Published in final edited form as:
J Genet Genomics. 2012 June 20; 39(6): 253–259. doi:10.1016/j.jgg.2012.04.006.

Pluripotent Stem Cells Models for Huntington's Disease: Prospects and Challenges

Richard L. Carter[1,2,3] and **Anthony W.S. Chan**[1,2,3,*]

[1]Yerkes National Primate Research Center, 954 Gatewood Rd., N.E. Atlanta, GA 39329

[2]Genetic and Molecular Biology Program, Graduate Division of Biological and Biomedical Sciences, Emory University, Atlanta, GA 30322, USA

[3]Department of Human Genetics, Emory University School of Medicine, 615 Michael St., Atlanta, GA 30322, USA

Abstract

Pluripotent cellular models have shown great promise in the study of a number of neurological disorders. Several advantages of using a stem cell model include the potential for cells to derive disease relevant neuronal cell types, providing a system for researchers to monitor disease progression during neurogenesis, along with serving as a platform for drug discovery. A number of stem cell derived models have been employed to establish *in vitro* research models of Huntington's disease that can be used to investigate cellular pathology and screen for drug and cell-based therapies. Although some progress has been made, there are a number of challenges and limitations that must be overcome before the true potential of this research strategy is achieved. In this article we review current stem cell models that have been reported, as well as discuss the issues that impair these studies. We also highlight the prospective application of Huntington's disease stem cell models in the development of novel therapeutic strategies and advancement of personalized medicine.

Keywords

stem cell models; Huntington's disease; induced pluripotent stem cells; drug discovery

1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder. The disease is caused by an unstable expansion of CAG repeats in the coding region of the Huntingtin gene IT15 (MacDonald et al., 1993). The mutation produces a stretch of glutamine residues spanning the N-terminus of the Huntingtin protein (HTT). HD on estimate affects 7–10 per 100,000 individuals and is most prevalent in population of European origin (Gil and Rego, 2008). In general populations the repeat average is less than 36 units. Individuals with repeats of ≥ 40 units are at risk of developing HD as their lives

Correspondence should be addressed to: Dr. Anthony W.S. Chan, Yerkes National Primate Research Center, Emory University, 954 Gatewood Rd., N.E. Atlanta, Georgia 30329, USA. Tel: 1-404-712-8347, Fax: 1-404-727-5289, awchan@emory.edu.

We have no commercial association that might create a conflict of interest in connection with the submitted manuscript.

progress (Li and Li, 2006; Gil and Rego, 2008). Currently HD is a fatal diagnosis for which there is no cure. Existing treatments are aimed at the alleviation of symptoms, however, therapies that slow or reverse disease progression have yet to be implemented. Studies suggest that the aggregation of mutant HTT fragments is the major cause of toxicity, specifically damaging cortical and striatal medium spiny neurons in HD patients (Davies and Ramsden, 2001; Li and Li, 2006; Gil and Rego, 2008; Imarisio et al., 2008; Ross and Shoulson, 2009; Sassone et al., 2009; Johnson and Davidson, 2010). The mechanisms placing these specific neuron populations at risk is a critical question.

Throughout the literature, a number of strategies have been used to uncover the pathology of HD and other neurological disorders. The hallmark of HD is neurodegeneration, predominantly in the striatum and cortex (Sapp et al., 1997). Nuclear inclusions of HTT in striatal neurons actually precede symptom onset (Laforet et al., 2001). A loss of enkephalinergic neurons in the external segment of the globus pallidus is also typical of presymptomatic HD (Deng et al., 2004). During the symptomatic phase of HD, the external segment of the globus pallidus, the substantia nigra pars reticulata, and the substantia nigra pars compacta are severely degenerated (Deng et al., 2004). GABAergic and parvalbuminergic striatal projection neurons are also severely affected (Hedreen and Folstein, 1995). Initial insight regarding the neuropathology of HD was identified in post-mortem brain tissue from human HD patients (DiFiglia, 1997; Sapp et al., 1997). This method of study is limited in that it represents the end-stages of the disease (Marchetto et al., 2010; Marchetto et al., 2011). Observations made from post-mortem brain tissue have identified key cellular phenotypes associated with HD, however, these may only uncover secondary phenotypes leaving the primary causes unidentified (Marchetto et al., 2010; Marchetto et al., 2011). A number of transgenic animal models have been successfully developed for the study of HD and other neurodegenerative disease (Faber et al., 1999; Gunawardena et al., 2003; von Horsten et al., 2003; Miller, 2005; Yang et al., 2008; Jacobsen et al., 2010; Yang et al., 2010). This has allowed researchers to study the progression of disease longitudinally providing greater insight into causal disease mechanisms. However, in the study of neurological disorders, rodent models are limited by the fundamental differences from humans. Often rodent models do not fully recapitulate human neuronal phenotypes (Chan, 2009; Marchetto et al., 2010; Marchetto et al., 2011).

To overcome the limitations of using post-mortem tissues and rodent models, a number of recent studies have explored the use of embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) as cellular models for disease research and the development of biomedical applications. The ability of pluriotent cellular models to differentiate to neuronal lineages is an attractive feature for the study of neurodegenerative and neurodevelopment diseases including HD (Marchetto et al., 2010; Lunn et al., 2011). Furthermore developments in iPSC strategies are important for the advancement of personal cell therapy as well as the production of *in vitro* models for drug discovery research (Saha and Jaenisch, 2009; Tiscornia et al., 2011). In this review we discuss recent literature describing efforts to derive stem cell based models of HD and challenges that remain in the field. We also review the potential roles that stem cell strategies may play in drug discovery and translational applications.

2. Stem cell derived models of HD

A major area of HD research is directed toward understanding and modeling mechanisms contributing to the degeneration of GABAergic medium spiny neurons observed in patients (Li and Li, 2006; Ma et al., 2012). ESCs and iPSCs can be differentiated to neuronal lineages upon appropriate induction providing a unique opportunity to observe disease related changes as neurons and glia develop. Impressive advances in cellular reprogramming technology have driven the utilization of patient derived iPSCs that mirror the disease causing mutation found in the donor (Park et al., 2008). Human iPSCs with disease traits can be generated directly from human patients, a strategy that has shown promise in modeling a number of neurological diseases including autism spectrum disorders, Parkinson's disease, and amyotrophic lateral sclerosis (Dimos et al., 2008; Johansen et al., 2009; Marchetto et al., 2010).

2.1 Current established stem cell models of HD

In this section we describe the number of mammalian stem cell models for HD established by ESC and iPSC techniques, including primary neural progenitor cells (Table 1). The neuropathologic features of HD have been most extensively modeled *in vivo* in rodents. Using the transgenic R6/2 mice, the generation of 11 mouse HD iPS cell lines originating from fibroblast of R6/2 mice was reported (Mangiarini et al., 1996; Castiglioni et al., 2012). Mouse fibroblasts were reprogrammed using four Yamanaka factors in a single retroviral infection. In the cell lines, transcriptional alteration of genes was involved in cholesterol biosynthesis and lysosome biogenesis. Their cellular models, however, did not show any differences when compared to wild type cells in regards to differentiation and proliferation (Castiglioni et al., 2012). Dong et al. (2011) reported an alternative approach to model HD in a rat *in vitro* model. The authors transfected rat neural progenitor cells with an *HTT* exon-1 transgene with expanded CAG repeats. They observed mutant HTT aggregation and neuronal death paralleling neural development. The observed phenotypes were exacerbated in the cell line carrying a larger CAG repeat number (Dong et al., 2011). Although the R6/2 mouse is a valuable model for uncovering new cellular mechanisms or potential drug candidates for HD, it is also informative to study animal models with a slower phenotype development which parallel the more gradual progression of pathogenesis in humans. Transgenic mice which express the full-length protein of mutant HTT typically exhibit more moderate symptoms of HD, however, with distinguishable neurological impairment compared to wild-type controls (Gray et al., 2008). Indeed, the BACHD mouse expressing the full-length mutant human *HTT* gene exhibit many of the same neurobehavioral deficits as the R6/2 mouse, including decreased rotarod performance, diminished locomotion in open field tests, and increased anxiety (Gray et al., 2008). Accordingly, a recent study compared the behavioral patterns of various HD animal models and concluded that, overall, the BACHD mouse exhibited the most profound phenotype when expressing full-length mutant *HTT* and would be the most amenable for the development of novel treatments (Menalled et al., 2009).

Due to the anatomical and developmental similarities between non-human primates (NHPs) and humans, there is great interest in the development of NHP models for HD. Our group

produced the first transgenic HD rhesus macaques and have since then reported a number of stem cell derived *in vitro* studies (Yang et al., 2008; Chan et al., 2010; Laowtammathron et al., 2010; Snyder et al., 2011). Of the studies published by our group, all of the stem cell derived models showed enhanced expression and aggregation of the mutant HTT proteins as well as the development of nuclear inclusions at the advent of neuronal differentiation (Huang et al., 2008; Chan et al., 2010; Laowtammathron et al., 2010; Snyder et al., 2010; Snyder et al., 2011). Work is also being done to characterize a number of iPSC lines derived from rhesus monkeys currently being monitored in a longitudinal study (unpublished).

Perhaps the most clinically relevant work being done in the field is the establishment of human iPSC lines from patients with HD mutations. By deriving pluripotent cells directly from patients it is possible to capture and investigate gene mutations that directly reflect the disease population. Efforts toward this goal in HD were first described by Verlinsky (2005) followed by Mateizel (2006) using embryos identified in preimplantation diagnosis genetics (PDG). Human ESC lines were established from donated mutant embryos and characterized to show properties of pluripotency, genomic integrity, and presence of expanded CAG repeat size (Mateizel, 2005; Verlinsky et al., 2005; Niclis et al., 2009; Bradley et al., 2011). These lines were made available for research, however, follow-up study has been limited and no disease relevant phenotypes have been reported. The first human iPSC (hiPSC) line was described by Park et al. (2008), however, initial phenotypic characterization was not reported and a slight increase in caspase activity in iPSC derived neurons after the removal of growth factors from the culture medium was only observed in a follow-up study (Park et al., 2008; Zhang et al., 2010). In a more recent study, additional iPSC lines derived from patients with homozygous and heterozygous HTT*HTT* mutations were reported to show increased lysosomal activity when compared to control iPS cells. Similar to previous models, this study failed to recapitulate any other proposed neuronal phenotypes such as elevated apoptosis or the formation of nuclear inclusions.

2.2 Challenges in modeling HD in iPSCs

Great strides have been made in the advancement of iPSC technology, and the ability to generate pluripotent models that are genetically identical to disease patients remains an attractive feature. However, the recapitulation of neuropathologic phenotypes *in vitro* remains a challenge in the field. Due to the late onset and progressive nature of HD, it is unclear whether disease related cellular phenotypes can be robustly demonstrated in a stem cell model. Of the studies that showed a degree of success in mirroring pathologic cellular features, over-expressed mutant HTT fragments or exaggerated CAG repeat numbers are necessary to induce phenotypes (Table 1). It has been argued whether the expression of full length mutant HTT or truncated mutant HTT fragments is more advantageous in modeling HD (Crook and Housman, 2011). The full length HTT models can more closely replicate the genetic cause of the disease in humans, however, models of this sort have shown minimal cellular phenotypes and insignificant reduction in life span (Gusella and MacDonald, 2006; William Yang and Gray, 2011). In contrast, animal and cellular models expressing truncated forms of the mutant gene produce more dramatic phenotypes, but it is debated whether these genetic modifications truly represent the true disease etiology of HD (Crook and Housman, 2011; William Yang and Gray, 2011). Another concern in HD stem cell models is CAG

repeat length instability (Juopperi et al., 2011). Niclis et al. (2009) described the expansion of CAG repeats in a human ESC derived stem cell model for HD. It is not clear the impact of CAG expansion on stem cell model of HD after long term culture and needs to be determined

Challenges also remain in the establishment of methods to efficiently derive disease specific neuron sub-types. A major limitation is the sub optimal yield of mature functional neurons at an adequate level of homogeneity to make high-through put assays feasible (Gerrard et al., 2005; Li et al., 2005; Dhara et al., 2008). To resolve these issues, an increasing number of studies are focused on the establishment of neural stem cells (NSC) and neural progenitor cells (NPC) to serve as an intermediate in cell culture based neurological disease studies (Li et al., 2005; Erceg et al., 2009; Koch et al., 2009; Conti and Cattaneo, 2010; Winner et al., 2011). Additional work has been done to better define a neuronal restricted population of NSC/NPC in order to reduce contamination of unwanted cell types resulting from spontaneous differentiation protocols (Pruszak et al., 2007; Yuan et al., 2011).

It has been hypothesized that exposing disease cells to stress agents that mirror age related factors may enhance the development of cellular phenotypes (Jung et al., 2012). An example is the exposure to oxidative stress or hypoxic conditions (Marchetto et al., 2010). Popular hypotheses suggest HD may develop in a non-autonomous manner, and that pluripotent models should include attention to abnormalities in supporting neuronal cells, such as glial cells, which may play a role in HD pathology (Castiglioni et al., 2012).

3. HD stem cells as a platform for drug discovery

A popular and promising direction in the search for novel therapeutic strategies in neurodegenerative disorders is the use of stem cells and stem cell derived neural precursors as a platform for drug discovery (Grskovic et al., 2011; Inoue and Yamanaka, 2011). Patients with HD have a very few disease modifying treatments available, and the search for novel therapeutics is an active field of research. The inherent property of stem cells to differentiate to neuronal subtypes allows for studies in neurogenesis and differentiation (Johnson and Davidson, 2010; Zuccato et al., 2010). Optimal HD stem cell models should produce robust and reproducible cellular phenotypes that mirror pathological features observed in human patients (Niclis et al., 2009; Saha and Jaenisch, 2009). The establishment of such models will allow researchers to monitor phenotype progression as neurons develop, and may provide a key advantage in evaluating the timing at which therapy is most efficacious (Grskovic et al., 2011). In humanized stem cell models of HD, iPSCs provide a patient specific drug evaluation platform that may serve as a preclinical indicator as to how the unique genetic background of the patients will respond to a candidate therapy.

3.1 Stem cells models for drug screening

The few treatments that are available to the HD patient population are mainly for alleviation of symptoms, suppression of involuntary movements, improving mood, and regulation of appetite and sleep (Ross and Shoulson, 2009; Mestre and Ferreira, 2011; Morse et al., 2011). There has been very little progress in the discovery of treatments that slow disease progression. There is a particular interest in the discovery of small molecule compounds that

inhibit the toxic effects of mutant HTT and reduce neurodegeneration (Fecke et al., 2009; Morse et al., 2011). Stem cell models for HD have the potential as power tools for high-throughput screening of compounds and small molecules that may mediate HD toxicity. Patient derived iPSCs also will provide valuable data on the efficacy and safety of drugs on a non-cancerous, non-immortalized human cell line. This approach depends on the identification and validation of effective targets, followed by phenotypic assays that screen for the reversal of cellular phenotypes observed in cellular based assays (Fecke et al., 2009; Johnson and Davidson, 2010; Morse et al., 2011). Challenges to this approach include the identification of consistent, robust disease markers. This will be a major obstacle to overcome before we see any major progress in this field.

3.2 Stem cell derived neurons serve as a platform to study neurogenesis and nueroprotection

Among the new therapeutic development in HD, promoting neuorogenesis in the adult brain is one of the most popular targets. It is hypothesized that supplementation with growth factors stimulating expansion and differentiation of the adult neural stem cell population may result in the replacement of damaged apoptotic neurons (Wu et al., 2010; Morse et al., 2011). Numerous animal studies have reported the effects of neurotophic factors as a neuroprotective strategy to slow the degeneration of affected neurons in HD (Zuccato and Cattaneo, 2009). Brain derived neurotrophic factor (BDNF) is one such protein that has received much attention across a broad spectrum of neurological disorders (Zuccato and Cattaneo, 2009; Zuccato et al., 2010). HD stem cells can be used for the evaluation of single cell properties that are impacted by supplementation with neuroprotective compounds before efficacy is investigated *in vivo.*

3.3 HD is a good candidate for gene therapy

HD is caused by a single gene repeat expansion (MacDonald et al., 1993). The predictable inheritance and dominant penetrance of the disorder make HD a prime candidate for gene therapy approaches. There has been much progress in the area of using small non-coding RNAs as a therapy to mediate *HTT* gene expression (Bilsen et al., 2008; Johnson and Davidson, 2010; Zhang and Friedlander, 2011). Multiple studies in rodent models report the benefit and tolerance of silencing mutant and normal alleles of *HTT* gene (Harper, 2005; Boudreau et al., 2009; Drouet et al., 2009). McBride et al. (2011) confirm the safety of *HTT* knockdown in rhesus macaque, further validating the non-coding RNAs as a potential therapy in HD (McBride et al., 2011). The majority of current studies are based on animal models, however, HD iPSCs derived from patients may provide a platform to investigate the impact of gene silencing on human cells against patient specific genetic background.

4. Prospect of stem cell based therapy in HD

In recent years, stem cell based transplantation studies have provided new and exciting avenues for the treatment of numerous neurological disorders (Kim et al., 2008). Several studies utilizing genetic and chemical rodent HD models have demonstrated the potential of neural stem transplantation as a therapeutic option (Lee et al., 2009; McBride et al., 2011; Ma et al., 2012). There have also been several cellular transplantation trials with human HD

patients that show mixed results as to the benefit of cellular therapy for HD (Bachoud-Levi et al., 2006; Krystkowiak et al., 2007; Reuter et al., 2008; Cicchetti et al., 2009). Although this therapeutic approach is promising, there are a number of barriers that impede progress in this field. A major concern is the propensity of grafted stem cell to form tumors. To overcome this, researchers are exploring the use of lineage restricted pluripotent populations such as neural stem cells and mesenchymal stem cells (Jung et al., 2012). Exploring these strategies in NHP models of HD will also provide important insight into the efficacy and safety of stem cell therapy, as well as provide pre-clinical models in which novel applications of the research in this field can be explored.

5. Concluding remarks

Advancements in the fields of cellular reprogramming and stem cell technology provide new opportunities for the investigation of neurodegenerative diseases and therapies using stem cell models. Features of pluripotent cellular models allow researchers to observe disease related phenotypes during neurogenesis, as well as establish a starting population from which to derive disease relevant cell types for the identification of pathological phenotypes. Although several stem cell models of HD have been established in multiple species, few models robustly recapitulate HD phenotypes (Table 1). It is clear that modeling late-onset progressive diseases will require further advances. Furthermore, optimization of neuronal differentiation and development of phenotypic assays will increase the utility of HD stem cell models as platforms for the discovery of drug targets and the screening of therapeutic compounds. As advancements are made in stem cell technology and HD mechanisms are uncovered, stem cell models will play a critical role in conjunction with animal models towards breakthroughs in the translational research of HD and personalized medicine.

Acknowledgments

All protocols involving animal care and handling were approved by Emory University's IACUC.

We thank Yerkes National Primate Research Center (YNPRC) veterinarian and animal care staff in providing outstanding services. YNPRC is supported by the National Center for Research Resources P51RR165 and is currently supported by the Office of Research and Infrastructure Program (ORIP)/OD P51OD11132. This study was supported by the grant awarded by the ORIP/NIH (RR018827) and the Atlanta Clinical and Translational Science Institute to AWSC.

References

Bachoud-Levi AC, Gaura V, Brugieres P, Lefaucheur JP, Boisse MF, Maison P, Baudic S, Ribeiro MJ, Bourdet C, Remy P, Cesaro P, Hantraye P, Peschanski M. Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study. Lancet Neurol. 2006; 5:303–309. [PubMed: 16545746]

Bilsen, PHJv; Jaspers, L.; Lombardi, MS.; Odekerken, JCE.; Burright, EN.; Kaemmerer, WF. Identification and Allele-Specific Silencing of the Mutant Huntingtin Allele in Huntington's Disease Patient-Derived Fibroblasts. Hum Gene Ther. 2008; 19:710–718. [PubMed: 18549309]

Boudreau RL, McBride JL, Martins I, Shen S, Xing Y, Carter BJ, Davidson BL. Nonallele-specific silencing of mutant and wild-type Huntingtin demonstrates therapeutic efficacy in Huntington's disease mice. Mol Ther. 2009; 17:1053–1063. [PubMed: 19240687]

Bradley CK, Scott HA, Chami O, Peura TT, Dumevska B, Schmidt U, Stojanov T. Derivation of Huntington's disease-affected human embryonic stem cell lines. Stem Cells Dev. 2011; 20:495–502. [PubMed: 20649476]

Castiglioni V, Onorati M, Rochon C, Cattaneo E. Induced pluripotent stem cell lines from Huntington's disease mice undergo neuronal differentiation while showing alterations in the lysosomal pathway. Neurobiol Dis. 2012; 46:30–40. [PubMed: 22227000]

Chan AW. Transgenic primate research paves the path to a better animal model: are we a step closer to curing inherited human genetic disorders? J Mol Cell Biol. 2009; 1:13–14. [PubMed: 19671628]

Chan AWS, Cheng P-H, Neumann A, Yang J-J. Reprogramming Huntington Monkey Skin Cells into Pluripotent Stem Cells. Cell Reprogram (Formerly "Cloning and Stem Cells"). 2010; 12:509–517.

Cicchetti F, Saporta S, Hauser RA, Parent M, Saint-Pierre M, Sanberg PR, Li XJ, Parker JR, Chu Y, Mufson EJ, Kordower JH, Freeman TB. Neural transplants in patients with Huntington's disease undergo disease-like neuronal degeneration. Proc Natl Acad Sci USA. 2009; 106:12483–12488. [PubMed: 19620721]

Conti L, Cattaneo E. Neural stem cell systems: physiological players or in vitro entities? Nat Rev Neurosci. 2010; 11:176–187. [PubMed: 20107441]

Crook ZR, Housman D. Huntington's Disease: Can Mice Lead the Way to Treatment? Neuron. 2011; 69:423–435. [PubMed: 21315254]

Davies S, Ramsden DB. Huntington's disease. Mol Pathol. 2001; 54:409–413. [PubMed: 11724916]

Deng YP, Albin RL, Penney JB, Young AB, Anderson KD, Reiner A. Differential loss of striatal projection systems in Huntington's disease: a quantitative immunohistochemical study. J Chem Neuroanat. 2004; 27:143–164. [PubMed: 15183201]

Dhara SK, Hasneen K, Machacek DW, Boyd NL, Rao RR, Stice SL. Human neural progenitor cells derived from embryonic stem cells in feeder-free cultures. Differentiation. 2008; 76:454–464. [PubMed: 18177420]

DiFiglia M. Aggregation of Huntingtin in Neuronal Intranuclear Inclusions and Dystrophic Neurites in Brain. Science. 1997; 277:1990–1993. [PubMed: 9302293]

Dimos JT, Rodolfa KT, Niakan KK, Weisenthal LM, Mitsumoto H, Chung W, Croft GF, Saphier G, Leibel R, Goland R, Wichterle H, Henderson CE, Eggan K. Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons. Science. 2008; 321:1218–1221. [PubMed: 18669821]

Dong G, Ferguson JM, Duling AJ, Nicholas RG, Zhang D, Rezvani K, Fang S, Monteiro MJ, Li S, Li XJ, Wang H. Modeling Pathogenesis of Huntington's Disease with Inducible Neuroprogenitor Cells. Cell Mol Neurobiol. 2011; 31:737–747. [PubMed: 21452052]

Drouet V, Perrin V, Hassig R, Dufour N, Auregan G, Alves S, Bonvento G, Brouillet E, Luthi-Carter R, Hantraye P, Déglon N. Sustained effects of nonallele-specific Huntingtin silencing. Annal Neurol. 2009; 65:276–285. [PubMed: 19334076]

Erceg S, Ronaghi M, Stojković M. Human Embryonic Stem Cell Differentiation Toward Regional Specific Neural Precursors. Stem Cells. 2009; 27:78–87. [PubMed: 18845761]

Faber PW, Alter JR, MacDonald ME, Hart AC. Polyglutamine-mediated dysfunction and apoptotic death of a Caenorhabditis elegans sensory neuron. Proc Natl Acad Sci USA. 1999; 96:179–184. [PubMed: 9874792]

Fecke W, Gianfriddo M, Gaviraghi G, Terstappen GC, Heitz F. Small molecule drug discovery for Huntington's Disease. Drug Discov Today. 2009; 14:453–464. [PubMed: 19429504]

Gerrard L, Rodgers L, Cui W. Differentiation of Human Embryonic Stem Cells to Neural Lineages in Adherent Culture by Blocking Bone Morphogenetic Protein Signaling. Stem Cells. 2005; 23:1234–1241. [PubMed: 16002783]

Gil J, Rego MAC. Mechanisms of neurodegeneration in Huntington's disease. Eur J Neurosci. 2008; 27:2803–2820. [PubMed: 18588526]

Gray M, Shirasaki DI, Cepeda C, Andre VM, Wilburn B, Lu XH, Tao J, Yamazaki I, Li SH, Sun YE, Li XJ, Levine MS, Yang XW. Full-length human mutant huntingtin with a stable polyglutamine repeat can elicit progressive and selective neuropathogenesis in BACHD mice. J Neurosci. 2008; 28:6182–6195. [PubMed: 18550760]

Grskovic M, Javaherian A, Strulovici B, Daley GQ. Induced pluripotent stem cells — opportunities for disease modelling and drug discovery. Nat Rev Drug Discov. 2011; 10:915–929. [PubMed: 22076509]

Gunawardena S, Her LS, Brusch RG, Laymon RA, Niesman IR, Gordesky-Gold B, Sintasath L, Bonini NM, Goldstein LS. Disruption of axonal transport by loss of huntingtin or expression of pathogenic polyQ proteins in *Drosophila*. Neuron. 2003; 40:25–40. [PubMed: 14527431]

Gusella JF, MacDonald ME. Huntington's disease: seeing the pathogenic process through a genetic lens. Trends Biochem Sci. 2006; 31:533–540. [PubMed: 16829072]

Harper SQ. From the Cover: RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. Proceedings of the National Academy of Sciences. 2005; 102:5820–5825.

Hedreen JC, Folstein SE. Early loss of neostriatal striosome neurons in Huntington's disease. J Neuropathol Exp Neurol. 1995; 54:105–120. [PubMed: 7815073]

Huang AH-C, Snyder BR, Cheng P-H, Chan AWS. Putative Dental Pulp-Derived Stem/Stromal Cells Promote Proliferation and Differentiation of Endogenous Neural Cells in the Hippocampus of Mice. Stem Cells. 2008; 26:2654–2663. [PubMed: 18687995]

Imarisio S, Carmichael J, Korolchuk V, Chen C-W, Saiki S, Rose C, Krishna G, Davies Janet E, Ttofi E. Underwood Benjamin RRubinsztein David C. Huntington's disease: from pathology and genetics to potential therapies. Biochem J. 2008; 412:191. [PubMed: 18466116]

Inoue H, Yamanaka S. The Use of Induced Pluripotent Stem Cells in Drug Development. Clin Pharmacol Ther. 2011; 89:655–661. [PubMed: 21430656]

Jacobsen JC, Bawden CS, Rudiger SR, McLaughlan CJ, Reid SJ, Waldvogel HJ, MacDonald ME, Gusella JF, Walker SK, Kelly JM, Webb GC, Faull RLM, Rees MI, Snell RG. An ovine transgenic Huntington's disease model. Hum Mol Gent. 2010; 19:1873–1882.

Johansen KK, Wang L, Aasly JO, White LR, Matson WR, Henchcliffe C, Beal MF, Bogdanov M. Metabolomic profiling in LRRK2-related Parkinson's disease. PLoS ONE. 2009; 4:e7551. [PubMed: 19847307]

Johnson CD, Davidson BL. Huntington's disease: progress toward effective disease-modifying treatments and a cure. Hum Mol Genet. 2010; 19:R98–R102. [PubMed: 20421366]

Jung YW, Hysolli E, Kim K-Y, Tanaka Y, Park I-H. Human induced pluripotent stem cells and neurodegenerative disease. Curr Opin Neurol. 2012; 25:125–130. [PubMed: 22357218]

Juopperi TA, Song H, Ming GL. Modeling neurological diseases using patient-derived induced pluripotent stem cells. Future Neurol. 2011; 6:363–373. [PubMed: 21731471]

Kim M, Lee S-T, Chu K, Kim SU. Stem cell-based cell therapy for Huntington disease: A review. Neuropathology. 2008; 28:1–9. [PubMed: 18069970]

Koch P, Opitz T, Steinbeck JA, Ladewig J, Brustle O. A rosette-type, self-renewing human ES cell-derived neural stem cell with potential for in vitro instruction and synaptic integration. Proc Natl Acad Sci USA. 2009; 106:3225–3230. [PubMed: 19218428]

Krystkowiak P, Gaura V, Labalette M, Rialland A, Remy P, Peschanski M, Bachoud-Levi AC. Alloimmunisation to donor antigens and immune rejection following foetal neural grafts to the brain in patients with Huntington's disease. PLoS ONE. 2007; 2:e166. [PubMed: 17245442]

Laforet GA, Sapp E, Chase K, McIntyre C, Boyce FM, Campbell M, Cadigan BA, Warzecki L, Tagle DA, Reddy PH, Cepeda C, Calvert CR, Jokel ES, Klapstein GJ, Ariano MA, Levine MS, DiFiglia M, Aronin N. Changes in cortical and striatal neurons predict behavioral and electrophysiological abnormalities in a transgenic murine model of Huntington's disease. J Neurosci. 2001; 21:9112–9123. [PubMed: 11717344]

Laowtammathron C, Cheng ECH, Cheng P-H, Snyder BR, Yang S-H, Johnson Z, Lorthongpanich C, Kuo H-C, Parnpai R, Chan AWS. Monkey hybrid stem cells develop cellular features of Huntington's disease. BMC Cell Biol. 2010; 11:12. [PubMed: 20132560]

Lee ST, Chu K, Jung KH, Im WS, Park JE, Lim HC, Won CH, Shin SH, Lee SK, Kim M, Roh JK. Slowed progression in models of Huntington disease by adipose stem cell transplantation. Ann Neurol. 2009; 66:671–681. [PubMed: 19938161]

Li S, Li XJ. Multiple pathways contribute to the pathogenesis of Huntington disease. Mol Neurodegener. 2006; 1:19. [PubMed: 17173700]

Li T, Zheng J, Xie Y, Wang S, Zhang X, Li J, Jin L, Ma Y, Wolf DP, Zhou Q, Ji W. Transplantable neural progenitor populations derived from rhesus monkey embryonic stem cells. Stem Cells. 2005; 23:1295–1303. [PubMed: 16051986]

Lunn JS, Sakowski SA, Hur J, Feldman EL. Stem cell technology for neurodegenerative diseases. Ann Neurol. 2011; 70:353–361. [PubMed: 21905078]

Ma L, Hu B, Liu Y, Vermilyea SC, Liu H, Gao L, Sun Y, Zhang X, Zhang SC. Human Embryonic Stem Cell-Derived GABA Neurons Correct Locomotion Deficits in Quinolinic Acid-Lesioned Mice. Cell Stem Cell. 2012

MacDonald ME, Ambrose CM, Duyao MP, Myers RH, Lin C, Srinidhi L, Barnes G, Taylor SA, James M, Groot N, MacFarlane H, Jenkins B, Anderson MA, Wexler NS, Gusella JF, Bates GP, Baxendale S, Hummerich H, Kirby S, North M, Youngman S, Mott R, Zehetner G, Sedlacek Z, Poustka A, Frischauf A-M, Lehrach H, Buckler AJ, Church D, Doucette-Stamm L, O'Donovan MC, Riba-Ramirez L, Shah M, Stanton VP, Strobel SA, Draths KM, Wales JL, Dervan P, Housman DE, Altherr M, Shiang R, Thompson L, Fielder T, Wasmuth JJ, Tagle D, Valdes J, Elmer L, Allard M, Castilla L, Swaroop M, Blanchard K, Collins FS, Snell R, Holloway T, Gillespie K, Datson N, Shaw D, Harper PS. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993; 72:971–983. [PubMed: 8458085]

Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, Lawton M, Trottier Y, Lehrach H, Davies SW, Bates GP. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell. 1996; 87:493–506. [PubMed: 8898202]

Marchetto MC, Brennand KJ, Boyer LF, Gage FH. Induced pluripotent stem cells (iPSCs) and neurological disease modeling: progress and promises. Hum Mol Gen. 2011; 20:R109–R115. [PubMed: 21828073]

Marchetto MCN, Carromeu C, Acab A, Yu D, Yeo GW, Mu Y, Chen G, Gage FH, Muotri AR. A Model for Neural Development and Treatment of Rett Syndrome Using Human Induced Pluripotent Stem Cells. Cell. 2010; 143:527–539. [PubMed: 21074045]

Marchetto MCN, Winner B, Gage FH. Pluripotent stem cells in neurodegenerative and neurodevelopmental diseases. Hum Mol Gen. 2010; 19:R71–R76. [PubMed: 20418487]

Mateizel I. Derivation of human embryonic stem cell lines from embryos obtained after IVF and after PGD for monogenic disorders. Hum Reprod. 2005; 21:503–511. [PubMed: 16284066]

McBride JL, Pitzer MR, Boudreau RL, Dufour B, Hobbs T, Ojeda SR, Davidson BL. Preclinical Safety of RNAi-Mediated HTT Suppression in the Rhesus Macaque as a Potential Therapy for Huntington's Disease. Mol Thera. 2011; 19:2152–2162.

Menalled L, El-Khodor BF, Patry M, Suarez-Farinas M, Orenstein SJ, Zahasky B, Leahy C, Wheeler V, Yang XW, MacDonald M, Morton AJ, Bates G, Leeds J, Park L, Howland D, Signer E, Tobin A, Brunner D. Systematic behavioral evaluation of Huntington's disease transgenic and knock-in mouse models. Neurobiol Dis. 2009; 35:319–336. [PubMed: 19464370]

Mestre TA, Ferreira JJ. An evidence-based approach in the treatment of Huntington's disease. Parkinsonism Relat Disord. 2011 Epub 2011/12/20.

Miller VM. CHIP suppresses polyglutamine aggregation and toxicity *in vitro* and *in vivo*. J Neurosci. 2005; 25:9152–9161. [PubMed: 16207874]

Morse, RJ.; Leeds, JM.; Macdonald, D.; Park, L.; Toledo-Sherman, L.; Pacifici, R. Pharmaceutical Development for Huntington's Disease. In: Lo; Hughes, editors. Neurobiology of Huntington's disease: Appliations to drug discovery. CRC Press; Boca Raton (FL): 2011.

Niclis JC, Trounson AO, Dottori M, Ellisdon AM, Bottomley SP, Verlinsky Y, Cram DS. Human embryonic stem cell models of Huntington disease. Reprod Biomed Online. 2009; 19:106–113. [PubMed: 19573298]

Park I-H, Arora N, Huo H, Maherali N, Ahfeldt T, Shimamura A, Lensch MW, Cowan C, Hochedlinger K, Daley GQ. Disease-Specific Induced Pluripotent Stem Cells. Cell. 2008; 134:877–886. [PubMed: 18691744]

Pruszak J, Sonntag KC, Aung MH, Sanchez-Pernaute R, Isacson O. Markers and methods for cell sorting of human embryonic stem cell-derived neural cell populations. Stem Cells. 2007; 25:2257–2268. [PubMed: 17588935]

Reuter I, Tai YF, Pavese N, Chaudhuri KR, Mason S, Polkey CE, Clough C, Brooks DJ, Barker RA, Piccini P. Long-term clinical and positron emission tomography outcome of fetal striatal

transplantation in Huntington's disease. J Neurol Neurosurg Psychiatry. 2008; 79:948–951. [PubMed: 18356253]

Ross CA, Shoulson I. Huntington disease: pathogenesis, biomarkers, and approaches to experimental therapeutics. Parkinsonism Relat Disord. 2009; 15(Suppl 3):S135–138. [PubMed: 20082975]

Saha K, Jaenisch R. Technical Challenges in Using Human Induced Pluripotent Stem Cells to Model Disease. Cell Stem Cell. 2009; 5:584–595. [PubMed: 19951687]

Sapp E, Schwarz C, Chase K, Bhide PG, Young AB, Penney J, Vonsattel JP, Aronin N, DiFiglia M. Huntingtin localization in brains of normal and Huntington's disease patients. Ann Neurol. 1997; 42:604–612. [PubMed: 9382472]

Sassone J, Colciago C, Cislaghi G, Silani V, Ciammola A. Huntington's disease: The current state of research with peripheral tissues. Exp Neurol. 2009; 219:385–397. [PubMed: 19460373]

Snyder BR, Cheng P-H, Yang J, Yang S-H, Huang AHC, Chan AWS. Characterization of dental pulp stem/stromal cells of Huntington monkey tooth germs. BMC Cell Biol. 2011; 12:39. [PubMed: 21910887]

Snyder BR, Chiu AM, Prockop DJ, Chan AW. Human multipotent stromal cells (MSCs) increase neurogenesis and decrease atrophy of the striatum in a transgenic mouse model for Huntington's disease. PLoS ONE. 2010; 5:e9347. [PubMed: 20179764]

Tiscornia G, Vivas EL, Belmonte JCI. Diseases in a dish: modeling human genetic disorders using induced pluripotent cells. Nat Med. 2011:1570–1576. [PubMed: 22146428]

Verlinsky Y, Strelchenko N, Kukharenko V, Rechitsky S, Verlinsky O, Galat V, Kuliev A. Human embryonic stem cell lines with genetic disorders. Reprod Biomed Online. 2005; 10:105–110. [PubMed: 15705304]

von Horsten S, Schmitt I, Nguyen HP, Holzmann C, Schmidt T, Walther T, Bader M, Pabst R, Kobbe P, Krotova J, Stiller D, Kask A, Vaarmann A, Rathke-Hartlieb S, Schulz JB, Grasshoff U, Bauer I, Vieira-Saecker AM, Paul M, Jones L, Lindenberg KS, Landwehrmeyer B, Bauer A, Li XJ, Riess O. Transgenic rat model of Huntington's disease. Hum Mol Genet. 2003; 12:617–624. [PubMed: 12620967]

William Yang X, Gray M. Mouse Models for Validating Preclinical Candidates for Huntington's Disease. 2011

Winner B, Kohl Z, Gage FH. Neurodegenerative disease and adult neurogenesis. Eur J Neurosci. 2011; 33:1139–1151. [PubMed: 21395858]

Wu C-L, Hwang C-S, Chen S-D, Yin J-H, Yang D-I. Neuroprotective mechanisms of brain-derived neurotrophic factor against 3-nitropropionic acid toxicity: therapeutic implications for Huntington's disease. Ann NY Acad Sci. 2010; 1201:8–12. [PubMed: 20649532]

Yang D, Wang CE, Zhao B, Li W, Ouyang Z, Liu Z, Yang H, Fan P, O'Neill A, Gu W, Yi H, Li S, Lai L, Li XJ. Expression of Huntington's disease protein results in apoptotic neurons in the brains of cloned transgenic pigs. Hum Mol Gent. 2010; 19:3983–3994.

Yang S-H, Cheng P-H, Banta H, Piotrowska-Nitsche K, Yang J-J, Cheng ECH, Snyder B, Larkin K, Liu J, Orkin J, Fang Z-H, Smith Y, Bachevalier J, Zola SM, Li S-H, Li X-J, Chan AWS. Towards a transgenic model of Huntington's disease in a non-human primate. Nature. 2008; 453:921–924. [PubMed: 18488016]

Yuan SH, Martin J, Elia J, Flippin J, Paramban RI, Hefferan MP, Vidal JG, Mu Y, Killian RL, Israel MA, Emre N, Marsala S, Marsala M, Gage FH, Goldstein LS, Carson CT. Cell-surface marker signatures for the isolation of neural stem cells, glia and neurons derived from human pluripotent stem cells. PLoS ONE. 2011; 6:e17540. [PubMed: 21407814]

Zhang N, An MC, Montoro D, Ellerby LM. Characterization of Human Huntington's Disease Cell Model from Induced Pluripotent Stem Cells. PLoS Curr. 2010; 2:RRN1193. [PubMed: 21037797]

Zhang Y, Friedlander RM. Using non-coding small RNAs to develop therapies for Huntington's disease. Gene Ther. 2011; 18:1139–1149. [PubMed: 22158031]

Zuccato C, Cattaneo E. Brain-derived neurotrophic factor in neurodegenerative diseases. Nat Rev Neurol. 2009; 5:311–322. [PubMed: 19498435]

Zuccato C, Valenza M, Cattaneo E. Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiol Rev. 2010; 90:905–981. [PubMed: 20664076]

Table 1

Stem cell derived models of Huntington's disease

Mammalian species	Stem cell class	Source	Promoter	*HTT* Mutation	Phenotype observed	Reference
Human	ESC	Embryos	Human *HTT*	Human *HTT*; 44 CAG repeats	None reported	Mateizel et al. (2005)
Human	ESC	Embryos	Human *HTT*	Not reported	None reported	Verlinsky et al. (2005)
Human	iPSC	HD patient fibroblast	Human *HTT*	Human *HTT*; 72 CAG repeats	Elevated caspase activity	Park et al. (2008) Zhang et al. (2010)
Human	ESC	Embryos	Human *HTT*	Human *HTT*; 37,51 CAG repeats	Expansion of CAG repeat	Niclis et al. (2009)
Human	ESC	Embryos	Human *HTT*	Human *HTT*; 40–48 CAG repeats	None reported	Bradley et al. (2011)
Rhesus macaque	ESC	Embryos	Human polyubiquitin	Human *HTT* exon-1 fragment; 72 CAG repeats	Oligomeric mutant HTT aggregation; formation of nuclear inclusions	Laowtammathron et al. (2010)
Rhesus macaque	iPSC	HD monkey fibroblast	Human polyubiquitin	Human *HTT* exon-1 fragment; 72 CAG repeats	Oligomeric mutant HTT aggregation; formation of nuclear inclusions	Chan et al. (2010)
Rhesus macaque	DPSC	HD monkey teeth buds	Human polyubiquitin	Human *HTT* exon-1 fragment; various CAG repeats	Oligomeric mutant HTT aggregation; formation of nuclear inclusions	Snyder et al. (2011)
Mouse	iPSC	R6/2 mouse fibroblast	Human *HTT*	Human *HTT* 5′ fragment; 144 CAG repeats	Transcriptional alteration in lysosome biogenesis and cholesterol biosynthesis	Castiglioni et al. (2012)
Rat	NPC	Transfected with mutant HTT exon-1	Cytomegalovirus immediate early promoter	EGFP-HTT-74Q fusion protein	Mutant HTT aggregation, increased cell death, neuritic degeneration	Dong et al. (2011)

ESC, embryonic stem cell; iPSC, induced pluripotent stem cell; NPC, neural progenitor cell; DPSC, dental pulp stem/stromal cell