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Modeling the genomic instability of Huntington's Disease with iPSC technology

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Summary

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric decline. The hallmark of HD pathophysiology is the selective loss of neurons in the striatum.

HD is caused by the expansion of a CAG trinucleotide repeat in the *HTT* gene, leading to the production of mutant huntingtin (mHTT), a protein with toxic gain-of-function properties. CAG repeat length influences disease onset and progression, with longer repeats linked to more severe phenotypes. The region is somatically unstable and expands over time, making the detection and monitoring of CAG expansion critical for understanding disease variability and evaluating new therapies.

There are currently no FDA-approved therapies that halt or reverse HD progression. Therapeutic development has focused on symptomatic management, however recent advances in genetic targeting and small-molecule discovery offer potential for disease-modifying interventions.

Drug discovery researchers utilize both animal (*in vivo*) and cell culture (*in vitro*) models to study HD. *In vivo* models primarily help evaluate therapeutic efficacy and systemic effects, while *in vitro* models enable human-specific investigations such as customized disease models and identification of potential therapeutics that may alter disease progression.

Human induced pluripotent stem cell (iPSC)-derived models are showing promise as a scalable and physiologically relevant platform for HD research. Importantly, these models retain the donor's genetic background, CAG repeat mutations and can be differentiated into relevant cell populations including striatal neurons.

Axol Bioscience has developed iPSC lines from five HD patients and one asymptomatic carrier. One of these, the CENSOi019-B line (*HTT*: 14/125 CAG, now CAG143) contains an atypical allele that displays instability in culture and is associated with accelerated disease onset. Striatal neurons derived from this iPSC line provide a model for longitudinal studies of repeat expansion and neurodegeneration.

To replicate HD pathology *in vitro*, morphological and functional endpoints such as trinucleotide instability, neurite outgrowth and spontaneous firing can be assessed. These assays provide functional insights into HD progression and support evaluation of therapeutic candidates.

Here, we outline the development and characterization of iPSC-derived striatal neurons and their application in the modeling of Huntington's Disease *in vitro*.

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Huntington's Disease therapeutic landscape

Huntington's disease (HD) is a progressive neurodegenerative disorder that leads to neuron loss in the striatum, resulting in cognitive, behavioral, and motor function decline. Motor signs, such as involuntary movements (chorea), rigidity, dystonia, and impaired voluntary movement, typically worsen over time. Cognitive decline is marked by executive dysfunction, memory loss, and slowed processing. In addition, psychiatric features, including depression, irritability, anxiety, and psychosis, are common and often emerge early in the disease course [1].

The symptoms of HD frequently start when people are in their 30s or 40s, but they can develop at any time.

Once diagnosed, HD patient life expectancy is usually 15–20 years, with disease progression varying widely.

The variation in age of onset and clinical presentations of HD suggests distinct clinical profiles within the disease, but the association between symptoms and different profiles is poorly understood.

HD is a complex disease, and several features remain unexplained, for example, the cell-type-specific pathology, long pre-symptomatic latency, and mechanisms by which inherited alleles lead to neurodegeneration.

Despite extensive research, no single cellular or molecular pathway has emerged as a definitive target for therapy. Current symptomatic treatments primarily address motor symptoms: Tetrabenazine and deutetrabenazine reduce chorea by modulating dopamine signaling but do not affect progression .

Additionally, antidepressants, antipsychotics, and mood stabilizers target psychiatric manifestations but also lack neuroprotective effects [2].

However, as of mid-2025, several innovative treatments are advancing through clinical trials and regulatory review.

- The Cure Huntington's Disease Initiative (CHDI) and companies like uniQure, Roche, Wave Life Sciences, and PTC Therapeutics are advancing promising therapies. They aim to "rapidly develop therapeutics that slow the progression of HD" [3].

- uniQure's AMT-130 gene therapy is a promising candidate, demonstrating around 75% slowing of disease progression in phase 1/2 trials with sustained improvement in motor, cognitive, and functional outcomes after three years, marking the first potential disease-modifying therapy, giving hope to patients and researchers working to find a widely available cure[4] . It is delivered via one-time neurosurgery directly to the striatum.

- Vutoplam from PTC Therapeutics, tominersen from Roche, and WVE-003 from Wave Life Sciences are investigational platforms focusing on lowering mutant huntingtin expression mostly in early clinical phases and trials.

Several HD therapies are in development. Each approach reflects a different strategy, for example gene silencing, selective targeting, or repair pathway modulation.

The genetics of Huntington's Disease: an unstable CAG repeat

HD is an autosomal dominant disease. The HD mutation is a triplet repeat (CAG)n of variable length in exon 1 of the huntingtin protein (*HTT*) gene. This CAG region translates into an expanded polyglutamine stretch near the N-terminus of the HTT protein. The mutant HTT (mHTT) protein affects multiple cellular processes including mitochondrial dynamics, transcription regulation, and protein aggregation. mHTT protein aggregates lead to neuronal degeneration, but the mechanisms by which this occurs are not yet fully understood.

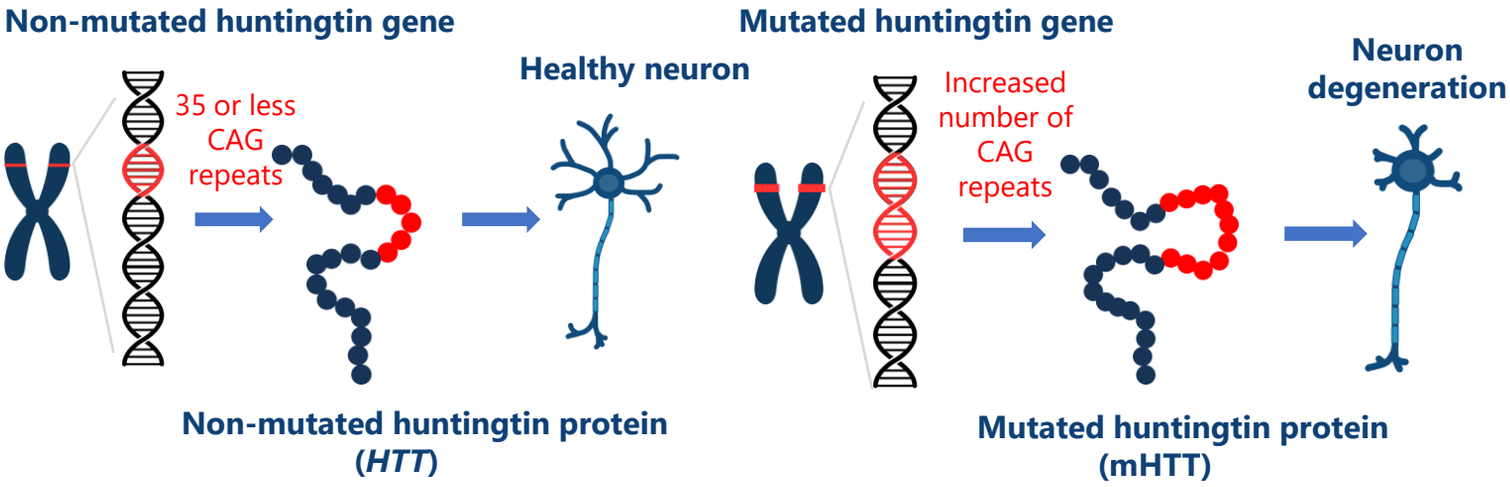


Figure 1. Increased numbers of CAG repeats in the *HTT* gene lead to mutated huntingtin protein and neuron degeneration.

Most people inherit alleles with 15–30 consecutive CAGs, but HD patients inherit an allele with 36 or more consecutive CAGs.

In 2019, Kaum et al observed that the rate at which HD manifestations emerge is determined by length-dependent somatic expansion of the CAG repeat in critical target cells[5].

The timing of HD onset is influenced by polymorphic loci in several DNA repair genes, suggesting that length instability of the CAG repeat leads to somatic expansion[6]. Understanding this expansion is crucial for diagnosing and managing HD, as well as for the development of potential treatments and therapies aimed at halting the expansion of CAG repeats.

Handsaker et al. (2025)[7] highlighted a critical tipping point beyond 150 CAG repeats, where neuronal identity collapses and cells die. Their work suggested that HD pathogenesis is fundamentally a DNA-driven process, with neurons maintaining normal function throughout most of their lives as somatic expansion advances. This presents a wide therapeutic window, where even a modest slowing of expansion could substantially slow progression.

Other studies have investigated the mechanisms behind the expansion of the CAG repeat, for example Goold et al., (2019)[8] showed that increased FAN1 expression is significantly associated with delayed age of onset (AAO) and slower progression of HD. Their work suggests that FAN1 is protective in the context of an expanded *HTT* CAG repeat. In a 2025 GWAS study[9], somatic expansion of the CAG repeat is driven by a mismatch repair-related process and that non-DNA repair genes also differentially influence cognitive and motor dysfunction. This study also demonstrated that a synonymous CAG-adjacent variant in *HTT* dramatically hastens motor onset without increasing somatic expansion, while a cis-acting 5′-untranslated region variant promotes blood repeat expansion without influencing clinical HD.

Alongside inherited HD, sporadic or *de novo* mutations contribute at least 5–8% of genetically proven HD cases [10].

Challenges in developing treatments for HD

Therapeutic development in HD faces several challenges:

- The wild-type HTT protein is essential for cellular function, making selective targeting of the mutant form difficult. Most current therapies focus on symptom relief rather than modifying disease progression.
- HD progresses slowly and varies between individuals, complicating clinical trial design and timing, particularly as neuronal loss may begin long before symptoms appear.
- Reliable biomarkers for tracking progression and treatment response are lacking.
- Effective CNS delivery remains a hurdle, as large molecules like gene therapies and oligonucleotides struggle to cross the blood-brain barrier (BBB).

Nonetheless, therapies aimed at lowering levels of mHTT using anti-sense oligonucleotides (ASOs), microRNAs, RNA interference (RNAi) or small molecule splicing inhibitors are looking promising [12].

Other trinucleotide repeat (TNR) diseases such as Friedreich's ataxia are caused by expanded genomic TNRs that become unstable in a length-dependent manner. A recent study by Mutasek et al. (2025) demonstrated that introducing interruptions in pathogenic TNRs can mitigate a key neurological feature of TNR diseases *in vivo*[13].

The translation of research findings from existing HD models to human clinical trials has not been successful and there is an urgent need for models that mimic human HD pathology and better recapitulate the complexity of the disease, especially in terms of disease progression, to understand the underlying mechanisms and develop more effective treatments.

Modeling HD in the laboratory

The HD research community is focused on two main approaches to halt disease progression: reducing the expression of the mHTT protein and reducing the somatic instability of the CAG repeat region.

In vivo models, including mouse, rat, pig and primate systems, provide whole-organism complexity and physiological relevance. However, they are often constrained by species differences, ethical considerations, and limited scalability. *In vitro* models, include immortalized cell lines, primary cells, and human iPSCs offer controlled environments for mechanistic studies, genetic manipulation, and high-throughput screening.

In vivo models

In vivo (animal) models for cognitive decline and behavioral changes, for example motor deficits such as chorea-like movements, tremors, or gait abnormalities can be used to investigate interactions between the nervous system and other organs. Models often show progressive symptoms and shortened lifespans, useful for assessing disease severity and treatment efficacy.

- **Rodent models:** genetically-engineered (transgenic or knock-in), however these do not fully replicate human HD [14] as rodent models lack the extensive striatal neuron loss seen in humans.
- **Large animal models:** For example, pig or non-human primate models are often used for gene therapy development and biomarker identification. These models can exhibit complexity and similarity to human disease progression however they need genetic manipulation to introduce CAG expansion [15].

Modeling Huntington's Disease in the laboratory

- **Transgenic:** include R6/2 (N-terminal fragment) and BACHD/YAC128 (full-length *HTT*), each with distinct phenotypic profiles.
- **Knock-in:** HdhQ111 and Q150 replicate human mutations in the mouse *HTT* gene.
- **Non-genetic:** toxin-induced (e.g., quinolinic acid) mimic striatal damage but lack genetic relevance.

In vitro models

In vitro models of HD using animal or human cells provide scalability for high-throughput screening and customizable disease modeling such as investigation of different CAG repeat lengths or cell types.

- **Primary cells and tissues:** while primary cells offer unmatched physiological relevance, limited availability, scalability, and challenges with maintaining them for longitudinal studies, have led to a shift away from using them as HD models. Human primary striatal tissue is difficult to source, and its use is regulated. Unless genetically modified, primary cells lack the mutant *HTT* gene.

- **Immortalized cell lines:** immortalized cell lines offer a platform for HD research, particularly in early-stage drug discovery and mechanistic studies. They can display a stable phenotype across passages and are easy to genetically modify. However, immortalization can introduce mutations or alter cellular responses, and immortalized cells may lack neuron-specific features.

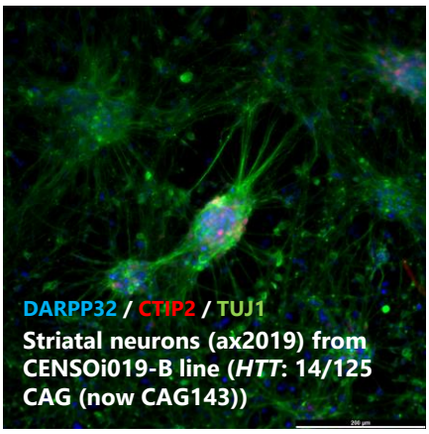
- **iPSC-derived models:** a major advance in the study of HD has been the development of human disease models using iPSCs-derived from patients with HD [16]. Human iPSCs are generated through the process of reprogramming primary blood or fibroblast materials obtained from consenting patients. The iPSC can subsequently be differentiated and matured into functional endpoint cells, including striatal neurons.

In 2008, Park et al. created the first human iPSCs from HD patient fibroblasts. They used retroviral induction to introduce the four key pluripotency factors, cMyc, Klf4, Oct4, and Sox2, into the cells. These groundbreaking iPSCs carried huntingtin gene mutations with 54 and 72 CAG repeats [17].

In 2010, Zhang et al reported the creation and characterization of an *in vitro* cell model of HD using iPSCs derived from patient fibroblasts[17]. The iPSCs were then differentiated into neural cell types, which demonstrated disease-associated cellular and functional abnormalities including changes in electrophysiology and cellular behavior, providing a platform for studying pathogenesis and developing new therapeutic strategies.

Since then, several HD lines have been created by groups including the Cure for Huntington's Disease Initiative (CHDI), European Bank for induced Pluripotent Stem Cell, HD iPSC Consortium and NINDS Human Cell and Data Repository. The attraction of iPSC-derived models is the direct genetic connection to the donor. The ability to produce functional cells at scale for use in a range of cellular assays has led to broad adoption of iPSC-derived medium spiny neurons or striatal neurons across academic, biotech and pharma research groups, with over 5000 citations related to the use of iPSCs in HD research to date.

iPSC-derived *in vitro* models are suitable for small scale studies or large-scale screens, for high-content imaging and functional phenotypic screening. Utilizing cells from multiple donors should enable the study of patient-specific or CAG-length specific responses, paving the way for new treatments for HD and personalized therapeutic approaches.



Axol Bioscience HD iPSC collection

Patient-derived iPSC lines allow the development of physiologically relevant cellular models with clear disease phenotypes for target identification and drug screening. iPSC lines derived from patient cells contain the CAG repeat disease mutations and the genetic background which contributes to disease onset and severity. Therefore, these lines can be used for models that enable the screening of potential genetic modifiers that are part of the "genetic background" that may impact disease onset, progression, and symptoms. Genetic modifiers themselves are also molecular targets for drug discovery.

Axol Bioscience has created five iPSC lines from materials donated from HD patients and one from an asymptomatic carrier. Each line undergoes rigorous quality control such as assessments of morphology, karyotype, pluripotency, sterility and CAG repeat sizing.

Cell line name	Disease	Disease Status	Sex	Age	Gene	Confirmed Genetic Mutation
CENSOi019-B	Huntington's Disease	Affected	F	7	*HTT*	CAG14/CAG127
CENSOi019-A	Huntington's Disease	Affected	F	7	*HTT*	CAG14/CAG127
CENSOi052-A	Huntington's disease	Affected	M	16	*HTT*	CAG28/CAG66
CENSOi017-A	Huntington's Disease	Affected	F	51	*HTT*	CAG17/CAG42
CENSOi011-D	Huntington's Disease	Affected	F	40-50	*HTT*	CAG18/CAG39
CENSOi053-A	Huntington's disease	Asymptomatic Carrier	M	64	*HTT*	CAG17/CAG38

Increasing CAG repeats

Table 1. Axol Bioscience lines for HD drug discovery and research. Note: the donor of CENSOi53-A is the parent of the donor of CENSOi052-A.

Axol human iPSC lines derived from both asymptomatic and HD patients (Table 1) are differentiated into HD-relevant brain cell types, including striatal neurons, astrocytes, and microglia. These models enable the study of neuronal and neuroinflammatory processes play a role in HD pathogenesis.

Striatal neurons, astrocytes and microglial cells can be combined *in vitro* to develop complex physiologically relevant co-culture models to better understand and replicate disease phenotypes *in vitro*, and study brain regional differences in the disease process, as well as the cell-cell dependencies involved in HD-associated neurodegeneration.

The CENSOi019-B line demonstrates CAG repeat instability

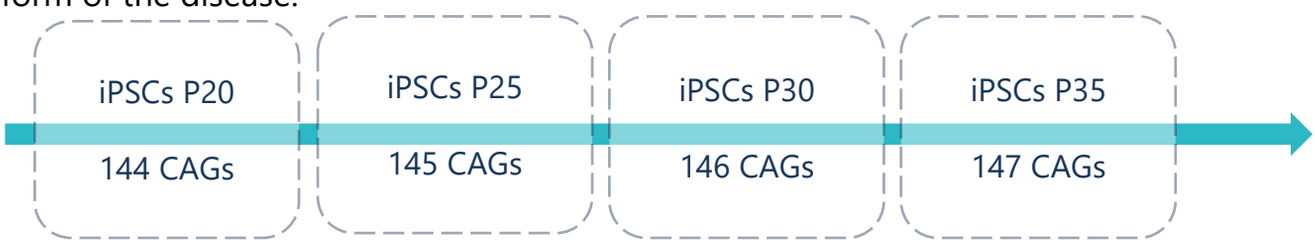
The donor for the CENSOi019-B line was a 7-year-old female patient with severe, early onset HD. Genotypic analysis showed a CAG14/CAG125 genotype.

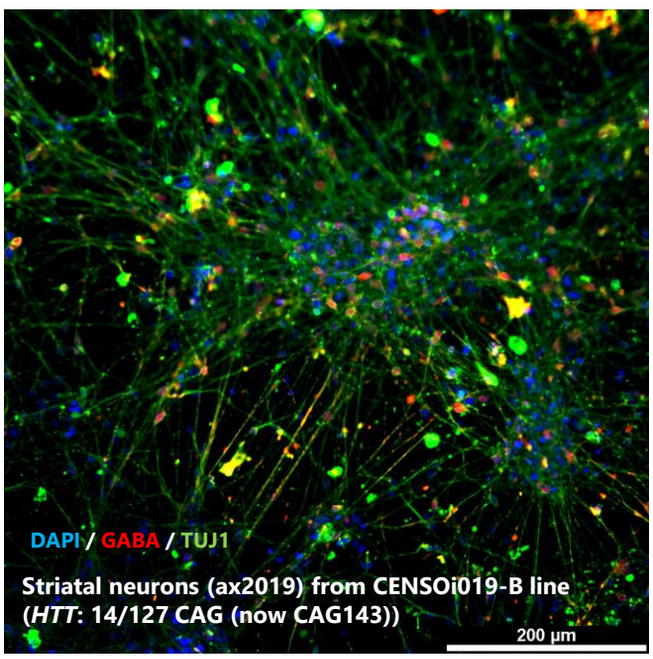
Further study suggested that this line has an atypical allele associated with hastened onset and progression of the disease.

The line proved to have instability in CAG repeat length with the number of repeats growing over time. After reprogramming and generation of the master bank, the number of CAG repeats was 144.

CENSOi019-B iPSC	CENSOi019-B iPSC-derived striatal neurons
expand at 0.5X CAG/week	expand at 0.13X CAG/week

CAG expansion analysis during 15 passages showed an increase of 1 x CAG repeat every 5 passages. Whole Genome Sequencing (WGS) data from this iPSC line suggests the loss of the CAA interruption and presence of certain SNPs/INDELS in the mutant *HTT* allele that can be disease modifiers, driving somatic instability, age of onset and HD progression. Striatal neurons derived from this iPSC line exhibit CAG repeat instability, a hallmark of HD. This instability is critical for studying disease progression, as CAG repeat expansion contributes to neuronal dysfunction and degeneration. To better replicate HD pathology *in vitro*, iPSC-derived cells are used to assess morphology as well as functional endpoints such as trinucleotide instability, neurite outgrowth and spontaneous firing. Other endpoints can be explored, such as mitochondrial function and protein aggregation. As a result of these characteristics, the CENSOi019-B line and striatal neurons derived from this line have become a vital resource to the HD research community. The study of repeat expansion dynamics provides an *in vitro* model for early-onset HD, which is often more severe and less understood than the adult-onset form of the disease.





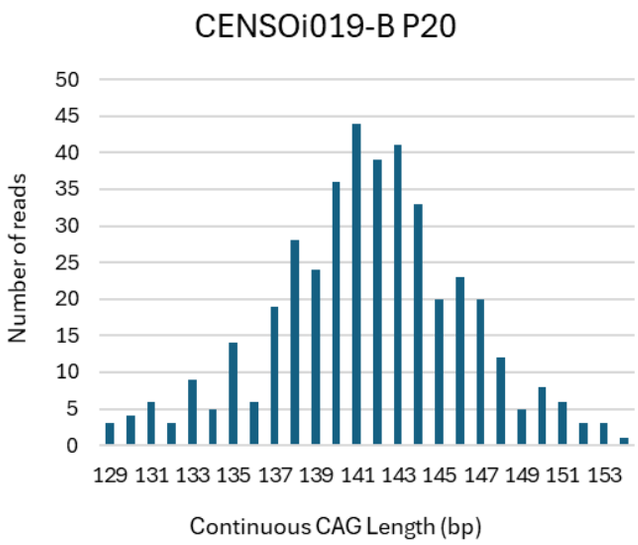


Figure 3. CAG repeat size was assessed at each passage using fragment analysis. iPSCs expand 1x CAG repeat every 5 passages ~0.4 CAG/week

Importantly, to HD research, the CAG repeat number is unstable in both the iPSC and the derived striatal neurons, offering the opportunity to conduct 'instability' studies over time.

While the CENSOiO19 -B iPSCs line expands on average 1X CAG repeat every 5 passages (0.5X CAG/week) the expansion in differentiated striatal neurons is slower rate with an average CAG repeat expansion of 0.13 × CAG/week.

To accelerate this process, researchers have investigated the modulation of FANCI-associated nuclease 1 (FAN1) expression level within these iPSC-derived striatal neurons. In the clinical setting, FAN1 is associated with delayed age at onset (AAO) and slower progression of HD, suggesting that FAN1 is protective in the context of an expanded *HTT* CAG repeat[19].

In preliminary studies, we have oberved ~80% knock-down of FAN1 at day 20 and conducted long range studies that resulted in accelerated expansion.

Emerging trends and future directions for HD modeling

Combining transcriptomics, proteomics, and metabolomics with iPSC-derived cell models are key for patient stratification and tracking treatment efficacy in clinical trials. The next generation of HD research and drug discovery will likely rely on multi-lineage, patient-specific, and functionally validated models that enable more predictive science and lower the risk of clinical failure.

Recent developments in microfluidic and organoid-on-chip technologies using iPSCs are providing insights into intercellular communication in HD and allowing real-time monitoring of cellular interactions and disease progression.

Striatal neurons and co-culture systems, for example, with astrocytes and microglia will help researchers better mimic the complex cellular environment of the human brain.

The use of CRISPR gene editing to generate isogenic controls and allelic series (for example, 40, 50, 70 CAG repeats) will help researchers isolate the effects of the mutation from other variables, defining disease thresholds and validating drug targets.

To support this, at Axol, we are producing control cell lines with a non-pathogenic CAG repeat allele with same genetic background as the pathogenic parent line. These studies use CRISPR Cas9 technology (under license) to edit the CENSOiO19-B iPSC line to reduce the number of CAG repeats to <36. Isogenic pairs of cell lines that carry different CAG repeat lengths can be then be differentiated into neuronal cell types including striatal neurons, astrocytes and microglia. These isogenic lines can be used to avoid differences in genetic backgrounds when comparing different lines.

Conclusion

Techniques integrating *in vitro* and *in vivo* models are improving our understanding of how HD develops and progresses. iPSC models will be central to de-risking clinical trials, accelerating discovery, and ultimately bringing effective therapies to patients. iPSCs reprogrammed from HD patients, especially those with different CAG repeat lengths, will enable more personalized disease models, capturing clinical heterogeneity to support targeted therapeutic development.

The CENSOi019-B line is a crucial tool to study the repeat instability and expansion dynamics of the CAG repeat and can be used to provide an *in vitro* model for early-onset HD, offering essential insights into disease mechanisms for therapeutic development, drug screening, and the discovery of HD biomarkers.

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Glossary

Abbreviation / Term	Definition
HD	Huntington's Disease – a fatal, autosomal dominant neurodegenerative disorder characterized by motor, cognitive, and psychiatric decline.
HTT	Huntingtin gene – the gene where CAG repeat expansion causes HD.
mHTT	Mutant huntingtin protein – the toxic protein produced due to expanded CAG repeats in the *HTT* gene.
CAG	Cytosine-Adenine-Guanine – a trinucleotide repeat in the *HTT* gene; its expansion is the genetic cause of HD.
iPSC	Induced Pluripotent Stem Cell – stem cells reprogrammed from adult cells, used to model diseases like HD.
ASO	Antisense Oligonucleotide – a therapeutic molecule designed to reduce mHTT levels.
RNAi	RNA Interference – a biological process used to silence gene expression, including mHTT.
FAN1	FANCI-associated nuclease 1 – a DNA repair enzyme associated with delayed HD onset and reduced CAG expansion.
AAO	Age at Onset – the age when HD symptoms first appear.
GWAS	Genome-Wide Association Study – a study type used to identify genetic modifiers in HD.
WGS	Whole Genome Sequencing – a method used to analyze the full DNA sequence of iPSC lines.
BBB	Blood-Brain Barrier – a selective barrier that limits drug delivery to the brain.
TNR	Trinucleotide Repeat – a type of genetic mutation involving repeated sequences like CAG.
CHDI	Cure Huntington's Disease Initiative – a research organization focused on HD therapeutics.
NHP	Non-Human Primate – used in large animal models for HD research.
CRISPR/Cas9	A gene-editing technology used to modify CAG repeat lengths in iPSC lines.
TUJ1	Neuronal Class III β-Tubulin – a marker used to identify neurons in cell cultures.
DARPP32	Dopamine- and cAMP-regulated neuronal phosphoprotein – a marker for striatal neurons.
CTIP2	COUP-TF Interacting Protein 2 – a transcription factor used as a neuronal marker.
DAPI	4′,6-diamidino-2-phenylindole – a fluorescent stain that binds to DNA, used in imaging.
GABA	Gamma-Aminobutyric Acid – a neurotransmitter used to identify inhibitory neurons.

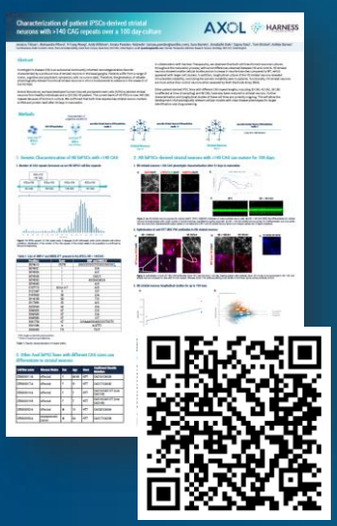
Axol Bioscience

Axol Bioscience is a leading provider of human induced pluripotent stem cell (iPSC) technologies, specializing in the manufacture of high-performance iPSC-derived cells and the delivery of industry-leading laboratory services. With over a decade of expertise, Axol partners with global pharmaceutical companies, contract research organizations (CROs), biotechnology firms, start-ups, and academic institutions to advance the use of iPSC-based models in drug discovery and disease research.

The company operates across five key areas, neuroscience - including ALS, Alzheimer's, Huntington's, Parkinson's - neuroinflammation, pain & sensation, ophthalmology dermatology and cardiovascular.

Axol offers scalable solutions including iPSC banking, reprogramming, gene editing, cell manufacturing, and quality control. The company is committed to closing the translational gap and developing physiologically relevant *in vitro* systems that improve consistency and relevance in human disease modeling and compound testing.

Axol is recognized for its scientific excellence, transparent collaboration and rigorous quality standards. Manufacturing operations are ISO 9001:2015 certified.



POSTER:
Characterization of patient iPSCs-derived striatal neurons with >140 CAG repeats over a 100 day-culture

Further reading

HD mouse models Rodent Models of Huntington's Disease: An Overview.

HD large animal models Large animal models for Huntington's disease research - PMC.

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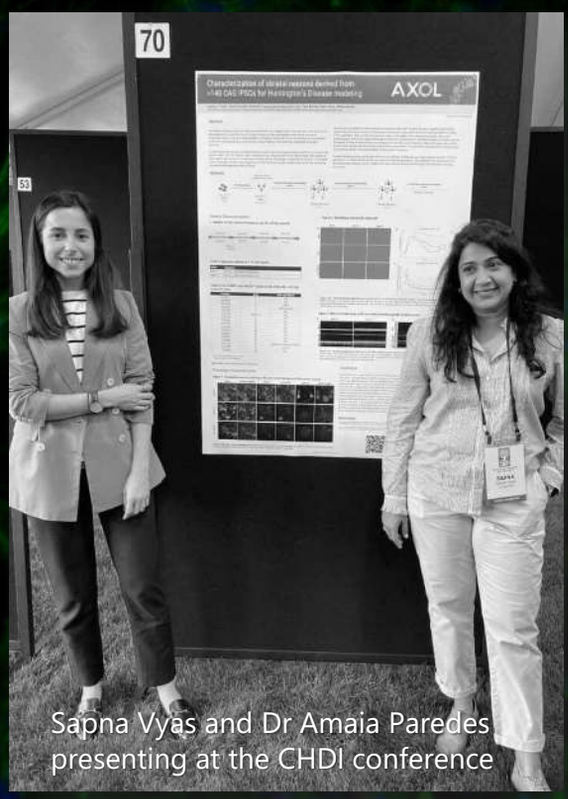

Sapna Vyas and Dr Amaia Paredes presenting at the CHDI conference