNF cannot travel along nerve fibers, neurons die. Because embryos of a mouse model of HD die when normal htt is inactivated, the disease develops from lack of the normal protein as well as accumulation of abnormal htt.

The actions of mutant htt, however, are many and complex. It binds a host of other proteins and, in so doing, wreaks havoc on a cell, disrupting transcription factors, impairing endocytosis and axonal transport, and hampering the ubiquitin-proteasome system, thereby clogging the cell with bits of aggregated protein. Levels of neurotrophins fall as glutamate excitotoxicity rises. Mitochondria leak calcium, presaging apoptosis.

Given such a convoluted etiology, with cause and effect blurred in a cascade of malfunction, research often glimpses parts of the big picture. For example, Ilya Bezprozvanny, PhD, associate professor of physiology at the University of Texas Southwestern Medical Center at Dallas, showed, using mouse models of HD, that the toxic gain of function could be binding of mutant htt to InsP3R1 (a receptor for the signaling molecule inositol) and NR2B (a glutamate receptor) on mitochondria.

"The connection between glutamate signaling and calcium overload is specific for HD. I think the expanded htt adapts a conformation that stimulates InsP3R1 and NR2B, leading to calcium overload," he said. His group is studying drugs that affect calcium release from mitochondria, including the anticoagulant enoxaparin (Lovenox, Sanofi Aventis), the antidepressants nortriptyline and desipramine, and the antipsychotic trifluoperazine.

Much effort is directed at another puzzle, the protein aggregates found in the brains of people who inherited the mutant gene but died of other causes before symptoms began. "We don't know if the protein aggregates are pathological or protective. That is a raging debate," said Mark Forman, MD, PhD, assistant professor of pathology and laboratory medicine at the University of Pennsylvania. As for connecting all the mechanistic dots, "Nobody is even close to putting it all together," he added.

The complexity of HD continues macroscopically. Mutant htt is widely synthesized throughout the brain and even in the skin. Yet only some cells die. The "selectively vulnerable" areas are the g-aminobutyric acid-producing medium-sized spiny neurons in the putamen and caudate and cortical pyramidal neurons. Studies with a mouse model that can turn the polyQ part of the mutant gene on or off suggested that this widespread expression is necessary for disease: restricting the damage leads to protein aggregation, but not the motor symptoms or cortical pathology. Full-fledged disease occurred only with global brain expression. The restricted response to global insult reverberates at higher levels. "There are defensive responses, both of cells and systems, so by the time someone gets sick, there have been lots of changes and something just gives," Tobin explained.

Perhaps the best news about HD comes at the population level. Recent research on the Venezuelan families has focused on the shades of gray of the illness--variability in age at onset and course of the symptoms. Statistical analyses reveal that the mutant gene exerts only a partial effect. For people with the longest repeats, the gene accounts for 72% of the variance in the age at onset, but for those with shorter repeats, the gene accounts for 44%. The implication is that other genes or environmental factors influence how many disease-free years a person will have. The same may be true of symptom severity and the pace of pathogenesis. Further evidence for an environmental connection comes from comparing populations. The average ages at onset in Venezuela, the United States, and Canada are 34.35, 37.47, and 40.36 years, respectively.

WHAT'S NEW
Biomarkers A source of intense worry to HD family members is anticipating when and how the disease will start, whether tapping a foot or twisting a lock of hair is the beginning of the end, particularly for people who know they have inherited the mutant gene. Biomarkers are measurements that can detect the first inklings of illness and monitor progression. Biomarkers include following patterns of gene expression and small molecules in plasma, urine, and cerebrospinal fluid; cognitive tests; brain imaging; eye tracking; and motor studies. Several biomarker investigations are under way. Researchers at Harvard Medical School have correlated cortical thinning among patients with presymptomatic HD with cognitive decline and identified a dozen genes whose expression is significantly elevated in HD patients and increases as the disease progresses. Expression of these genes fell after patients took sodium phenylbutyrate for 4 weeks. This drug is an inhibitor of histone deacetylase, the enzyme that enables DNA to be transcribed, a process that mutant htt represses.

Several large-scale investigations are identifying early signs and are tracking the course of the illness. The Prospective Huntington At Risk Observational Study (PHAROS) is tracking first signs among 1001 at-risk individuals, aged 26 to 55 years, at 43 clinical sites. Participants do not know their HD status. The National Institute of Neurological Disorders and Stroke and the National Human Genome Research Institute fund PHAROS. The High Q Foundation supports the Huntington Study Group's Cohort project and the European HD Network's Registry, which will collect clinical data and biological samples from HD patients yearly for longitudinal assessments.

Current Drugs At the San Francisco VA Medical Center, Clinical Assistant Professor of Neurology Stephen Massa, MD, PhD, and his group are looking at the effects of clioquinol on mice and human cells in culture (see also, “Controversial Antibiotic Shows Utility in Treating Huntington Disease, Applied Neurology, November 2005, page 42). This antibiotic is a copper/zinc chelator that has been banned for internal use in the United States since 1971 because its use resulted in subacute myelo-optic neuropathy among thousands of Japanese in the 1960s.

Because lower doses and vitamin B₁₂ supplementation prevent this side effect, and because the drug chelates amyloid b, the researchers decided to try it for HD. Treated mice lived 20% longer, had better motor coordination, lost less weight, and had a 4-fold decrease in protein aggregation compared with controls. Cells in culture stayed alive longer and accumulated less protein. The selective serotonin reuptake inhibitors may smooth mood in HD patients. Paroxetine (Paxil, GlaxoSmithKline) made it to SET-HD's first list of drug candidates after mouse experiments showed delayed symptoms and improved motor skills and survival. Fluoxetine (Prozac, Eli Lilly) demonstrated similar effects in a mouse model.

Coenzyme Q₁₀, part of the electron transport chain in mitochondria, is still in the running after a study that showed a “favorable though not statistically significant trend toward slowing disease progression” at 600 mg/d. Transient decreases in lactic acid in the cortex supported the rationale that the compound improves mitochondrial function. Current investigations are testing higher doses. "Coenzyme Q₁₀ is useful for modifying the course of the illness, as opposed to improving symptoms in the short term," said Kieburtz.

Surveying existing drugs also has led to disappointments. Negative results for riluzole (Rilutek, Sanofi Aventis), which moderates glutamate toxicity and is used to treat ALS, were just announced at the World Congress on Huntington's Disease in Manchester, UK.

New Drugs Top on many lists for most promising drug is tetrabenazine, which has been marketed in Europe for years. The drug binds the type-2 vesicular monoamine transporter and improves chorea. "It has a high likelihood of success, but no one has ever picked it up here because it's a small market," said Kieburtz.

A candidate with mixed success is ultra-pure ethyl-EPA, a semisynthetic derivative of the fatty acid EPA, being developed as Miraxion at Amaran Neuroscience in Stirling, UK. Ethyl-EPA lowers levels of caspases in mitochondria and thus could prevent neuronal apoptosis. It is effective in mitochondrial disorders and seems promising in case reports and pilot studies. However, a phase 3 clinical trial found improved motor skills on one scale but not another, and use of the compound actually worsened behavioral symptoms in a subset of patients.

Perhaps the strangest new approach to treating HD is what its inventors call "choroid plexus sushi." NeurotrophinCell, from Living Cell Technologies in Providence, RI, consists of pig cells wrapped in seaweed, the effects of which have been studied in the striatum of a primate model. The pig cells, from the choroid plexus, secrete a protein "protection cocktail" that the researchers said decreased cell death from 50% to 10%. "We are working in conjunction with Mother Nature," said Chief Scientific Officer Dwaine Emerich, PhD.

A little over half a century ago, Woody Guthrie, who lent a name and voice to HD, began to recognize...
in himself the signs he knew all too well from his mother. Wrote he, "Huntington's chorea means
there's no help in the science of medicine for me, and all you Choreanites like me . . . there is just
not no hope nor not no treatment known to man to cure me."
Guthrie's mother, Nora Belle, had taught Woody and his 4 siblings the songs of their home,
Oklahoma, singing often of dust storms and tornadoes. More recently, a caregiver evoked a telling
comparison of the disease to a tornado: like the storm, HD strikes seemingly at random, felling one
individual but not the next, cutting a swath of twisted destruction through a brain, and through a
family. Although the current state of HD research may seem like a maelstrom of effects and
derangements, perhaps when the pieces are assembled, in place and time within the cell, a way to
halt the pathology triggered by the triplet repeats will emerge. *
REFERENCES
2. Gusella JF, Wexler NS, Conneally PM, et al. A polymorphic DNA marker genetically linked to
3. Wexler NS. The Tiresias complex: Huntington's disease as a paradigm of testing for late-onset
4. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's
5. Gu X, Li C, Wei W, et al. Pathological cell-cell interactions elicited by a neuropathogenic form of
7. Rosas HD, Hevelone ND, Zaleta AK, et al. Regional cortical thinning in preclinical Huntington
and mitigates pathology in a Huntington's disease mouse model. Proc Natl Acad Sci U S A.
11. Huntington Study Group. A randomized, placebo-controlled trial of coenzyme Q10 and


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