

## Milestones in Huntington Disease

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**ABSTRACT:** There have been extraordinary advances in our knowledge of the underlying gene, the protein it encodes, various models of disease, and potential targets for effective therapies for Huntington disease. Huntington disease research has increased exponentially in the past 25 years, and we now understand many of the molecular mechanisms underlying the disease. Still, more work needs to be done before we have a full understanding of the pathophysiology of

the disease. Clinical research on biomarkers and clinical trials on potential neuroprotective agents are underway. Here we review our progress in these areas over the last 25 years and speculate on what the next 25 years may hold. ©2011 *Movement Disorder Society*

**Key Words:** Huntington disease; experimental therapeutics; review

In 1872, George Huntington described the key hereditary and clinical features of the disorder that was to bear his name,<sup>1</sup> in the same era when Gregor Mendel was formulating the fundamental principles of genetics. Many decades passed before the significance of Huntington's insightful clinical description and the brilliance of Mendel's scientific contributions would be widely appreciated. It would be nearly a century until DNA was discovered and clinical and genetic interest in Huntington disease (HD) converged. When the *Movement Disorders* journal was launched 25 years ago, the general terrain of DNA corresponding to HD had just been mapped to chromosome 4<sup>2</sup>—a prelude to 1993, when the single gene responsible for HD was identified, and the mutation was found to consist of an expanded repetition of the cytosine-adenine-guanine (CAG) trinucleotide.<sup>3</sup> In the past 25 years, much has been learned about HD, and accrued knowledge has been applied in anticipation of developing more substantive treatment for this progressively disabling neurodegenerative disease.

### Genetics and Epidemiology

The prevalence of manifest HD in the United States has been approximated to be between 7 and 10 per 100,000 of the population, leading to the estimate of 30,000 manifest individuals.<sup>4</sup> In Europe, the prevalence of HD may be higher, with as many as 45,000 manifest individuals.<sup>5</sup> For every manifest individual, there are about 5 persons immediately at risk for having inherited the HD gene; on average, 2 of these 5 persons will have indeed inherited the HD gene mutation, whereas 3 of these 5 will not. Since 1993, adults at risk for HD have been able to learn of their actual HD gene-carrier status, but fewer than 10% in the United States have actually chosen to be tested. Although there is some evidence that more adults at risk for HD are opting for DNA predictive testing, the vast majority of such individuals prefer to live with uncertainty or perhaps are unaware of their HD risk status.<sup>6</sup>

CAG encodes the amino acid glutamine, which is repeated many times in the huntingtin protein. The gene is large (11 kB), as is the protein (~3300 aa), and it has 67 exons. The triplet repeat is in the first exon. Alleles from 29 to 35 repeats do not cause HD but are potentially unstable during inheritance. Intermediate alleles, from 35 to 39 repeats, have variable penetrance and instability in terms of inheritance.<sup>7–9</sup> There is instability of the gene during gametogenesis, and this can lead to so-called anticipation in the offspring.<sup>10</sup> In this case, the offspring can get the disease

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at an earlier age than their parent. Usually this anticipation occurs with paternal descent.

The extent of the CAG expansion is inversely related to the age of clinical onset among large populations of HD gene carriers, such that very large expansions beyond 60–70 CAG repeats are associated with very early onset in childhood or adolescence. Expansions in the 40–55 range account for nearly 90% of HD carriers, who typically manifest HD in young to midadulthood, well into peak reproductive years. There is great variance in clinical onset among individuals with the same number of CAG expansions, which translates into an abundance of caution in predicting clinical onset for an individual in the most commonly expanded CAG range. Individuals who have inherited 35–39 repeats seem to have reduced penetrance and may not show signs of HD until very late in life, if at all. Data from Venezuela indicate that about 70% of the variability of age of onset is a result of the CAG repeat. Of the remaining 30%, about 40% is due to modifying genes and about 60% to environmental factors.<sup>8</sup>

Although the extent of the CAG expansion has a profound effect on age at clinical onset, expanded CAG repeats also exert a related burden on the course of the illness, especially when adjusted for the age of the individual.<sup>11</sup> Penney et al found in the examination of HD postmortem brains that the extent of CAG expansion was associated with more severe age-adjusted neurodegeneration.<sup>12</sup> Langbehn et al devised a formula based on CAG expansions that may predict whether an HD gene carrier of a given age is “close to” or “far from” onset.<sup>13</sup> The contributions of CAG repeat length and age may prove useful for enriching clinical trial cohorts in preventive trials of premanifest HD carriers, perhaps by enrolling those with greater disease burdens, who have a higher likelihood of more imminent clinical onset. However, these estimates of disease and genetic burdens are more useful in designing experimental studies than in predicting the onset or course of the illness for any individual carrier of the HD mutation.

## Prodromal and Clinical Manifestations

HD is manifested by motor, cognitive, and behavioral characteristics that typically emerge gradually in young adulthood and are diagnosed on average by age 40; however, the range of clinical onset varies from childhood to well into the eighth decade of life. Large observational studies of adults at risk for HD who have chosen not to undergo predictive testing<sup>14</sup> and of clinically unaffected adults who have learned of their HD gene-carrier status<sup>15–17</sup> have portrayed a prodromal period for HD in which motor abnormalities,

including subtle involuntary movements and oculomotor dysfunction, may be present for many years before diagnosis. Evidence of early cognitive abnormalities, especially the ability to shift cognitive sets, may antedate motor abnormalities. Behavioral problems occur in the prodromal period but are abnormal early even in far-from-onset patients and do not progress as overt motor and cognitive abnormalities do.<sup>18</sup>

The prodromal emergence of HD may last a decade or more based on imaging studies conducted longitudinally in premanifest individuals who harbor the HD gene. Striatal atrophy as well as white matter loss as measured by standardized MRI volumetric analysis can be detected at least 15 years prior to predicted onset and progresses steadily during the prodromal premanifest period.<sup>19,20</sup> In addition, cortical thinning develops during the prodromal period in parallel with the emergence of clinical features.<sup>21</sup> A slow but steady unexplained loss of body mass in the face of seemingly normal caloric intake is observed in the prodromal phase, perhaps related to subtle hypothalamic-pituitary dysfunction and the ubiquitous presence of the mutant HD gene in all cells.<sup>22</sup>

Once manifest, the course of HD is slowly but inexorably progressive and is characterized by increasing motor and cognitive dysfunction, resulting in gradual loss of capacities related to occupation, financial management, domestic tasks, and self-care skills. The prototypical individual who has inherited the HD gene develops normally and spends the initial two thirds of life in a relatively healthy condition, often marked by educational achievement, occupational satisfaction, and progeny. The last one third of life is typified by slowly progressive illness over a course of 15–20 years until the patient succumbs to the lethal effects of neurodegeneration and the resulting dysphagia and inanition.

## Pathological Features

The brain in end-stage Huntington disease is about 400 g smaller than the average brain weight of 1300–1400 g.<sup>23,24</sup> This gross atrophy results from profound atrophy of the caudate nucleus and putamen but also severe loss of neurons<sup>25</sup> in the deeper layers of the cerebral cortex. The hippocampus and thalamus are also affected but the cerebellum much less so. The white matter including the corpus callosum is atrophied.<sup>26</sup> The cortical atrophy progresses from the motor/sensory cortex to the occipital, parietal, and limbic cortices.<sup>27</sup> It progresses from unimodal to multimodal cortices in apparent sequence. Atrophy of the basal ganglia, thinning of the cortex, and atrophy of the whole brain all precede the overt onset of clinical symptoms by years.

In the caudate/putamen, the primary neuronal type is the medium spiny neuron, which makes up 90% of

the neurons in the nuclei. These neurons are the output neurons of the striatum, and they form 2 general populations—(1) those with GABA/substance P/dynorphin cells that project to substantia nigra pars reticulata and the medial globus pallidus (the so-called direct motor pathway) and (2) those with GABA/enkephalin that project to the lateral globus pallidus (the so-called indirect motor pathway).<sup>28,29</sup>

In Huntington disease, there is clear selective vulnerability of neurons,<sup>30–33</sup> and thus some neurons survive despite the expression of the huntingtin protein and the development of aggregates. Somatostatin/neuropeptide Y/NADPH diaphorase/NO synthetase interneurons are virtually spared in the disease,<sup>34</sup> and cholinergic interneurons<sup>35</sup> are partially spared, as are other interneuronal populations such as parvalbumin and calretinin neurons. In contrast, the earliest cell loss appears in the GABA/enkephalin neurons projecting to the lateral globus pallidus.<sup>29–32</sup> The loss of these indirect pathway neurons is thought to underlie the development of chorea. Later, the GABA/substance P/dynorphin cells projecting to the direct pathway are affected, leading to motor incoordination and abnormal eye movements. Loss of cortical neurons is likely to lead to cognitive and behavioral problems.

The huntingtin protein is widely expressed in the brain but is much more in neurons than in glia. The expression of huntingtin does not reflect the distribution of selective vulnerability. Interestingly, huntingtin was found to form intranuclear, cytoplasmic, and neuritic inclusions.<sup>36</sup> The intranuclear inclusions were first observed in 1974 but were not pursued.<sup>37</sup> Once huntingtin antibodies became available, aggregates of huntingtin were rediscovered and found to be distributed throughout vulnerable and nonvulnerable regions.<sup>36</sup> Aggregates are mostly ubiquitinated, and their role in the underlying pathogenesis remains controversial.

Recent data from Richard Faull's group in New Zealand correlated the clinical mood disorder with pathology in the anterior cingulate cortex and striosomal compartments of striatum, whereas the motor disorder was more associated with motor cortex pathology and striatal matrix cell loss.<sup>38,39</sup>

## Pathogenesis

The HD gene is necessary for life because knockouts of the gene are lethal during embryogenesis.<sup>40</sup> Knocking out the gene conditionally in adulthood appears to result in neurodegeneration.<sup>41</sup> The protein and gene are expressed ubiquitously, with the brain and testes showing the highest expression. The huntingtin protein is cytoplasmic, and its normal function is still unknown. It appears to be cleaved by proteases and caspases into smaller fragments that can have pathological and perhaps other functions. The cell tries to

manage the fragments by processing them through the proteasome or autophagosome, but the fragments build up nevertheless and cause aggregation in the nucleus, cytoplasm, and neurites.

It is not clear whether the nuclear aggregates themselves cause pathology or whether the fragments or the full-length mutated protein cause pathology prior to aggregation.<sup>42,43</sup> The general consensus is currently that the fragments and oligomers of the fragments may be the culprit.<sup>44</sup>

Mitochondrial dysfunction has long been a hypothesis in HD because of the weight loss and high metabolic demand in the disease. Inhibitors of complex II of the electron transport chain lead to selective striatal cell death that mimics that observed in the postmortem HD brain.<sup>45</sup> More recently, the mitochondrial master gene, *PGC1alpha*, has been found to be abnormally transcribed in HD, thus resulting in mitochondrial dysfunction.<sup>46</sup>

In 1998, evidence for transcriptional dysregulation was shown in exon 1 transgenic animals, and subsequently, gene expression studies in multiple animal models and human postmortem tissue provided concrete evidence for transcriptional dysfunction.<sup>47–49</sup> Mutant huntingtin binds to transcription factors and to DNA itself to alter normal gene transcription directly.<sup>50,51</sup> Alterations in transcription have led to many studies of histone deacetylases that modify transcription. HDAC inhibitors have even been in clinical trials. Other deacetylases including sirtuins have been found to influence huntingtin toxicity and are potential drug targets.<sup>52,53</sup> Recent work has found that 2 lysines in the first 17 amino acids of huntingtin just prior to the glutamine repeat can be phosphorylated, and when they are, the mutant protein is no longer toxic.<sup>54,55</sup> How phosphorylation works mechanistically is still unknown, although targeting of the protein to the proteasome and the lysosome appears to be involved.<sup>55</sup>

## Genetic Testing and Counseling

It is difficult to imagine a more personal, complex, and life-changing decision than the irreversible choice individuals at risk for HD may now opt for to learn their HD gene carrier status. Therefore, skilled yet time-consuming genetic and psychological counseling and abundant clinical sensibilities are essential prior to and following the administration of the predictive or prenatal test.<sup>56,57</sup>

Predictive HD testing typically involves analysis of blood DNA from a clinically unaffected adult at nominal 50:50 risk who has an affected HD parent (or sibling) or from an individual who has suggestive clinical features without a confirmed family history of HD. Although DNA testing is not required for an

individual who has developed clear clinical HD features in the setting of known and relevant family history, adults who have prodromal or equivocal clinical features may choose DNA testing to confirm or disprove the diagnosis.

Direct prenatal DNA testing, involving detection of the actual CAG expansion in fetal cells, is accurate but also reveals the HD gene carrier status of the parent who is at risk to have inherited the HD gene. Alternatively, testing using linkage analysis can exclude the allele of the at-risk grandparent, if DNA is available, whereas the at-risk parent remains nominally at 50% risk and unaware of his or her individual gene status. In both approaches to prenatal testing, the implication is that the pregnancy will be aborted if the fetus is found to be at high risk for HD. Experiences with prenatal testing vary, and prenatal testing is a highly personal decision.<sup>58</sup> In a European study in which 305 individuals underwent prenatal testing between 1993 and 1998, 131 tests (43%) were high risk for HD, and 8 of these pregnancies (6%) continued.<sup>59</sup> There is some controversy about prenatal screening for HD where gene carriers may remain healthy for 30–50 years prior to the onset of illness.<sup>59–61</sup>

For a potential parent who is at risk for or known to carry the HD gene, preimplantation genetic diagnosis (PGD) of HD is an alternative to prenatal testing that may mitigate some ethical dilemmas.<sup>62</sup> This high-technology option involves in vitro fertilization to prompt ovulation and the development of multiple fertilized eggs that are in turn retrieved, fertilized, and screened for the HD gene. Embryos not containing the HD gene are returned to the mother to complete pregnancy.<sup>63,64</sup> This complicated and expensive approach is not without its own ethical dilemmas and societal implications.<sup>65</sup>

Currently, few adults at risk for HD choose to be tested, perhaps fewer than 10% of this group in North America. Even fewer individuals choose prenatal testing.

Surprisingly meager data have been accrued prospectively about the long-term reproductive choices, outcomes, and behaviors of individuals who learn they are at risk for HD and choose whether to learn if they carry the HD gene.

Oster et al analyzed data from the PHAROS project and found less investment in human capital (eg, insurance, education, preventive health surveillance) for those who learned they carried the genetic mutation compared with individuals who did not choose DNA testing, suggesting the importance of certainty and uncertainty in weighing such decisions.<sup>66</sup> Quaid et al used qualitative methods to explore reproductive decision-making in 3 groups of PHAROS research participants: (1) those who knew of their risk and decided to have children, (2) those who had children before they knew of their risk, and (3) those who chose not to have children based on their risk.<sup>67</sup> Among all groups, there was a fine psychological balance between the comforts and discom-

forts of lingering uncertainty, their faith in technology, and perceived prospects for substantive treatments.

## Clinical Care and Treatment

The care of HD patients and their families has improved with increasing recognition of this hereditary disorder, access to genetic counseling, and the availability of specialized care programs that incorporate comprehensive neurological, psychiatric, behavioral, and rehabilitation assessments. Patients and families greatly appreciate and benefit from skilled and accessible care that is knowledgeable, accessible, and respectful of the challenging choices and future they face.<sup>68</sup>

Pharmacotherapeutic interventions remain limited but are being increasingly assessed in an evidence-based fashion.<sup>69–71</sup> Tetrabenazine, which depletes vesicular stores of catecholamines, has been demonstrated to suppress the severity of chorea and is associated with improvement in clinical global impression.<sup>72</sup> Neuroleptic drugs that block postsynaptic dopamine receptors (eg, fluphenazine,<sup>73</sup> haloperidol<sup>74</sup>) may be effective in suppressing chorea, but their long-term use has not been systematically evaluated. There have been few controlled studies of treatments for the cognitive, affective, or behavioral disorders of HD. Antidepressants have not been systematically evaluated in depressed HD patients, but both traditional tricyclic and selective serotonin reuptake inhibitors antidepressants are widely considered to benefit HD.<sup>69</sup> Although cognitive impairment is a major source of disability, there is no persuasive evidence of benefit from medications used to temporarily improve cognition in other dementing disorders.

## Experimental Therapeutics

Twenty-five years ago, there were just a handful of controlled clinical trials in HD and no multicenter trials to examine relevant effects, safety concerns, and generalizability of findings. In 2010, clinicaltrials.gov lists more than 20 active HD trials, including the first PRE-QUEL (NCT00920699) to examine the safety and tolerability of an experimental treatment (coenzyme Q10) in individuals with premanifest HD who are known to carry the mutant gene but have not yet manifested clinical features. This robust increase in the clinical experimental therapeutics of HD has been catalyzed by an increasing understanding of its pathogenesis, the powerful impact of CAG expansions on clinical onset, the identification of “druggable” pharmacological targets, and the welcome participation of research participants in this still-early stage of clinical research.

So-called symptomatic and neuroprotective treatments for neurodegenerative disorders are distinguished by the endurance of treatment effects. Symptomatic therapies improve the signs and symptoms of illness without

necessarily affecting underlying disease progression; therefore, benefits are only temporary in the setting of progressive neurodegeneration. Neuroprotection is aimed at producing enduring benefits by favorably influencing the underlying etiology or pathogenesis.<sup>75</sup> Restorative therapies promote regrowth or repair of areas of neuronal injury or cell loss. Both neuroprotective and restorative treatments exert disease-modifying effects that could be measured by slowing clinical decline in manifest HD or forestalling onset of illness in premanifest HD (“secondary prevention”). In their evidence-based review, Bonelli and Wenning and the Cochrane collaboration also reviewed the outcomes of disease-modifying clinical trials for HD.<sup>69–71</sup> No studies have demonstrated a slowing of clinical progression in manifest HD or evidence of restorative effects.

CARE-HD was a randomized controlled trial in ambulatory HD patients examining coenzyme Q10, an antioxidant and cofactor involved in mitochondrial electron transfer, and remacemide, a noncompetitive NMDA receptor antagonist. Employing a double-blind, placebo-controlled, parallel-group 2 × 2 factorial design, 347 patients with early HD were evaluated for a minimum of 30 months by Huntington Study Group investigators at 23 sites in the United States and Canada. Research participants were randomized to 1 of 4 treatment groups: coenzyme Q10 600 mg daily, remacemide 600 mg daily, the combination of coenzyme Q10 and remacemide, or placebo. Remacemide exerted a modest anticholinergic effect but did not slow functional capacity, the prespecified primary outcome. In contrast, individuals treated with coenzyme Q10 showed about a 13% slowing in functional decline ( $P = .15$ ) as well as a benefit on cognitive measures compared with individuals not receiving coenzyme Q10.<sup>76</sup> Based on studies of coenzyme Q10 showing good tolerability at dosages up to 2400 mg/day,<sup>77</sup> a 5-year placebo-controlled study (2-CARE) of coenzyme Q10 2400 mg/day in early HD is in progress (clinicaltrials.gov registration no. NCT00608881).

Creatine increases cytoplasmic brain phosphocreatine to maintain cellular ATP levels and buffer energy metabolism,<sup>78</sup> and like Coenzyme Q10, exerts antioxidative effects and neuroprotective effects in HD animal models.<sup>79,80</sup> The disease-modifying rationale and dose-ranging and safety studies in HD have prompted the development of a multicenter, placebo-controlled, randomized controlled trial of high-dosage creatine (CREST-E), which is being conducted by the Huntington Study Group and is currently enrolling research participants (clinicaltrials.gov registration no. NCT00712426).

Potential disease-modifying treatments might best be initiated prior to the onset of HD, when pathogenic mechanisms are potentially more reversible.<sup>81</sup> A randomized, controlled study (PREQUEL) has been designed to examine the safety, tolerability, and dosage of coenzyme Q10 in unaffected (premanifest) individuals who, through predictive DNA testing, are known to

carry the HD gene (clinicaltrials.gov registration no. NCT00920699).

Two large, prospective observational studies are well under way to better inform about research methodology and potential biomarkers in premanifest HD. The Prospective Huntington At Risk Observational Study (PHAROS) enrolled 1001 clinically unaffected adults at risk for HD who have chosen not to undergo predictive DNA testing but agreed to be followed in a multiyear, double-blinded longitudinal study to examine the precursors of clinical onset and the specificity of emerging phenotype to CAG repeat length.<sup>14</sup> Neurobiological Predictors of HD (PREDICT-HD) is a similarly large, prospective observational study that largely involves unaffected adults who have chosen to undergo predictive DNA testing and have learned that they have inherited the HD gene. PREDICT-HD research participants have also consented to be followed prospectively and undergo extensive cognitive assessments and standardized magnetic resonance imaging (MRI) in order to assess the predictive value of quantitative clinical assessments and emerging biomarkers relative to the clinical onset of HD.<sup>15</sup> The clinical and biological markers corresponding to clinical onset from PREDICT-HD and other longitudinal studies<sup>20</sup> are providing useful clinical end points for clinical trials aimed at postponing the onset and progressive disability of HD.

More proximal experimental approaches are being focused at transcriptional mechanisms in an effort to inhibit mutant RNA expression or make use of oligonucleotide antisense interventions. Specificity of action on the mutant rather than wild-type mutations and effective delivery to the vulnerable brain targets represent important challenges in realizing the potential of these innovative strategies.

The Huntington Study Group (<http://www.huntington-study-group.org>), through the sponsorship of government, industry, and foundations, as well as the European HD Network (see <http://www.euro-hd.net>) are committed to the development and conduct of randomized clinical trials and observational studies to improve treatment and our understanding of genetic factors that may modify the onset and course of HD. The participation of individuals affected clinically by HD and those unaffected who carry the mutant HD gene are critical to the success of these collaborative efforts.

## The Next 25 Years

Identification of the HD gene, the rapid pace of scientific discovery, and expanding knowledge about the clinical and biological features of manifest and premanifest HD hold great promise for substantive therapeutic advances in the next 25 years. The option to

learn one's gene carrier status, the expanding group of individuals who learn they have premanifest HD, technological advances such as preimplantation genetic diagnosis, and incremental gains in developing disease-modifying therapies carry potential risks as well as benefit. The challenges remain, but now there is a rational and evidence-based pathway forward to lessen the burden and improve the quality of life for patients and families affected by HD.

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