Building on the past, we’re striving to unlock the future of Huntington’s disease

Learn more about the mutant huntingtin (mHTT) protein and its role in disease progression.\textsuperscript{1,2}
Huntington’s disease (HD) is a genetic, neurodegenerative disease characterized by cognitive and motor decline and behavioral symptoms. HD impacts families across generations, with each child of a parent with HD having a 50/50 chance of developing the disease.¹,²

**Triad of HD Symptoms**

**Cognitive**
- Language difficulties, decreased attention, difficulty retrieving information, deficits in learning and memory, emotional recognition problems, lack of awareness, reduced mental flexibility, cognitive slowing, and problems with planning²⁵

**Motor**
- Chorea, bradykinesia, impaired speech, impaired walking, dystonia, akinesia, rigidity, decreased saccades, dysphagia, poor balance/risk of falls, and tics²

**Behavioral**
- Apathy, depression, impaired judgement, irritability, sleep problems, impulsivity, suicidality, aggression, and psychosis²⁵

**Disease Progression**

**HD progression can be described in the following phases:**

**Presymptomatic:**
Patients have the HD gene mutation, but have not yet developed any symptoms²

**Prodromal:**
Patients have neurobiological changes and striatal atrophy. This is usually when behavioral and/or cognitive symptoms may present, but they also may experience subtle motor symptoms as well²

**Manifest HD:**
Patients have unequivocal motor symptoms and are clinically diagnosed with HD²

*This is not a comprehensive list of HD symptoms.*
We’re learning more about the mutation that causes Huntington’s disease

Evidence connects neuronal cell death with downstream effects of a genetic mutation.

Normal gene—Normal huntingtin gene (HTT) produces a protein whose function is unclear but is thought to include nervous system development.

- All humans have the HTT gene
- The HTT gene contains a cytosine-adenosine-guanine (CAG) trinucleotide repeat segment

![Diagram](image)

Mutant gene—One mutant HTT allele can lead to the production of the mHTT protein.

- A mutation in the HTT gene can lead to CAG repeat expansion, resulting in the formation of the toxic mHTT protein.
- Research suggests that the mHTT protein may interfere with a number of cellular processes such as DNA transcription and axonal transport and the symptoms associated with HD.
Production of mHTT protein is toxic and leads to the Huntington’s disease cascade.

The number of CAG trinucleotide repeats is key to pathogenesis.

<table>
<thead>
<tr>
<th>Description of gene</th>
<th>CAG repeat range</th>
<th>Risk of HD</th>
<th>Risk of HD in next generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤26</td>
<td>No HD</td>
<td>No</td>
</tr>
<tr>
<td>High Normal</td>
<td>27-35</td>
<td>No HD</td>
<td>Possible</td>
</tr>
<tr>
<td>Reduced Penetrance</td>
<td>36-39</td>
<td>Possible HD</td>
<td>Yes</td>
</tr>
<tr>
<td>Full Penetrance</td>
<td>≥40</td>
<td>Definite HD</td>
<td>Yes</td>
</tr>
</tbody>
</table>

A blood test can be performed to determine the CAG repeat length.

mHTT protein’s role in disease progression

- The production of toxic mHTT protein levels is what leads to HD.
- Levels of mHTT protein in cerebrospinal fluid have been shown to correlate with disease phase, symptom severity, and markers of neuronal damage.
- Preclinical and animal models provide the support to further research the role of mHTT in humans.
While there are no currently approved treatments that target the underlying cause of HD, there are symptomatic treatments and therapies that can provide relief for your patients. Since HD has such varied symptoms, it is important for you to work closely with the other healthcare professionals on your patients’ care team to create personalized care plans. The multidisciplinary approach may help address your patients’ diverse needs.\textsuperscript{2,7}
Can a deeper understanding of the mHTT protein inform the future of Huntington’s disease?

Partnering with the Huntington’s disease (HD) community, we’re proud to help further the knowledge of HD.

The more we learn about the fundamental cause of Huntington’s disease, the more prepared we are to fight it—for you and for your patients with HD and their families.