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.[1,2]

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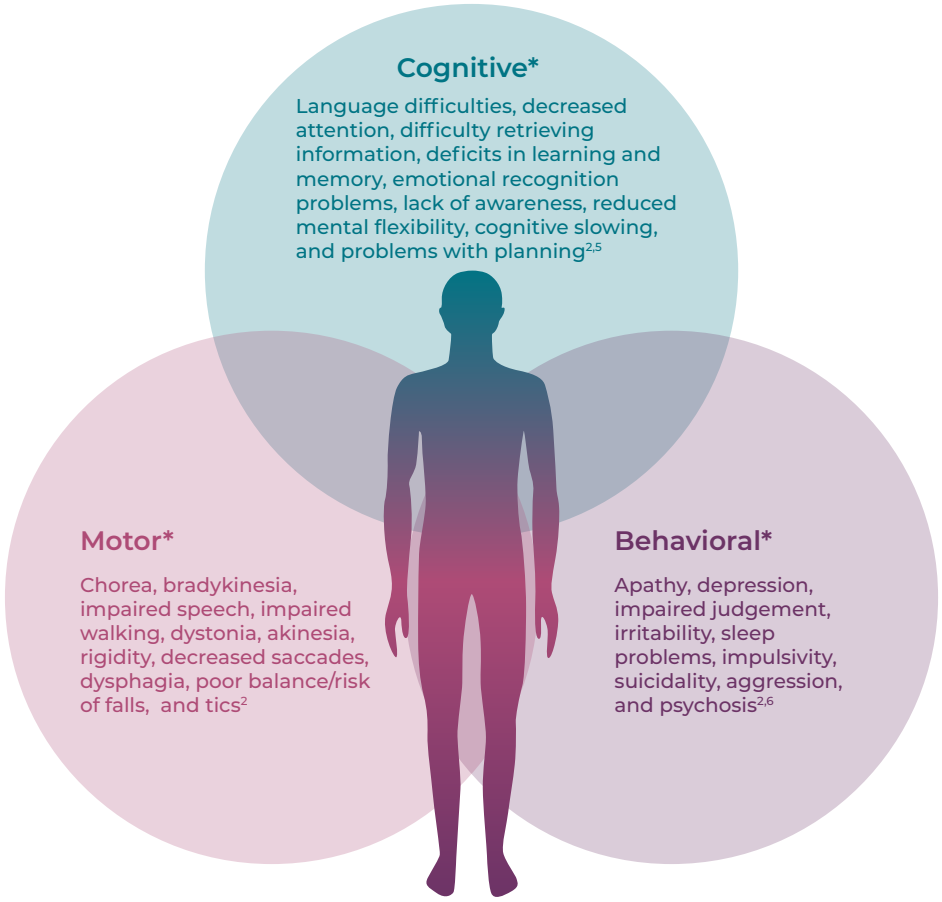
>30,000 people live with Huntington's disease today with many more at risk[3,4]

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



Disease Progression

HD progression can be described in the following phases:

Presymptomatic:

Patients have the HD gene mutation, but have not yet developed any symptoms[2]

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 well[2]

Manifest HD:

Patients have unequivocal motor symptoms and are clinically diagnosed with HD[2]

*This is not a comprehensive list of HD symptoms.

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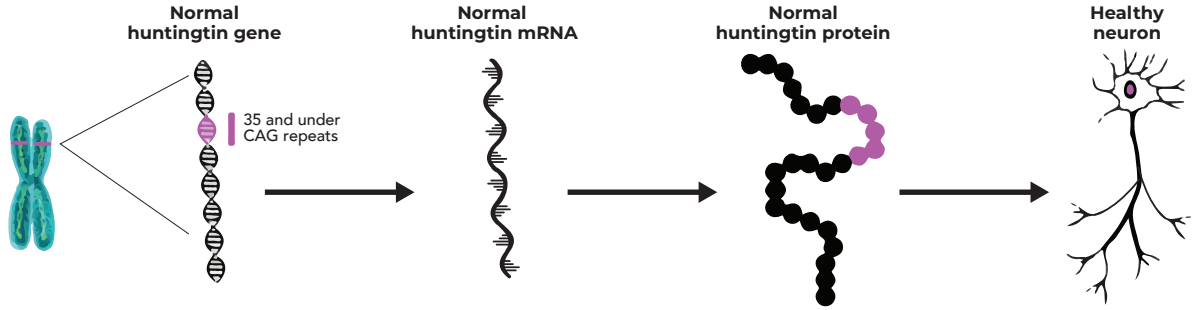
We're learning more about the mutation that causes Huntington's disease

Evidence connects neuronal cell death with downstream effects of a genetic mutation.[2]

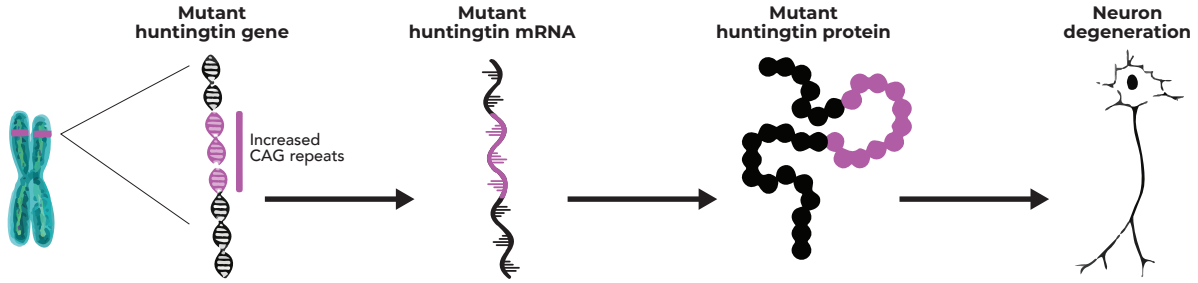
Normal gene—Normal huntingtin gene (*HTT*) produces a protein whose function is unclear but is thought to include nervous system development[7]

- All humans have the *HTT* gene[7]
- The *HTT* gene contains a cytosine-adenosine-guanine (CAG) trinucleotide repeat segment[7]



Mutant gene—One mutant *HTT* allele can lead to the production of the mHTT protein[7]

- A mutation in the *HTT* gene can lead to CAG repeat expansion, resulting in the formation of the toxic mHTT protein[1,2]
- 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[2,8]



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Production of mHTT protein is toxic and leads to the Huntington's disease cascade[2]

The number of CAG trinucleotide repeats is key to pathogenesis.[2]

Description of gene	CAG repeat range	Risk of HD	Risk of HD in next generation
Normal	≤26	No HD	No
High Normal	27-35	No HD	Possible
Reduced Penetrance	36-39	Possible HD	Yes
Full Penetrance	≥40	Definite HD	Yes

A blood test can be performed to determine the CAG repeat length.[2]

mHTT protein's role in disease progression

- The production of toxic mHTT protein levels is what leads to HD[9]
- Levels of mHTT protein in cerebrospinal fluid have been shown to correlate with disease phase, symptom severity, and markers of neuronal damage[9]
- Preclinical and animal models provide the support to further research the role of mHTT in humans[2]

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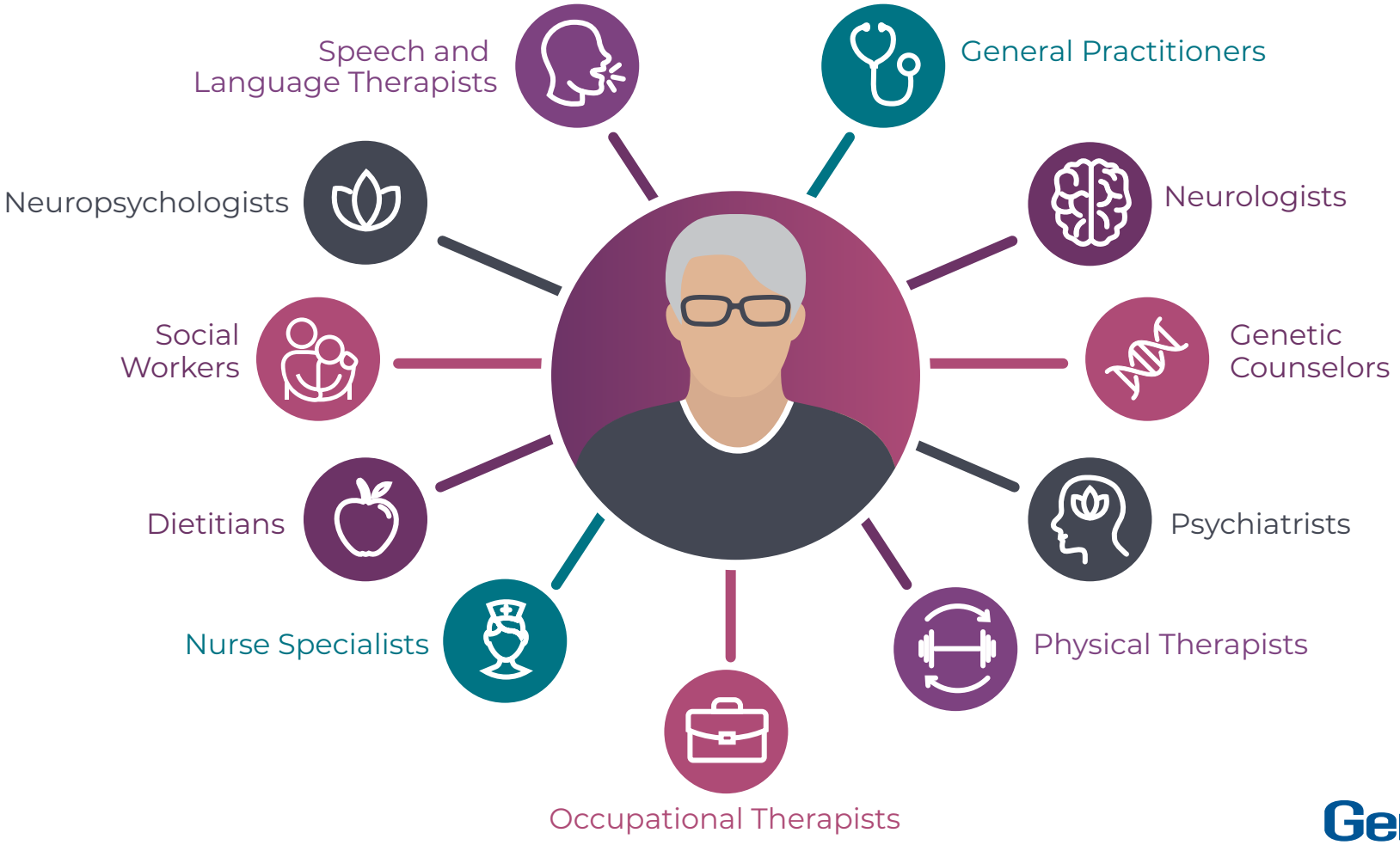
A multidisciplinary approach may help improve disease management[7]

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.[2,7]



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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.

References: 1. Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72:971-983. **2.** Ghosh R, Tabrizi SJ. Huntington disease. In: Geschwind DH, Paulson HL, Klein C, eds. *Handbook of Clinical Neurology*, Vol 147. Elsevier BV; 2018;255-278. https://doi.org/10.1016/B978-0-444-63233-3.00017-8. **3.** National Institute of Neurological Disorders and Stroke, National Institutes of Health. *Huntington's Disease: Hope Through Research*. National Institutes of Health website. https://catalog.ninds.nih.gov/pubstatic//17-NS-19/17-NS-19.pdf. Accessed May 16, 2019. **4.** Fisher ER, Hayden MR. Multisource ascertainment of Huntington disease in Canada: prevalence and population at risk. *Mov Disord*. 2014;29(1):105-114. **5.** Bates GP, Dorsey R, Gusella JF, et al. Huntington disease. *Nat Rev Dis Primers*. 2015;1:15005. **6.** Anderson KE, van Duijn E, Craufurd D, et al. Clinical management of neuropsychiatric symptoms of Huntington disease: expert-based consensus guidelines on agitation, anxiety, apathy, psychosis and sleep disorders. *J Huntingtons Dis*. 2018;7(3):355-366. **7.** Roos RAC. Huntington disease: a clinical review. *Orphanet J Rare Dis*. 2010;5:40. doi:10.1186/1750-1172-5-40. **8.** Frank S. Huntington disease. *Neurotherapeutics*. 2014;11(1):153-160. **9.** Wild EJ, Boggio R, Langbehn D, et al. Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients. *J Clin Invest*. 2015;125(5):1979-1986.

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