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Review

Towards Standardizing Nomenclature in Huntington's Disease Research

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Abstract. The field of Huntington's disease research covers many different scientific disciplines, from molecular biology all the way through to clinical practice, and as our understanding of the disease has progressed over the decades, a great deal of different terminology has accrued. The field is also renowned for its collaborative spirit and use of standardized reagents, assays, datasets, models, and clinical measures, so the use of standardized terms is especially important. We have set out to determine, through a consensus exercise involving basic and clinical scientists working in the field, the most appropriate language to use across disciplines. Nominally, this article will serve as the style guide for the *Journal of Huntington's Disease (JHD)*, the only journal devoted exclusively to HD, and we lay out the preferred and standardized terminology and nomenclature for use in *JHD* publications. However, we hope that this article will also serve as a useful resource to the HD research community at large and that these recommended naming conventions will be adopted widely.

Keywords: Nomenclature, Huntington's disease, HTT, mHTT, preclinical models, neuropathology, neuroanatomy

INTRODUCTION

Huntington's disease (HD, MIM# 143100) is an autosomal-dominant neurodegenerative condition caused by a CAG-repeat expansion in the first exon of the gene huntingtin (*HTT*), and this expansion lengthens a polyglutamine segment in the encoded huntingtin protein (HTT). Symptoms involve impair-

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ment in motor, cognitive, and behavioral/psychiatric domains, generally appearing during midlife with slowly progressive decline over the course of two decades. There is a wealth of scientific and clinical literature related to the disorder, but no disease-modifying treatment has been approved for HD as yet.

The primary authors of this position paper recognized a need for consistency of nomenclature in preclinical and clinical HD research. We assembled working groups to survey the current use of terms in the following fields: clinical genetics, genes and proteins, animal and cell models, and neuropathology. These working groups met over a series of conference calls, contributed writing and each of the members reviewed the recommendations across all four fields, culminating in this consensus paper. Specific HD-related terms are ranked as follows:

Preferred usage – Authors are advised to use this form of the term.

Acceptable alternative usage – Authors may use this form if done consistently in text.

Non-preferred usage – *JHD* will require justification by authors and approval of editors.

Not acceptable – Term is misleading or inappropriate and will not be accepted in *JHD*.

OVERVIEW OF SECTIONS

1. **Clinical and Genetic Terms**
2. **Gene and Protein Nomenclature**
3. **Preclinical Animal and Cellular Models**
4. **Neuroanatomy and Neuropathology**
5. **Glossary of *JHD* preferred terms**
6. **References**

1. CLINICAL AND GENETIC TERMS

There are good arguments to be made for the use of both "Huntington disease" and "Huntington's disease". That George Huntington did not himself have the disease, but rather first published a description of its clinical features, is the basis for using "Huntington disease", but much like Parkinson's disease and Alzheimer's disease, the more commonly accepted term and the term generally used by the patient community is "Huntington's disease". For publications in *JHD*, "Huntington's disease" is preferred, but we recognize that both forms are acceptable as long as authors are consistent. A common grammatical error to be avoided is capitalization of "disease", which is not correct in text, despite the standard abbreviation "HD".

The human huntingtin gene's Human Genome Organization (HUGO) Nomenclature Committee-approved symbol is *HTT* and the mutant gene, containing the expanded CAG repeat, is referred to as the mutant huntingtin gene (m*HTT*). Previous historical designations of the gene such as "*IT-15*" or "*HD gene*" are not acceptable usage in *JHD*. The protein product of an *HTT* allele that has an expanded, disease-associated CAG repeat is called "mutant huntingtin protein" (standard abbreviation, mHTT). This is the preferred term in *JHD*, rather than other terms such as "variant huntingtin protein" which are not acceptable (although required in some other journals such as *JAMA*). Acceptable alternatives include "expanded huntingtin protein", "expanded repeat huntingtin protein" or "expanded polyglutamine huntingtin protein", although these are not the standard or preferred terms in *JHD*.

The preferred *JHD* term for the protein produced from an *HTT* allele that is not associated with a disease phenotype (CAG-repeat length less than 36) is huntingtin (HTT). The terms "normal" and "non-polyglutamine expanded huntingtin" are not acceptable for *JHD*.

HD is most commonly an adult-onset disorder with an average age of symptom onset in the mid-forties. Although the *HTT* CAG repeat is highly polymorphic in the population with a continuum of repeat sizes, the relationship between repeat length and development of clinical signs of HD is often predictable (Table 1). HD is caused by a single *HTT* CAG-repeat expanded allele, such that repeats of greater than 35 are associated with a risk of developing HD during that individual's lifetime.

The preferred term for an individual known to have such an allele is "person with HD" (PwHD). The term "huntingtin gene expansion carrier" (HGEC) is non-preferred but can be used because of its current use in clinical practice (3). The commonly used term "Huntington disease gene expansion carrier (HDGEC)" is not acceptable, as it does not use the preferred gene name. HD with clinical onset before the age of 20 is usually associated with large CAG-repeat expansions in *HTT* of greater than ∼50. The preferred term for this is "juvenile-onset Huntington's disease" (JoHD). The term "juvenile HD" is not acceptable, as this is less precise and can lead to confusion in individuals who had clinical onset before age 20 but are currently much older. The older term "Westphal variant" is non-preferred, but can be used to describe the com-

Table 1
Classification of *HTT* CAG-repeat lengths (adapted from [1])

CAG-repeat count	Allele classification	Disease status
<27	Wild-type or non-expanded	Will not develop disease phenotype
27–35	Intermediate	Will not develop disease phenotype
36–39	Reduced penetrance	May or may not develop disease phenotype
40+	Full penetrance	Will develop disease phenotype

mon clinical phenotype seen in juvenile-onset HD. A form of chorea-predominant HD with a slowly progressive phenotype is often seen with clinical onset after the age of 70 and the term "late-onset HD" is acceptable for this form of HD, but the term "senile chorea" is not acceptable and should no longer be used to refer to HD.

For individuals who have CAG-repeat expansions of less than 36, the preferred term is "non-huntingtin gene expansion carrier (non-HGEC)" but "non-Huntington's disease gene expansion carrier (non-HDGEC)" is not acceptable. The protocol of the study being reported should provide a definition of the individuals who were used as controls. Importantly, control participants in HD studies are not necessarily "healthy" because they may have other diseases. A subset of these individuals who have *HTT* CAG repeats of 27–35 should be referred to as "carriers of an intermediate allele". The great majority of these individuals have no known risk of developing HD during their lifetime, but they do have a low risk of passing on an expanded (HD-associated) allele to their offspring, typically through the paternal lineage, due to intergenerational instability of the CAG repeat. In some contexts, these alleles can also be referred to as "pre-mutation alleles". Although this is an acceptable alternative usage, most notably when discussing the development of HD in an offspring who has inherited a fully penetrant repeat from a parent with an intermediate CAG repeat, the preferred term for individuals with CAG-repeat expansions of 36–39 is "carriers of reduced penetrance alleles". Alternatively, authors can use the acceptable alternative usage "incomplete penetrance alleles" since many individuals with repeat sizes in this range do not live long enough to manifest overt symptoms or obtain a clinical diagnosis of HD. These terms are outlined in Table 1.

Although some cognitive and psychiatric deficits may precede the onset of overt motor symptoms by many years, the current formal criteria for clinical diagnosis of HD are based on the determination by an appropriate health care professional that a person with a CAG-expanded *HTT* allele has developed the unequivocal presence of a constellation of otherwise unexplained extrapyramidal movement deficits such as chorea, dystonia, bradykinesia, or rigidity (Fig. 1). This is a clinical judgement by an experienced clinician and can be captured through the diagnostic confidence score (1–4), where a score of 4 represents >99% confidence of motor symptom onset [2]. Thus, it is assumed that "HD clinical diagnosis" is based on the onset of motor signs, unless otherwise defined in the manuscript. Other terms, such as "psychiatric onset or diagnosis" and "cognitive diagnosis" should be avoided unless specifically defined in the manuscript. Similarly, variations of "genetic diagnosis of HD" are non-preferred and should be avoided in *JHD* manuscripts.

The period following motor diagnosis is considered "manifest HD" and preceding motor diagnosis "premanifest HD". Premanifest HD can be divided into presymptomatic and prodromal phases, depending on whether any signs or symptoms consistent with HD are present. There are no precise consensus definitions of the terms presymptomatic and prodromal phases, therefore these terms should be avoided unless specifically defined in the manuscript.

The preferred term for individuals who have a CAG-expanded HTT allele at any disease stage is "persons with HD (PwHD)". Manifest HD, the period after clinical motor diagnosis, can be divided into several stages based on functional scales but must be clearly defined for use in *JHD* manuscripts. Definitions such as "Shoulson-Fahn Stages (I–V)", "early, moderate, advanced stage HD" that are based on specific scores in the Unified Huntington's Disease Rating Scale, (UHDRS; [2] (e.g., the Total Functional Capacity (TFC) scale), are acceptable.

PwHD can have an onset of symptoms at any age and, when taking into account large groups of PwHD, the age of clinical motor diagnosis is inversely correlated with the length of the *HTT* CAG-repeat expanded allele. In addition, the phenomenon of anticipation (i.e., the tendency toward younger age at symptom onset in subsequent generations) is due to the propensity of the CAG-repeat expansion to further expand on intergenerational transmission. This

tends to occur with paternal transmission of expanded *HTT* CAG repeats (the "sex-of-parent effect").

The HD-Integrated Staging System (HD-ISS) (Fig. 1) is an evidence-based staging system that is based on a biologic definition of HD [3]. In the HD-ISS, each disease case is defined as the presence of a CAG expansion in *HTT* exon 1 of either (i) 40 or more CAG repeats, OR (ii) 36 or more CAG repeats and the presence of a disease-specific biomarker or clinical syndrome. The HD-ISS encompasses the entire disease course and indexes progression based on specific landmark assessments that determine stage entry (Fig. 1). Stage 0 starts at birth, and people with HD enter HD-ISS Stage 1 when they surpass a threshold for a biomarker of pathogenesis (caudate or putamen volume loss as determined by MRI). Stage 2 entry is based on the presence of specific clinical signs or symptoms (Total Motor Score (TMS) or Symbol Digit Modalities Test (SDMT)), and Stage 3 is marked by functional *changes* based on a threshold for the Total Functional Capacity and the Independence Scale.

The former terminology referring to the clinical phases can be mapped onto the HD-ISS. For example, clinical motor diagnosis occurs most frequently by the end of HD-ISS Stage 2. Still the main qualitative dichotomy among HD-ISS stages is presymptomatic (Stages 0 and 1) versus symptomatic (Stages 2 and 3). The former terminology has been widely used over many decades, so we expect a relatively long transition period as publications slowly adopt HD-ISS language. We anticipate that the HD-ISS will eventually become the standard research framework for cohort stratification and for inclusion and exclusion criteria in new observational studies and clinical trials, and increased use of the HD-ISS, in turn, will influence the commonly accepted terminology (see accompanying editorial in this issue). We therefore recommend using terminology consistent with the HD-ISS but acknowledge that other terms may still be acceptable if specifically defined in the manuscript.

Prognostic scores and clinical combination variables

CAG-Age Product (CAP)

The discovery that CAG length is a strong predictor of symptom onset and progression, particularly the emergence of clinically diagnosable motor symptoms, led to the development of prognostic scores. These scores make use of two variables—age and CAG length—either to predict landmark events over the course of the disease, or to provide a time referential (often the *x*-axis in a graph) to depict disease progression across age adjusted for CAG-repeat length. The interaction of age and CAG-repeat length are incorporated, which motivates the term CAG-age product (CAP).

There are various scoring systems in use because the statistical models to calculate them were developed from different perspectives, and they all used different datasets for validation. Ideally, only one scoring system should be used to enhance research comparability. To this end, Warren et al. [4] presented a general formula for CAP:

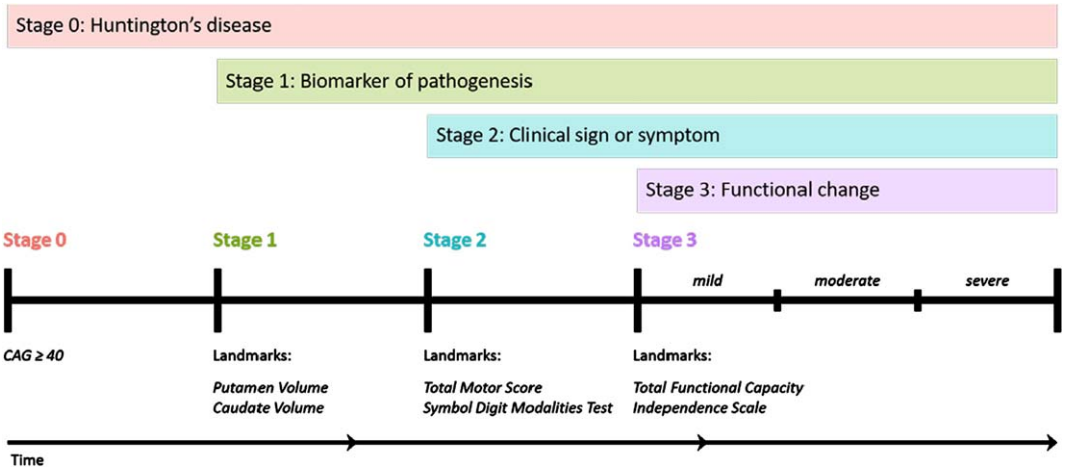

Fig. 1. The HD-Integrated Staging System (HD-ISS): Cumulative staging framework and landmarks. Graphical representation of the temporal sequence of Stage progression and the associated landmark assessments that define Stage entry. (Note: time not to scale). From accompanying editorial: "*Refining the Language of Huntington's Disease Progression with the Huntington disease integrated staging system (HD-ISS)*".

$$CAP = Age(CAG - L)/K$$

The L and K parameters define three of the major CAP scores, with $L = 35.5$ and $K = 1$ used for the Penney et al. version [5] (sometimes referred to as the disease burden score), $L = 36.66$ and $K = 1$ defining the version based on PREDICT-HD [6] and $L = 30$ and $K = 6.49$ defining CAP_{100}, so-named because a value of 100 is associated with clinical motor diagnosis in Enroll-HD [4]. CAP_{100} has the advantage of the anchor value, and is the score we recommend for general use.

Expected age of clinical motor diagnosis

An alternative approach for the risk of HD progression has been proposed by Langbehn et al. [7, 8] based on survival analysis modeling. It too incorporates age and CAG length. For a given CAG length, the probability of not experiencing clinical motor diagnosis by a given age is estimated by

$$\left(1 + exp\left\{\frac{\pi}{\sqrt{3}} \times \frac{-21.54 - \exp(9.56 - .146CAG) + AGE}{\sqrt{35.55 + exp(17.72 - .327CAG)}}\right\}\right)^{-1}$$

Perhaps the most commonly cited statistic related to the above formula is the expected age of clinical motor diagnosis onset (from birth) for a given CAG length,

$$21.54 + exp(9.56 - .146 \times CAG),$$

referred to as the expected age of clinical motor diagnosis.

The underlying data for this model included a maximum CAG length of 56, and these formulae may be inaccurate for extreme CAG lengths associated with juvenile onset HD.

PIN score

Prognostic value is enhanced when clinical variables are included along with age and CAG length. This motivated the prognostic index for HD (PI_{HD}) and the prognostic index normed (PIN) [9]. Both measures incorporate the UHDRS Total Motor Score (TMS) and Symbol Digit Modalities Test (SDMT), along with a version of CAP (with $L = 34$, $K = 1$):

$$PI_{HD} = 52 \times TMS + (-34)$$

$$\times SDMT + 7 \times [Age \times (CAG - 34)],$$

$$PIN = (PI_{HD} - 883)/1044.$$

PIN has been thoroughly examined by Langbehn et al. [10, 11] and is recommended for general use when a researcher wants to consider clinical information along with age and CAG length.

Combined/composite UHDRS

The combined (or composite) UHDRS (cUHDRS) was proposed as a more sensitive outcome measure than using a single clinical variable. The cUHDRS has been used as the primary endpoint in some recent pivotal trials [12]. The outcome combines scaled versions of the TMS, SDMT, Stroop word reading test (SWR), and Total Functional Capacity (TFC):

$$\text{cUHDRS} = \left[\left(\frac{TFC - 10.4}{1.9}\right) - \left(\frac{TMS - 29.7}{14.9}\right) + \left(\frac{SDMT - 28.4}{11.3}\right) + \left(\frac{SWR - 66.1}{20.1}\right)\right] + 10.$$

Smaller cUHDRS scores indicate greater decline (greater progression).

HD-CAB

Another combination outcome measure is the HD Cognitive Assessment Battery (HD-CAB) [13]. The HD-CAB combines six cognitive measures, Hopkins Verbal Learning Test (HVLT-R), Trail Making Test Part A & B (TMT A & B), Paced Tapping Test (PTAP), SDMT (see above), Emotion Recognition (EMO), and One Touch Stockings of Cambridge (OTS). The tests are combined by first computing a Z-score for each (Z = (score – mean)/SD), and then computing the mean of the Z-scores. Similar to the cUHDRS, smaller values indicate greater cognitive decline.

2. GENE AND PROTEIN NOMENCLATURE

The variable length of the polyglutamine domain in human HTT makes it difficult to specify a standard naming convention for the downstream amino acid residues towards the carboxy terminus. For example, serine 421 is a highly conserved phosphorylation site in HTT and has been shown to protect against the toxicity of the expanded polyglutamine tract in mHTT [14]. But with the variable length of the amino-

Table 2
Species gene and protein nomenclature. Huntingtin gene and protein symbol nomenclature in different animal species with associated polyglutamine length and HTT length [19, 22] from NCBI: XP_028704080.1, (XP_045247979.1, NP_001254674.1, NP_001136110.1, NP_999129.1, NP_077333, XP_030126485.3, XP_041443615.1, XP_031751173.1, NP509663.3; UniProt XP_645159.1.

Species	Huntingtin gene symbol	Huntingtin protein symbol	Polyglutamine repeat length	HTT residue length
Human/higher mammals				
Human *(Homo sapiens)*	*HTT*	HTT	Q23	3144
Human, HD *(Homo sapiens)*	N/A	mHTT	Q>35	3144
Human, HD *(Homo sapiens),* Exon 1	N/A	mHTT1a	Q ≥ 42	≥ 107
Rhesus Macaque (*Macaca mulatta*)	*HTT*	HTT	Q11	3132
Crab-eating macaque (cynomolgus, *Macaca fascicularis)*	*HTT*	HTT	Q12	3155
Marmoset *(Callithrix jacchus)*	*HTT*	HTT	Q9	3131
Sheep *(Ovis aires)*	*HTT*	HTT	Q10	3127
Miniature pig *(Sus scrofa domesticus)*	*HTT*	HTT	Q18	3139
Dog *(Canis familiaris)*	*HTT*	HTT	Q10	3130
Rodents				
Mouse *(Mus musculus)*	*Htt*	HTT	Q7	3119
Rat *(Rattus norvegicus*)	*Htt*	HTT	Q8	3120
Birds				
Song bird (zebra finch, *Taeniopygia guttata)*	*htt*	HTT	Q4	3095
Amphibians and fish				
Frog *(Xenopus laevis; Xenopus tropicalis)*	*htt*	HTT	Q4; Q4	3130; 3123
Zebrafish *(Danio rerio)*	*htt*	Htt	Q4	3121
Invertebrates				
Fruit Fly *(Drosophila melanogaster)*	*htt*	HTT	Q0	3758
Roundworm *(Caenorhabditis elegans)*	*htt*	HTT	Q0	2022
Amoeba (*Dictyostelium discoideum*)	*htt*	HTT	Q0	3095
Unicellular microorganisms				
Bacteria (most genera)	*htt*	Htt	N/A	N/A
Budding yeast *(Saccharomyces cerevisae)*	*HTT*	Htt	N/A	N/A

terminal polyglutamine region in both human wtHTT and mHTT, serine 421 is not necessarily the 421st amino acid residue in both HTT proteins, or indeed in other HTT variants.

The convention adopted by many groups is to utilize a fixed polyglutamine length no matter what the actual length, thereby creating consistency across all human HTT variants (Table 2). There are three predominant conventions used in the HD field: the use of a fixed polyglutamine length of 0 [15], of 23 [16, 17], and of 25 for CAGCAA repeats used in cell lines. For the purposes of publication in *JHD*, we recommend that a fixed polyglutamine length of 23 be used as the convention for human HTT (which has been used for the serine 421 example). To avoid any confusion, authors must always define the convention upfront and provide the sequence (including any tags on the proteins) as a supplement or provide a reference if previously published.

Furthermore, the animal species used in preclinical research have different endogenous wildtype pure or interrupted CAG repeats and polyglutamine lengths in their huntingtin orthologs and proteins (Table 2). For example, in several but not all mouse strains, murine HTT contains a polyglutamine repeat of 7, thus in the example above, serine 421 would be serine 399 using a fixed polyglutamine length domain of 7. For the purposes of publication in *JHD*, we recommend that a fixed polyglutamine length of 7 be used as the convention for all murine HTT with the supporting sequence as a supplement.

It should be noted that the Human Genome Variation Society has created guidelines for the nomenclature of proteins with variable domains (https://varnomen.hgvs.org/recommendations/protein/variant/repeated/). They suggest identifying the position of the first residue of the repeat and then indicate the length of the repeat. For example, "p.Gln18[23]" is the abbreviation for a repeated amino acid sequence with the first glutamine residue located at position 18 and is present in 23 copies (HD glutamine-repeat based on HTT reference sequence (GenBank NP_002102.4)). They also provide an example of estimated repeat domain sizes with "p.(Gln18)[(70_80)]" indicating that the predicted glutamine amino acid repeat, starting at position 18, has an estimated size of 70 to 80 repeats and everything downstream stays with the numbering of the reference sequence. The Human Genome Variation Society does not seem to have an explicit

convention for the residue nomenclature beyond a variable domain to keep the residue numbering consistent across multiple variable domain protein variants, but the downstream residues should be in the context of the numbering of the reference sequence. Here, we recommend that a fixed polyglutamine length of 23 be used as the convention for the human HTT reference sequence no matter what the repeat length is, thereby providing a consistent number of critical residues after the variable domain towards the C-terminus (e.g., serine 421).

Another variable domain of HTT to consider is the proline-rich domain (PRD) within exon 1 that displays sequence heterogeneity. The uninterrupted proline repeat most often is 7 or 10 residues in length in human HTT, but many other variants (longer and shorter) are also observed. For *JHD* publications, the PRD of the DNA construct or protein must be defined upfront and either the sequence provided as a supplement or referenced if previously published.

The first exon of *HTT*, when expressed on its own, encodes the HTT exon1 protein, which has been used for multiple studies and HD models including the highly utilized R6/1 and R6/2 mouse models [18]. The HTT exon 1 protein is designated as including 1–90 amino acids using the fixed Q23 polyglutamine convention. Furthermore, recent findings have shown that alternative processing of the *HTT* pre-mRNA by the activation of cryptic polyA sites in intron 1 can generate small single-exon transcripts called *HTT1a* in humans and *Htt1a* in mice [19, 20]. The *HTT1a* and *Htt1a* transcripts encode the HTT exon 1 protein (1–90) terminating in a proline residue, the correct nomenclature for which is HTT1a. Additional splice variants are encoded within exon 49/50 and need to be defined when relevant to the manuscript.

Another challenge in designating a repeat-region nomenclature convention is the recent finding that it is the number of pure CAGs in *HTT* that influences the timing of the emergence of clinical symptoms and that numbering requires consideration of the CAA interruptions within the CAG repeat [21]. Recent considerations by the Clinical Genetics Working Group and GeM-HD consortium have recommended that pure CAG repeats be designated as $(CAG)_n$, where n is the number of repeat units. Thus, the most common human *HTT* sequence, with its single CAA interruption, would be $(CAG)_nCAACAG$. We note that both CAG and CAA translate into a glutamine residue, so this variance does not affect the HTT sequence. Including the downstream PRD would yield $(CAG)_nCAACAGCCGCCA(CCG)_n$, and other sequence variations in these segments can be denoted in a similar manner.

3. PRECLINICAL ANIMAL AND CELLULAR MODELS

Animal models

There are a number of common names as well as formal/standardized nomenclature for preclinical animal models of HD (e.g., "JAX mouse nomenclature" from Jackson Labs, https://www.jax.org/jax-mice-and-services/solutions-by-therapeutic-area/neurobiology/huntingtons-disease-mouse-model-resource). For *JHD*, standardized nomenclature should be included in the materials and methods. The nature of the control animals should also be defined as siblings, wildtype animals, or other categories. Within the text, a common/accepted name can be used with standardized nomenclature cited in the methods section. If animals are obtained from, or are available at, Jackson Labs (JAX), then their standardized nomenclature followed by the common name is used with a link to the JAX website. CAG-repeat length should be defined if there are different variants of the mouse line. For example, R6/2, YAC128 and BACHD mice would be cited as follows:

- B6CBA-Tg(HDexon1)62Gpb/1J standardized nomenclature=R6/2 common name with CAG repeat of 160+/- 5 (https://www.jax.org/strain/002810)
- FVB-Tg(YAC128)53Hay/J standardized nomenclature=YAC128 common name (https://www.jax.org/strain/004938)
- FVB/N-Tg(HTT*97Q)IXwy/J standardized nomenclature=BACHD common name (https://www.jax.org/strain/008197)

If an animal is obtained from an alternative repository, the name of the repository and the same information as for JAX models should be included. If the animal model was obtained from a research lab, then the methods should include species and strain background, transgene or method of knock-in, pure CAG versus mixed CAG/CAA codon repeats, or a reference describing the model. Finally, metadata for the experiment should be included in materials and methods, including age of animals, genotype and CAG-repeat measurements from tail snips (reported with mean and standard deviation for in-house breeding). If animals are provided by a repository, *JHD*

Table 3
The basal ganglia and some connecting subcortical structures in human and non-human primates

Classification	Term	Consists of these regions:	Abbreviations
Neuroanatomical/neuropathological	Basal ganglia	Caudate nucleus Putamen Globus pallidus Amygdala Substantia nigra Subthalamic nucleus Pedunculopontine nucleus	Cd Put GP SN STN PPN
	Corpus striatum	Caudate nucleus, putamen, nucleus accumbens and globus pallidus	
	Lenticular nuclei	Putamen and globus pallidus	
	Cortex Brodmann terminology function (motor, sensory, visual, etc.)	Projections to caudate nucleus and putamen	
	Substantia nigra, pars compacta	Projections to caudate nucleus and putamen	SNpc
	Parafascicular nucleus	Projections to caudate nucleus and putamen	Pf
	Medial dorsal nucleus	Projections to caudate nucleus and putamen	MD
	Substantia nigra, pars reticulata	Inputs from caudate nucleus and putamen	SNpr
Phylogenetic	Neostriatum	Caudate nucleus Putamen Nucleus accumbens	Cd Put NAc or NAcc
	Paleostriatum	Internal globus pallidus External globus pallidus	iGP or GPi eGP or GPe

References for Table 3: [24–29]. Allen Atlas for Human Brain Online open access [30] https://help.brain-map.org/display/humanbrain/Allen+Human+Brain+Atlas.

manuscripts can include metadata from the repository. Potential exceptions include BACHD (original mixed repeats) or YAC128 that are stable in germline.

Cellular models

For cell models, authors should include full descriptions of the source (e.g., American Type Culture Collection (ATCC) or research lab with reference), the gene introduced into the system (*HTT* sequence, epitope tags, pure CAG versus mixed CAG/CAA codon repeats, promoter used, transient versus stable lines) as well as quality-control metrics (e.g., karyotype, source of cell line). For HD donor-derived cell lines (e.g., iPSCs), nomenclature should be clearly defined in the materials and methods, and include the source of the lines, for instance through the NINDS repository (https://nindsgenetics.org/). Recommended nomenclature is to include the repository ID number in the materials and methods (e.g., NDS00091) or to provide a reference source for the line and to provide CAG-repeat sizing as repeat lengths can be unstable over time. Common naming within the text should include CAG/polyglutamine repeat length such as CAG53 (or 55Q if allele has penultimate CAACAG codons). For controls, materials and methods should include whether these are family controls, non-family controls, or gene-corrected lines.

4. NEUROANATOMY AND NEUROPATHOLOGY

The anatomical names used to reference brain regions should be appropriate to the species. The abbreviations for these brain regions should be those recommended here, in atlases, or in common use. Non-standard abbreviations should be avoided. If multiple terms or abbreviations are available, literature source(s) should be cited for the terminology used. When many non-standard abbreviations are used in the text they should be listed and defined at the beginning of the *JHD* manuscript. It is helpful to cite the stereotaxic atlas used for brain region terminology, injections, or recordings. For figures,

Table 4
Neuron types in human and nonhuman primate neostriatum

Neuron type	Abbreviation	Neurotransmitters/peptides	References
Medium spiny neuron	MSN	GABA, enkephalin, substance P, dynorphine, calbindin-D28	[32, 33]
Medium aspiny neuron		Somatostatin, parvalbumin, nitric oxide synthase, calretinin	[34]
Large aspiny neuron		Acetylcholine	[35]
Neuron types 1-V	1-V		[33]
Unique interneuron		*Tac3*+	[31]

Table 5
The basal ganglia and some connecting subcortical structures in mouse

Term	Consists of these regions:	abbreviation
Striatal complex	Dorsal striatum, ventral striatum	
Dorsal striatum	Caudate-putamen (or caudoputamen), Globus pallidus	CP, CPu GP
Globus pallidus	Dorsal pallidum and ventral pallidum or lateral globus pallidus and medial globus pallidus (or entopeduncular nucleus)	lGP mGP GPe entopeduncular nucleu
	Globus pallidus external part	
	Globus pallidus internal part	
Ventral striatum	Nucleus accumbens	NAc
	Olfactory tubercle	OT
	Ventromedial parts of caudate putamen	CP
Substantia nigra	Substantia nigra compacta, sends afferents to CP	SNc SNr
	Substantia nigra reticulata, receives output from CP	
Subthalamic nucleus	Sends afferents to GP	STN
Parafascicular nucleus	Sends afferents to CP	Pf
Ventromedial nucleus	Sends afferents to CP	VM
Ventral anterior nucleus	Receives output from GP	VA
Ventral lateral nucleus	Receives output from GP	VL

use inserts of sectioned brain to indicate the location of high magnification images, injection sites, or dissected tissue.

Authentication of HD in human postmortem brain

The research use of postmortem tissue from a PwHD must meet genetic and neuropathological criteria, which include in order of preference: 1) PCR analysis of *HTT* CAG-repeat length should show 36 or more, and the brain region of determination should be specified, and if the cortex then the specific region; 2) western blot or ELISA-based assays for detection of mHTT; and 3) the presence of inclusions by immunohistochemistry.

A grading system describing the extent of atrophy and cellular changes in the postmortem neostriatum is a widely accepted standard [23]. The Vonsattel criteria are based on shape changes in the neostriatum and use a grading system from 0–4, with grades 1–4 denoting increasing degrees of atrophy, and "0" denoting no pathology.

Table 6
Neuron types in mouse and rat caudate putamen

Classification	Name	Abbreviation
Morphology	Medium spiny neurons Medium aspiny neurons Large aspiny neurons Types I–V in rat	MSN
Electrophysiology	Fast spiking interneurons; Low-threshold Ca^{2+} spiking interneurons; Spontaneously active cholinergic interneurons; Neuropeptide Y	FS LTS Spontaneously active ChIs NPY-PLTS NPY-neurogliaform
Location/pathway	Striosomes: patch and/or matrix; Direct or indirect pathway	
Neurotransmitter or peptide content	Gamma amino butyric acid Acetylcholine Parvalbumin Somatostatin Nitric oxide synthase Calbindin D28k or calcium binding protein-D28k Calretinin Tyrosine hydroxylase Caldec Methionine enkephalin Leucine enkephalin Substance P	GABA ACh PV Som NOS CaBP-D28k CR TH RasGRP2 Met-ENK Leu-ENK SP
Output	Spiny projection neuron	SPN
Receptor content	Metabotropic glutamate receptors N-methyl-D-aspartic acid (NMDA) receptor subtypes alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid Dopamine receptor D1 Dopamine receptor D2 Adenosine receptors Nicotinic acetylcholine receptors	mGluR1 NMDAR2A, or NMDAR2B AMPAR D1R, DrD1 D2, DrD2 A2a nAChr
Gene clusters based on single-cell RNA-seq	Subgroups of MSNs and non-neuronal cells enriched with different transcripts	

References for Table 6: [39–48].

Table 7
Terms used for the localization and accumulation of mutant huntingtin protein in human and mouse tissues and cells

Term	Meaning	References
Inclusions Also: inclusion bodies (IB), nuclear inclusions (NI), perinuclear inclusions, cytoplasmic inclusions, neuropil inclusions, axonal inclusions	Visible by light microscopy. Description often relates to subcellular location.	[49, 50] 7,900 refs in PubMed
Oligomers, fibrils and protofibrils	Smaller assemblies not visible by light microscopy that may be resolved by EM.	[51]
Aggregates	A collective term that includes all assemblies of mHTT.	[52–57]14,000 refs in PubMed
Aggresomes	Inclusions at a perinuclear location at the microtubule organizing center surrounded by a vimentin cage.	[58] 1,000 refs in PubMed
By antibody: EM48, 4C9, 1C2 (anti-TBP), MW8, S830, PHP1 and PHP2, p62	Antibodies with known or unknown epitopes that vary in the amount, composition and location of accumulated mHTT	[52, 59–64]

The basal ganglia and some of its subcortical connections in human and nonhuman primate and mouse brain

The nuclei that comprise the basal ganglia are grouped differently depending on whether a neuroanatomical/neuropathological or phylogenetic classification is adopted. For *JHD* submissions, the former is most commonly used and therefore is preferred. Table 3 summarizes the classifications, terms, nuclei, and abbreviations for regions of the basal ganglia in human and nonhuman primate with the neuroanatomical/neuropathological classification shown at the top and the phylogenetic classification shown at the bottom. Also included in Table 3 are some of the major interconnections of basal ganglia nuclei. Table 5 reviews the terms, brain regions and abbreviations for the basal ganglia in mouse.

Neuron types in human and nonhuman primate neostriatum

The terms for neuron types are based on morphology and/or neurotransmitter/neuropeptide content. Single nucleus RNA sequencing has defined a unique type of interneuron in the primate neostriatum [31]. Table 4 classifies neuron types and provides some pertinent references for human and nonhuman primates.

Neuron types in mouse and rat caudate putamen

The basis for classification of neurons in the rodent caudate putamen may include morphology, electrophysiology, location, pathways, neurotransmitter/peptide content, output, or receptor content. Table 6 summarizes these categories and includes some common abbreviations.

Localization and accumulation of mutant huntingtin in human and mouse

Aggregates represent a continuum of species that reflect disruption of protein folding and homeostasis. Various terms have been used to describe the presence, subcortical location, and type of accumulation of mutant huntingtin or fragments of mutant huntingtin in cells and in brain. These terms include inclusions, fibrils and oligomers, aggregates, and aggresomes. Table 7 provides a list of terms, the context in which they have been used, and relevant publications. These terms, as defined, should be used for manuscripts in *JHD*.

Sheep and minipig models

Sheep and minipig transgenic models of HD have been engineered. Brain atlases and relevant publications listed provide guidance on nomenclature. The Sheep Brain Atlas https://brains.anatomy.msu.edu/brains/sheep/index.html; [65]. For mini-pig, references are [66, 67].

5. GLOSSARY OF JHD PREFERRED ABBREVIATIONS

cUHDRS	composite Unified Huntington's Disease Rating Scale
HD	Huntington's disease
HD-CAB	HD Cognitive Assessment Battery
HD-ISS	HD Integrated Staging System
HGEC	huntingtin gene expansion carrier
Non-HGEC	non-huntingtin gene expansion carrier
mHTT	mutant HTT
wtHTT	wild type HTT
PBA	Problem Behaviors Assessment
PCA	Principal Component Analysis
PwHD	persons with HD
SDMT	Symbol Digit Modalities Test
SWR	Stroop Word Reading Test
TFC	Total Functional Capacity
TMS	Total Motor Score
UHDRS	Unified Huntington's Disease Rating Scale

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