CME

On the hunt for a cure: A guide to Huntington disease

Jennifer de la Cruz, MMSc, PA-C; Joseph Hwang, MMSc, PA-C

ABSTRACT

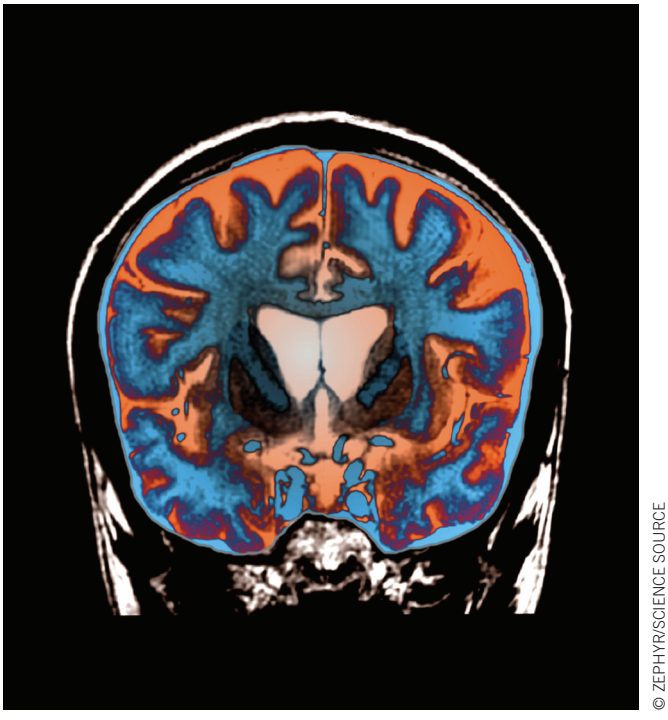
Huntington disease is a rare genetic disorder characterized by motor, cognitive, and psychiatric impairments. Although the typical patient has a positive family history and initially presents with chorea between ages 30 and 50 years, some patients do not have a typical presentation. Healthcare providers should know when to refer patients to neurology for testing for Huntington disease. The earlier the diagnosis is made, the earlier the patient and patient's family can receive education about the expected disease trajectory. A multidisciplinary approach is required to mitigate symptoms as the disease progresses. Although no cure exists, ongoing research is targeting genotypic abnormalities in hopes of finding a permanent treatment for Huntington disease.

Keywords: Huntington disease, genetic, motor disorder, neurodegenerative, huntingtin proteins, chorea

Learning objectives

- Define the pathophysiology, epidemiology, and genetic factors of Huntington disease.
- Describe the initial presentation, progression, and prognosis of Huntington disease.
- Understand the current diagnostic tests available.
- Summarize the treatment options for Huntington disease, including pharmacologic treatment, invasive non-pharmacologic treatment, and non-invasive, non-pharmacologic treatment.
- Describe the future direction of clinical trials and research regarding Huntington disease.

Huntington disease is a rare progressive neurodegenerative genetic disorder with an annual incidence of 0.38 per 100,000 and a worldwide prevalence of 2.71 per 100,000.[1] Huntington disease is 10 times more common in patients of European descent compared with those of pure African or Asian descent.[2] In the United States, the prevalence of Huntington disease, also known as Huntington chorea, is estimated to be 7 per 100,000.[2]



© ZEPHYR/SCIENCE SOURCE

FIGURE 1. Coronal view MRI of the brain of a 21-year-old patient with Huntington disease, showing atrophy of the cortex and caudate nuclei.

The disease is inherited in an autosomal dominant fashion. Earlier symptom onset and increased severity correlate to increased trinucleotide (CAG) repeats on chromosome 4 that result in mutant huntingtin (mHTT) proteins. Although huntingtin proteins are found in numerous tissues throughout the body, the mHTT seems to have the greatest effect on the central nervous system (CNS), particularly the caudate and putamen. Symptom onset typically occurs between ages 30 and 50 years, with a median survival of 15 to 20 years.[3]

The pathophysiology of mHTT protein is not completely understood, but is thought to be toxic to brain cells,

Jennifer de la Cruz is director of clinical education and a clinical assistant professor in the PA program at Mercer University in Atlanta, Ga. **Joseph Hwang** was a student in the PA program at Mercer University when this article was written, and now practices at Urgent Care of Oconee in Watkinsville, Ga. The authors have disclosed no potential conflicts of interest, financial or otherwise.

DOI:10.1097/01.JAA.0000735740.95438.60

Key points

- Huntington disease is an autosomal dominant progressive neurodegenerative disease that typically presents in patients ages 30 to 50 and is associated with significant motor, cognitive, and behavioral dysfunction.
- Clinicians must be aware of atypical presentations, especially with a negative family history, in order to include Huntington disease in the differential diagnosis.
- Early recognition of associated symptoms can prompt timely genetic counseling, diagnostic testing, and a treatment plan.
- Symptomatic management is aimed at addressing motor, cognitive, and behavior dysfunction in order to improve quality of life.
- Ongoing genetic research for a cure includes immunotherapy, targeting transcription factors, and gene silencing.

resulting in motor, cognitive, and psychiatric dysfunction. The most common initial clinical manifestation of Huntington disease is chorea (rhythmic, dance-like involuntary movements), but patients also may present with other motor, psychiatric, or cognitive symptoms (**Table 1**). Huntington disease is associated with progressive systemic dysfunction.

Because Huntington disease is an autosomal dominant genetic disorder, a positive family history is the most prominent risk factor. Children of an affected parent have a 50% chance of inheriting the disease. In addition, as Huntington disease is passed from generation to generation, CAG repeats lengthen, resulting in earlier symptom onset (especially if passed on paternally), a phenomenon called *anticipation* that also occurs in other diseases. Because of the variable penetrance of the mHTT gene, some patients who go on to develop symptomatic Huntington disease may have a completely negative family history, which makes diagnosis more difficult. Furthermore, patients with the same number of CAG repeats have considerable variation in symptom onset and severity.[4] This suggests that environmental factors may contribute to disease progression, and these factors are the targets for symptomatic management.

Two other presentations of Huntington disease exist: juvenile onset and late onset. Juvenile Huntington disease typically occurs in patients under age 20 years and has a worse prognosis, with a median survival of 10 to 15 years after symptom onset.[5] In patients with juvenile Huntington disease, dystonic and parkinsonian symptoms are seen more commonly than chorea. Late-onset Huntington disease occurs in patients over age 60 years, is associated more with cognitive impairment than chorea, and has a slower progression.[3]

This article focuses on the diagnosis, management, and treatment of Huntington disease.

CASE

A 42-year-old woman presented to her primary care provider (PCP) for progressive decline in coordination and abnormal muscle movements over the past few months.

History The patient's past medical history was significant only for major depressive disorder. Her husband, who accompanied her, stated that in the past 2 years, his wife seemed increasingly irritable, and they initially attributed the abnormal hand movements and twitching to stress and restlessness. The symptoms, however, have become more widespread and pronounced over the past year. The patient stated that she has difficulty holding onto objects and doing normal tasks such as writing and biking because of involuntary jerky movements of the hands and legs. She wondered if these could be due to an adverse reaction to the sertraline she has been taking for depression.

Upon further questioning, the husband stated that he also noticed declines in his wife's decision-making and multitasking abilities, which the patient denied. The patient stated that her mother had a movement disorder that began when she turned age 50 years that seemed "rhythmic and dance-like" and affected her ability to walk. In addition, her maternal grandmother was diagnosed with several psychiatric illnesses during her 40s and 50s and died by suicide at age 58 years.

Physical examination The patient was a well-developed, well-nourished woman in no acute distress. Cardiac and pulmonary examinations were unremarkable. A detailed neurologic examination was performed. The patient was alert and oriented to person, time, and place. Cranial nerves I through XII were intact, although the patient had difficulty initiating extraocular movements and tended to move her entire head to follow the clinician's finger. Light touch and pinprick sensations were intact in both the upper and lower extremities. The patient had occasional chorea of the upper extremities and had bilateral upper extremity hypotonia. Range of motion of the shoulder, elbow, wrist, and fingers was normal, but upper extremity strength at these joints was 3/5. The biceps, triceps, brachioradialis, patellar, and ankle reflexes were all 3+ bilaterally.

When asked to perform rapid alternating movements with her hands, the patient's movements were noticeably slow. She had difficulty with the finger-to-nose test because of chorea. During the evaluation for pronator drift, the patient had difficulty keeping both arms extended in front of her for more than 5 seconds. She had difficulty initiating movements with heel-to-shin testing and was unable to sustain the movements. She demonstrated poor balance when asked to walk heel-to-toe.

Physical examination of a patient with Huntington disease may demonstrate motor, neurologic, and cognitive abnormalities, which will vary as the disease course progresses (**Table 1**). Motor dysfunction in these patients is associated with various manifestations of parakinesis, commonly demonstrated as uncoordinated movements

and restlessness that gradually progress to chorea, dystonia, and bradykinesia. Initially, patients may not be aware of declining motor function. An early finding is hypotonia with hyperreflexia. Oculomotor apraxia is a defect in controlled extraocular movements and may present in patients as difficulty with initiating extraocular movements or controlling horizontal movements of the eyes. Motor impersistence (the inability to sustain movements) may be observed along with difficulties with initiating movements. As the disease progresses, patients may develop problems with their speech and swallowing. Additionally, some may lose weight and develop cachexia; the pathophysiology behind this is poorly understood.

Neurologic abnormalities include hyperreflexia, hypotonia, and various mental status changes that manifest as cognitive and psychiatric deficits. The cognitive deficits are gradually progressive and most commonly present with impairment in executive functioning, resulting in difficulties with decision-making, multitasking, and switching from one task to another. Patients also may experience slowed processing and memory recall. Gathering the history from family members or caregivers is especially important in identifying cognitive defects, as patients commonly have a lack of insight about their cognitive decline. Psychiatric symptoms may develop at any time throughout the course of Huntington disease and are unassociated with CAG length or motor symptoms. Patients with Huntington disease are more susceptible to irritability, depression, apathy, anxiety, impaired social relationships, and suicide associated with a progressive decline in their emotional state, coping skills, and behavioral patterns. Patients also may experience delusions, hallucinations, and paranoia.

Diagnostic testing The differential diagnoses for Huntington disease include hereditary disorders such as Wilson disease, Lesch-Nyhan syndrome, and familial amyotrophic lateral sclerosis, as well as autoimmune, metabolic, infectious, and drug-induced causes (**Table 2**).

The initial diagnostic workup should include a comprehensive metabolic panel, thyroid studies, and infectious disease testing. A careful review of the patient's medication list is essential. Testing for pharmacologic and nonpharmacologic toxicities should be conducted based on the patient's history, environment, and clinical suspicion to rule out drug-induced chorea. Perform follow-up testing with bloodwork and neuroimaging to rule out autoimmune conditions.

The case patient's presentation, history, and physical examination findings strongly suggested Huntington disease. After an appropriate initial workup that ruled out common causes of chorea, she was referred to neurology for confirmatory testing and management guidance. If a neurologic consult had not been readily accessible, the patient could have been offered confirmatory genetic testing. Genetic testing in this case is not necessary because there is no cure and the results do not change management, but it may be helpful to define the risk of disease in offspring and aid in family planning decisions.[6] If confirmatory testing is negative, refer to the patient to a movement disorders specialist for further evaluation.

TABLE 1. Symptom progression in patients with Huntington disease

Adapted with permission from Caron NS, Wright GEB, Hayden MR. Huntington disease. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 1993-2021. www.ncbi.nlm.nih.gov/books/NBK1305. Accessed January 12, 2021.

	Early (0-5 years)	Middle (5-10 years)	Late (more than 10 years)
Motor dysfunction	• Abnormal eye movements • Clumsiness • Involuntary movements • Olfactory dysfunction • Sexual trouble	• Chorea • Difficulty initiating movement • Dystonia • General weakness • Slow reaction time • Slow voluntary movements • Speech difficulties • Trouble with balance/walking • Trouble with manual dexterity • Weight loss	• Bradykinesia • Danger of choking • Inability to care for oneself • Inability to speak • Inability to walk • Incontinence • Rigidity • Severe chorea (less common) • Significant weight loss • Swallowing problems
Psychiatric symptoms	• Agitation • Anxiety • Apathy • Depression • Disinhibition • Hallucinations • Irritability • Lack of motivation • Paranoia • Sleep difficulties	• Delusion • Stubbornness	
Cognitive impairment		• Intellectual decline • Memory loss	Dementia

The gold standard for diagnosing Huntington disease is genetic testing for CAG repeats. Diagnostic testing is done in patients presenting with concerning symptoms for Huntington disease; predictive genetic testing is done in asymptomatic at-risk family members. Genetic counseling is recommended before the patient undergoes any genetic testing; because Huntington disease has no cure, its diagnosis could affect the patient's family and future family planning, employment, and health insurance coverage.[7]

Brain imaging studies may be used before or after genetic testing as an adjunct to diagnosis and to monitor disease progression. MRI, although not diagnostic, may detect progressive gray and white matter atrophy before symptom onset, and striatal atrophy can be seen on imaging studies in symptomatic patients. In later stages of Huntington disease, CT and MRI for bicaudate diameter can detect and monitor atrophy of the caudate nucleus.

TREATMENT AND MANAGEMENT

The case patient has signs and symptoms consistent with early- and middle-stage Huntington disease. The PCP's role in clinical management and treatment should focus on improving the patient's quality of life, reducing symptoms, and preparing the family and potential caregivers for the challenges that will develop as the disease progresses.

A multidisciplinary approach to management is ideal, and patients should be offered a variety of resources including psychiatry, social work, nutrition, physical therapy, and occupational therapy. The PCP should coordinate with neurology in establishing the multidisciplinary team. In many communities in the United States, a neurologist is not readily accessible, and the PCP will take over care coordination once the patient has been diagnosed with Huntington disease and initial treatment recommendations are prescribed by neurology. The PCP must begin addressing many topics with the patient once the diagnosis is established.

Occupational and physical therapy help patients remain as independent as possible for as long as possible. Therapists work with patients on improving activities of daily living, including bathing, dressing, eating, and writing. They also work with patients to develop an appropriate exercise regimen, as exercise has been shown to be a safe way to improve cardiovascular health and slow the progression of motor dysfunction.[8] Because fall prevention is important, physical therapy can assist in assessing patients' homes and establishing a safe home environment.

As the symptoms of Huntington disease progress, speech therapy and nutritionists should be involved to address the slurred speech and trouble with swallowing and eating that may develop. The PCP also should coordinate with psychiatry for ongoing mental health evaluation and management. Treatment for psychiatric symptoms in patients with Huntington disease is the same as for patients who do not have the disease. Monitoring for suicidal ideation is essential. Anxiety and depression are managed with cognitive behavioral therapy and pharmacologic agents such as selective serotonin reuptake inhibitors (SSRIs). Antipsychotic medications may be prescribed for paranoia or hallucinations. Sleep difficulties are addressed through appropriate sleep hygiene and pharmacologic agents such as the supplement melatonin or sedating medications. Regular follow-up with psychiatry every 3 to 6 months is appropriate for ongoing monitoring of the patient's symptoms and medication adverse reactions. Social work can assist the patient and family in finding an appropriate residence, applying for disability, finding support groups for the patient and caregivers, and identifying other resources in the community. Advance care planning also should be discussed with the patient's goals of care in mind, because patients often require a long-term care facility in their last few years of life.[9]

TABLE 2. Causes of chorea[13-18]

Past medical history

- Hereditary causes
- Autosomal dominant: familial frontotemporal dementia, familial amyotrophic lateral sclerosis, Huntington disease–like syndromes (HLD 1-4), benign hereditary chorea, spinocerebellar ataxias, neuroferritinopathy
- Autosomal recessive: porphyria, Wilson disease, phenylketonuria, ataxia-telangiectasia, ataxia with oculomotor apraxia
- X-linked: McLeod syndrome, Lesch-Nyhan syndrome

Acquired causes

- Autoimmune or inflammatory: Behcet syndrome, celiac disease, Henoch-Scholein purpura, polyarteritis nodosa, sarcoidosis, Sjogren syndrome, Syndenham chorea (paraneoplastic chorea)
- Metabolic and endocrine disorders: chorea gravidarum, electrolyte abnormalities, chronic acquired hepatocerebral degeneration, nonketotic hyperglycemia, thyroid and parathyroid disorders
- Infectious diseases: AIDS; HIV encephalitis; Lyme disease; meningitis; parasitic, fungal, and prion diseases; toxoplasmosis; tuberculosis
- Toxin exposure: carbon monoxide, cyanide, manganese, mercury, methanol, thallium, toluene
- Drug-induced: anticonvulsants, calcium channel blockers, CNS stimulants, dopamine-blocking agents, dopamine-depleting agents, dopaminergic agents, antihistamines, benzodiazepines, estrogens, oral contraceptives, glucocorticoids, opioids, antibiotics, selective serotonin reuptake inhibitors, sympathomimetics, tricyclic antidepressants
- Other: edentulous dyskinesia, senile chorea, structural lesion in basal ganglia, vascular disease

APPROVED MEDICATIONS

Two medications are FDA-approved for treating chorea associated with Huntington disease: tetrabenazine and deutetrabenazine. These are vesicular monoamine transport 2 (VMAT2) inhibitors that reduce hyperkinetic movements

TABLE 3. Management of Huntington disease[12,19-26]

Pharmacologic
- FDA-approved: tetrabenazine, deutetrabenazine
- Not FDA-approved: neuroleptics, anticonvulsants, antidepressants, antipsychotics

Nonpharmacologic
- Noninvasive: exercise therapy, music therapy, physical therapy, occupational therapy, speech therapy, circadian rhythm regulation
- Invasive: deep brain stimulation

Ongoing research
- Antisense oligonucleotide
- Gene silencing
- PPAR delta agonists
- Immunotherapy

by reducing dopaminergic neurotransmission. Although head-to-head studies have not been developed, current data suggest that although tetrabenazine may be slightly more efficacious, deutetrabenazine seems to have a more favorable adverse reaction profile, fewer drug interactions, and requires less-frequent dosing.[10] Common adverse reactions to VMAT2 inhibitors include somnolence, insomnia, confusion, and akathisia. For patients who do not respond to a VMAT2 inhibitor, consider switching to a neuroleptic medication. If chorea is still severe despite switching, a combination of a VMAT2 inhibitor and a neuroleptic may be helpful.[11]

Ongoing clinical studies are exploring nonpharmacologic approaches to slowing symptom progression in patients with Huntington disease. These studies have investigated various potential therapies, including exercise, music therapy, circadian rhythm regulation, and deep brain stimulation. Furthermore, investigative genetic studies searching for a cure are underway, using a variety of resources including immunotherapy, regulating transcription factors using PPAR delta agonists, gene silencing targeting clustered regularly interspaced short palindromic repeats (CRISPR), and antisense oligonucleotides (**Table 3**).[12] Patients should receive appropriate education on avoiding compounds that contain l-dopa, which may increase chorea.

CONCLUSION

Five years have passed since the case patient was diagnosed. Her symptoms have progressed somewhat, and she now needs a walker for long walks and adaptive utensils for self-feeding. She is followed by a multidisciplinary team that reports all new findings and interventions to her PCP. She started seeing a cognitive behavioral therapist shortly after her diagnosis and reports that this has helped tremendously in accepting her diagnosis. The patient has had many meetings with her PCP and voices clear understanding of the trajectory of her disease. She knows that eventually she may need to be followed by speech therapy to assist her in learning new ways to communicate with her family and to handle possible swallowing problems. Overall, the patient states that she feels much better about her diagnosis and future than she did at the time of her diagnosis. She attributes this to the multidisciplinary team that has worked to optimize her quality of life for now and in the future. Clinicians should include Huntington disease in their differential diagnosis and refer patients to neurology where appropriate, as detection and management early in the disease course can improve quality of life and family planning decisions for the patient and caregivers. **JAAPA**

Earn Category I CME Credit by reading both CME articles in this issue, reviewing the post-test, then taking the online test at http://cme.aapa.org. Successful completion is defined as a cumulative score of at least 70% correct. This material has been reviewed and is approved for 1 hour of clinical Category I (Preapproved) CME credit by the AAPA. The term of approval is for 1 year from the publication date of April 2021.

REFERENCES

1. Pringsheim T, Wiltshire K, Day L, et al. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. *Mov Disord*. 2012;27(9):1083-1091.
2. Bruzelius E, Scarpa J, Zhao Y, et al. Huntington's disease in the United States: variation by demographic and socioeconomic factors. *Mov Disord*. 2019;34(6):858-865.
3. Chaganti SS, McCusker EA, Loy CT. What do we know about late onset Huntington's disease? *J Huntingtons Dis*. 2017;6(2):95-103.
4. Gusella JF, MacDonald ME, Lee J-M. Genetic modifiers of Huntington's disease. *Mov Disord*. 2014;29(11):1359-1365.
5. Wheelock V. Juvenile Huntington's disease. UC Davis Health System. https://health.ucdavis.edu/huntingtons/images/HDSA_2015_JHD.pdf. Accessed January 5, 2021.
6. Losekoot M, van Belzen MJ, Seneca S, et al. European Molecular Genetic Quality Network (EMQN). EMQN/CMGS best practice guidelines for the molecular genetic testing of Huntington disease. *Eur J Hum Genet*. 2013;21(5):480-486.
7. Mayo Foundation for Medical Education and Research. Huntington's disease. www.mayoclinic.org/diseases-conditions/huntingtons-disease/symptoms-causes/syc-20356117. Accessed December 17, 2020.
8. Frese S, Petersen JA, Ligon-Auer M, et al. Exercise effects in Huntington disease. *J Neurol*. 2017;264(1):32-39.
9. Nance M. Management of late stage HD. In: *A Physician's Guide to the Management of Huntington's Disease*. 3rd ed. New York, NY: Huntington's Disease Society of America; 2011:99.
10. Dean M, Sung VW. Review of deutetrabenazine: a novel treatment for chorea associated with Huntington's disease. *Drug Des Devel Ther*. 2018;12:313-319.
11. Bonelli RM, Wenning GK. Pharmacological management of Huntington's disease: an evidence-based review. *Curr Pharm Des*. 2006;12(21):2701-2720.
12. Rodrigues FB, Quinn L, Wild EJ. Huntington's disease clinical trials corner: January 2019. *J Huntingtons Dis*. 2019;8(1):115-125.
13. Barton B, Zauber SE, Goetz CG. Movement disorders caused by medical disease. *Semin Neurol*. 2009;29(2):97-110.
14. Bhidayasiri R, Truong DD. Chorea and related disorders. *Postgrad Med J*. 2004;80(947):527-534.
15. Cardoso F, Seppi K, Mair KJ, et al. Seminar on choreas. *Lancet Neurol*. 2006;5(7):589-602.

16. Gövert F, Schneider SA. Huntington's disease and Huntington's disease-like syndromes: an overview. *Curr Opin Neurol.* 2013;26(4):420-427.
17. Schneider SA, Bird T. Huntington's disease, Huntington's disease look-alikes, and benign hereditary chorea: what's new? *Mov Disord Clin Pract*. 2016;3(4):342-354.
18. Termsarasab P. Chorea. *Continuum (Minneap Minn)*. 2019;25(4):1001-1035.
19. Chandra A, Sharma A, Calingasan NY, et al. Enhanced mitochondrial biogenesis ameliorates disease phenotype in a full-length mouse model of Huntington's disease. *Hum Mol Genet*. 2016;25(11):2269-2282.
20. Dickey AS, Pineda VV, Tsunemi T, et al. PPAR delta repression in Huntington's disease and its essential role in CNS translate into a potent agonist therapy. *Nat Med*. 2016;22(1):37-45.
21. Huntington Study Group; Frank S, Testa CM, Stamler D, et al. Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. *JAMA*. 2016;316(1):40-50.
22. Park H. Cortical axonal secretion of bdnf in the striatum is disrupted in the mutant-huntingtin knock-in mouse model of Huntington's disease. *Exp Neurobiol*. 2018;27(3):217-225.
23. Rosenblatt A. Overview and principles of treatment. In: *A Physician's Guide to the Management of Huntington's Disease*. 3rd ed. New York, NY: Huntington's Disease Society of America; 2011.
24. Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, et al. Targeting huntingtin expression in patients with Huntington's disease. *N Engl J Med*. 2019;380(24):2307-2316.
25. Wild EJ, Tabrizi SJ. Therapies targeting DNA and RNA in Huntington's disease. *Lancet Neurol*. 2017;16(10):837-847.
26. Xu X, Tay Y, Sim B, et al. Reversal of phenotypic abnormalities by CRISPR/Cas9-mediated gene correction in Huntington disease patient-derived induced pluripotent stem cells. *Stem Cell Reports*. 2017;8(3):619-633.