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# Huntington's Disease's Exclusivity to Humans from an Evolutionary Perspective

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## ABSTRACT

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by CAG repeat expansions in the huntingtin gene (*HTT*). Despite the evolutionary conservation of *HTT* across vertebrates, HD manifests almost exclusively in humans, yet the mechanisms remain poorly understood. This review aims to provide insight into why Huntington's disease is fundamentally a human affliction, despite the widespread presence of the *HTT* gene across species. By examining comparative aspects of huntingtin protein structure, CAG repeat stability, and expansion mechanisms between humans, our closest primate relatives, and other mammalian species, this review explores potential explanations for why only humans develop HD. Synthesis of peer-reviewed literature was conducted using Google Scholar and PubMed, supplemented by a comparative analysis of polyglutamine repeats across 10 mammalian genomes using UniProt. Collectively, the evidence suggests that humans possess a distinctly elongated and unstable CAG repeat, and that human-specific variations in DNA mismatch repair mechanisms may drive progressive somatic expansion within susceptible neurons. These findings support the hypothesis that evolutionary changes in the human *HTT* gene may have created an unintended susceptibility to Huntington's disease while identifying promising directions for future research.

## INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by CAG repeat expansions in the huntingtin gene (*HTT*). In humans, the normal repeat length is between 10-35; when CAG repeats exceed approximately 36, the resulting mutant huntingtin protein gains toxic properties that lead to selective neuronal death, particularly in the striatum.[1] This genetic mutation affects multiple domains: motor symptoms such as involuntary choreic movements, cognitive decline progressing to dementia, and psychiatric manifestations including irritability, apathy, and depression.[2] The *HTT* gene is highly conserved across vertebrates and is present in species ranging from rodents to primates, yet the pathological manifestation of HD occurs almost exclusively in humans.[3]

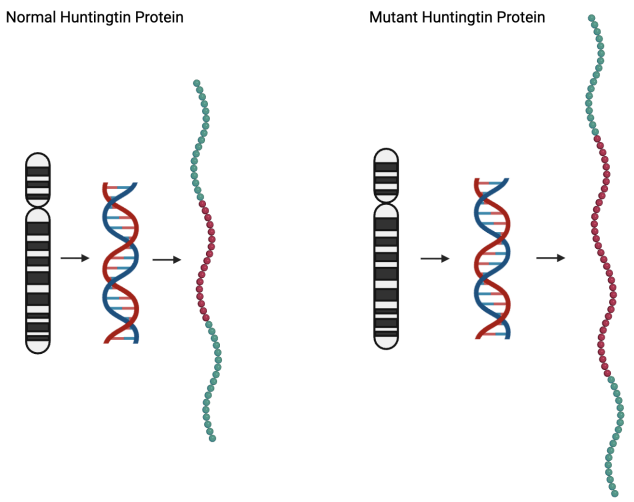


**Figure 1:** Comparison of normal and mutant huntingtin proteins. The normal *HTT* gene contains a non-pathogenic number of CAG repeats, producing a huntingtin protein with a polyglutamine tract (shown in dark pink) of typical length. Expansion of the CAG repeat region in the mutant *HTT* gene results in an elongated polyglutamine tract, which alters protein structure and contributes to Huntington's disease pathology.

Despite the evolutionary conservation of the *HTT* gene across vertebrates, Huntington's disease manifests almost exclusively in humans.[3] While chimpanzees and orangutans possess similar CAG repeat regions in their *HTT* genes, they do not naturally develop HD pathology.[4] In humans, healthy individuals typically possess 10–35 CAG repeats, whereas alleles containing 40 or more repeats invariably lead to HD during the individual's lifetime. A "reduced penetrance" range of 36–39 repeats represents an intermediate zone, where disease manifestation is uncertain; individuals in this range may or may not develop HD, and if they do, symptom onset is typically later in life.[5] In contrast, chimpanzees (14–20 repeats) and orangutans (15–25 repeats) maintain stable, non-pathogenic repeat ranges.[6]

Current research has not fully elucidated why CAG repeats in humans are uniquely prone to pathological expansion and somatic instability, the phenomenon where repeat lengthens further in brain neurons during a person's lifetime. Understanding the molecular, genetic, and cellular mechanisms underlying this species-specific vulnerability is essential for developing targeted therapeutic interventions and comprehending the evolutionary pressures that shaped human neurological susceptibility to HD.

This review aims to provide insight into why Huntington's disease is fundamentally a human affliction, despite the widespread presence of the *HTT* gene across species. By examining comparative aspects of huntingtin protein structure, CAG repeat stability, and expansion mechanisms between humans, our closest primate relatives, and other mammalian species, this review explores potential explanations for why only humans develop HD. It synthesises current evidence regarding the evolutionary changes in human *HTT* gene regulation and expression that may have created vulnerability to this neurodegenerative

disease. By comparing CAG repeat dynamics across species, this review seeks to improve our understanding of the factors underlying human susceptibility to HD.

This review synthesises current evidence regarding the evolutionary, molecular, and cellular factors that underlie human-specific susceptibility to HD. Specifically, this review: (1) examines comparative *HTT* gene structure and CAG repeat dynamics across species; (2) explores mechanisms of somatic instability that may contribute to the predominance of HD in humans; and (3) evaluates evolutionary changes in *HTT* gene regulation and expression that may have conferred vulnerability to pathological repeat expansion in humans.

## METHODS

Evidence was gathered through a structured literature review focusing on comparative genomic studies, molecular analyses of *HTT* repeat dynamics, and evolutionary biology research. A narrative synthesis approach was employed to integrate findings across disciplines.

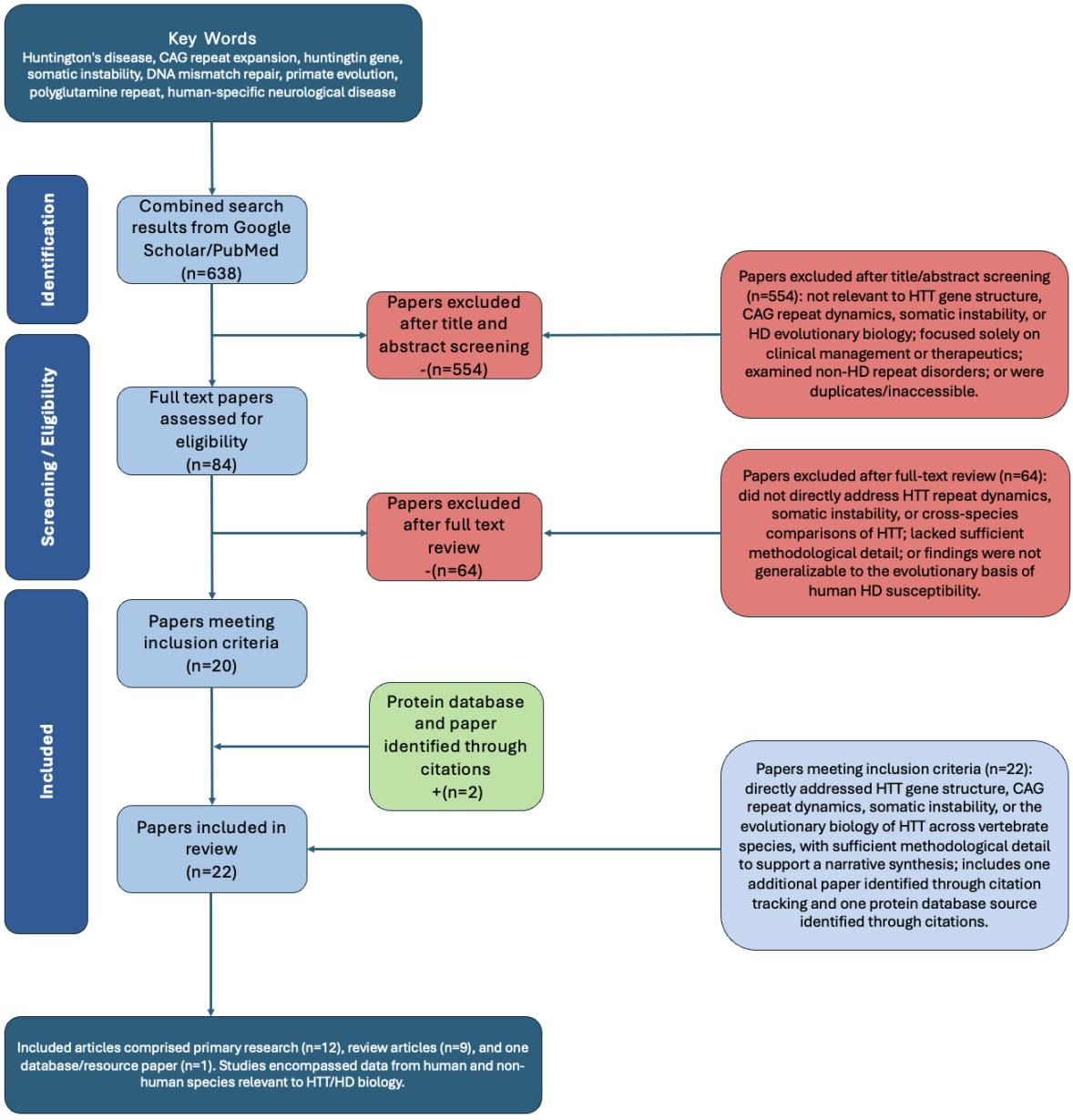


**Figure 2:** Flow diagram of the systematic literature search and paper selection process. Searches of PubMed and Google Scholar yielded 638 combined results. 84 potentially eligible papers remained after duplicates and inaccessible papers were removed and titles and abstracts were screened for relevance. These studies underwent full-text review and were assessed for direct relevance, resulting in 20 eligible papers. An additional paper was identified through citation tracking of included articles and a citation from the UniProt database was added, bringing the total number of sources included in this review to 22.

Studies were identified through searches of PubMed and Google Scholar using combinations of terms related to HTT, Huntington's disease, CAG repeat expansion, cognitive performance, intelligence, brain evolution, and primate evolution. The literature screening and selection process is summarised in Figure 2. The initial search yielded 638 results. Duplicate and inaccessible papers were removed, and the remaining titles and abstracts were screened for relevance to the research question, resulting in 84 potentially eligible papers.

Each of the 84 papers then underwent a full-text review and was assessed for direct relevance to *HTT* gene structure, CAG repeat dynamics, somatic instability, or the evolutionary biology of *HTT* across vertebrate species. Papers that did not fully meet these criteria were excluded from the final synthesis, resulting in the inclusion of 20 papers. An additional paper was identified through citation tracking, and UniProt was included as a source for identifying and comparing huntingtin protein sequences across species, bringing the total number of references to 22.

To complement the literature review, a comparative analysis of huntingtin protein sequences was conducted using UniProt to examine polyglutamine (PolyQ) repeat lengths across representative mammalian species. This analysis was performed to provide a consistent comparison of PolyQ repeat lengths using a single database and to illustrate the evolutionary trends discussed throughout the review.

PolyQ repeat lengths for a range of different mammalian species were obtained through UniProt by searching for the huntingtin (HTT) protein orthologue for each respective species. For each sequence, the PolyQ repeat length was recorded alongside the corresponding common name, binomial species name, and UniProt accession ID. From the resulting list of sequences, species of particular relevance were selected, with an emphasis on primates because of their close evolutionary relationship to humans. Commonly used rodent model organisms were also included because of their widespread use in Huntington's disease research. This process resulted in a total of 10 representative species, which are summarised in Table 1.

Species were selected to represent a phylogenetically diverse range of mammals, with an emphasis on primates and commonly used rodent models, to compare PolyQ repeat lengths across species and evaluate whether a directional evolutionary trend toward longer repeat tracts exists within the human lineage. The human HTT protein was first identified in UniProt and used as the reference sequence for identifying orthologous huntingtin proteins across mammalian species. Proteins sharing at least 90% sequence similarity with the human HTT protein were then reviewed for comparison, provided the PolyQ repeat region was present.

Humans (*Homo sapiens*) were included as the reference species because HD is a human-specific disorder. Chimpanzees (*Pan troglodytes*) and Sumatran orangutans (*Pongo abelii*) were selected as human's closest living relatives. The olive baboon (*Papio anubis*), golden snub-nosed monkey (*Rhinopithecus roxellana*), green monkey (*Chlorocebus sabaeus*), and Ma's night monkey (*Aotus nancymaae*) were selected to represent both Old World and New World monkey lineages, enabling a broader assessment of

evolutionary patterns in PolyQ repeat lengths across primates. The grey mouse lemur (*Microcebus murinus*) was included as a prosimian, representing the most basal primate lineage examined. The rat (*Rattus norvegicus*) and mouse (*Mus musculus*) were included due to their prevalent use as laboratory models in Huntinton's disease research.

This analysis was undertaken to contextualise the uniquely long PolyQ repeat tract observed in humans relative to other mammalian species and to evaluate whether the available sequence data support the hypothesis that human HTT repeat lengths lie near a threshold of pathological instability. The resulting data were compiled manually into Table 1 and ordered by descending PolyQ repeat length.

## RESULTS

Synthesis of the reviewed literature indicates a stepwise mechanism linking the evolutionary history of the *HTT* gene to the human-specific susceptibility to Huntington's disease, summarized in Figure 3.

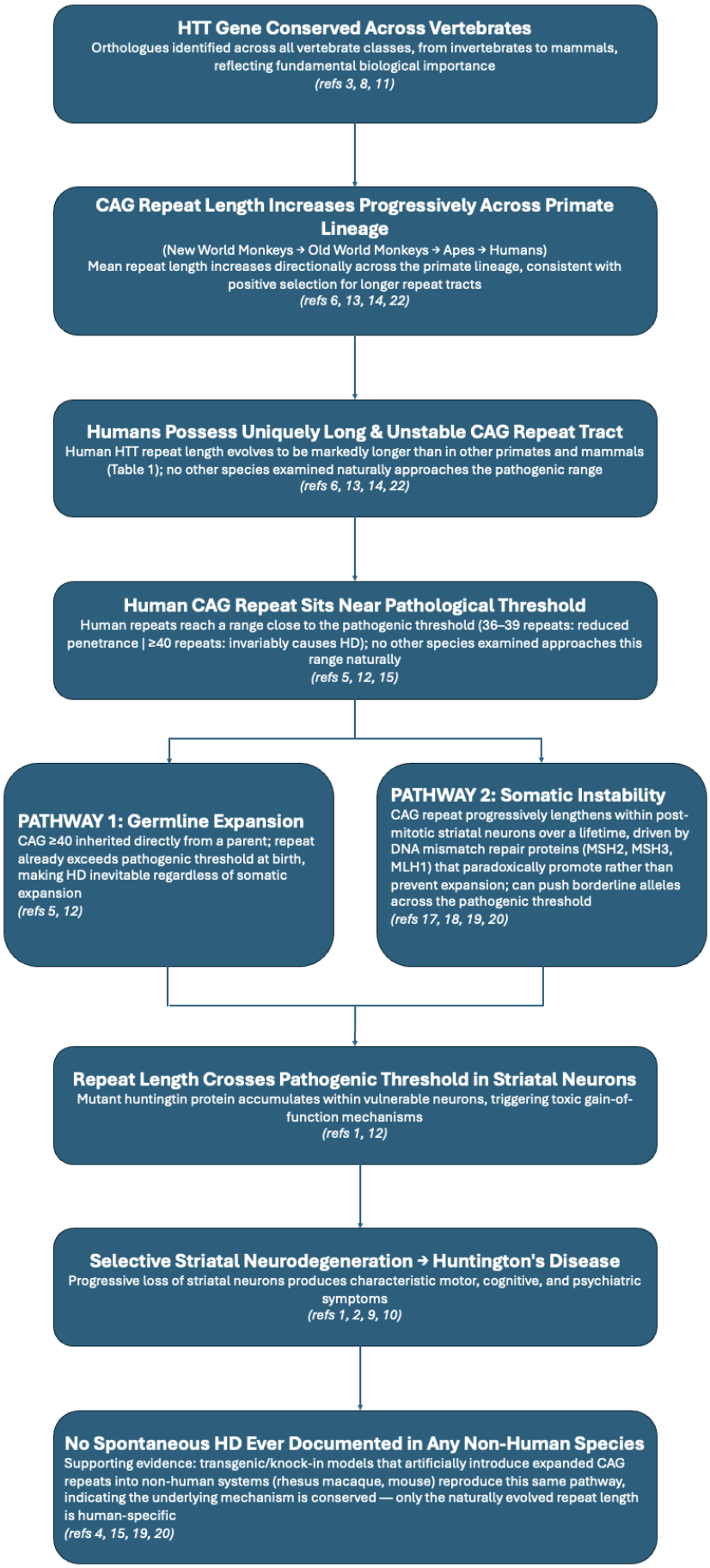
HTT Gene Conserved Across Vertebrates
Orthologues identified across all vertebrate classes, from invertebrates to mammals, reflecting fundamental biological importance
(refs 3, 8, 11)
CAG Repeat Length Increases Progressively Across Primate Lineage
(New World Monkeys → Old World Monkeys → Apes → Humans)
Mean repeat length increases directionally across the primate lineage, consistent with positive selection for longer repeat tracts
(refs 6, 13, 14, 22)
Humans Possess Uniquely Long & Unstable CAG Repeat Tract
Human HTT repeat length evolves to be markedly longer than in other primates and mammals (Table 1); no other species examined naturally approaches the pathogenic range
(refs 6, 13, 14, 22)
Human CAG Repeat Sits Near Pathological Threshold
Human repeats reach a range close to the pathogenic threshold (36–39 repeats: reduced penetrance | ≥40 repeats: invariably causes HD); no other species examined approaches this range naturally
(refs 5, 12, 15)
PATHWAY 1: Germline Expansion
CAG ≥40 inherited directly from a parent; repeat already exceeds pathogenic threshold at birth, making HD inevitable regardless of somatic expansion
(refs 5, 12)
PATHWAY 2: Somatic Instability
CAG repeat progressively lengthens within post-mitotic striatal neurons over a lifetime, driven by DNA mismatch repair proteins (MSH2, MSH3, MLH1) that paradoxically promote rather than prevent expansion; can push borderline alleles across the pathogenic threshold
(refs 17, 18, 19, 20)
Repeat Length Crosses Pathogenic Threshold in Striatal Neurons
Mutant huntingtin protein accumulates within vulnerable neurons, triggering toxic gain-of-function mechanisms
(refs 1, 12)
Selective Striatal Neurodegeneration → Huntington's Disease
Progressive loss of striatal neurons produces characteristic motor, cognitive, and psychiatric symptoms
(refs 1, 2, 9, 10)
No Spontaneous HD Ever Documented in Any Non-Human Species
Supporting evidence: transgenic/knock-in models that artificially introduce expanded CAG repeats into non-human systems (rhesus macaque, mouse) reproduce this same pathway, indicating the underlying mechanism is conserved — only the naturally evolved repeat length is human-specific
(refs 4, 15, 19, 20)

**Figure 3:** Proposed pathway linking the evolutionary expansion of CAG/PolyQ repeats in the human *HTT* gene to Huntington's disease. Somatic repeat expansion in vulnerable striatal neurons can cross the pathogenic threshold, leading to mutant huntingtin accumulation and selective neurodegeneration; transgenic and knock-in models support this conserved mechanism.

The findings synthesised in this review suggest that CAG repeat length in the *HTT* gene has been favoured for longer repeat lengths in certain primate species, with human repeat tracts appearing abnormally longer and more unstable than those of any other examined species, potentially reflecting positive selection for neurological or developmental benefits.[10,21,22] This evolutionary lengthening appears to have brought human CAG repeats closer to pathogenic threshold than those of any other species, with alleles of 36-39 repeats falling within a reduced-penetrance range and those of 40 or more invariably causing HD.[5] No other species examined naturally reaches this interval, and no case of spontaneous HD has been documented in any non-human species under wild or captive conditions.[3,4]

Beyond the inherited germline length, CAG repeats may undergo progressive somatic instability within post-mitotic striatal neurons over an individual's lifetime, a process driven by mismatch repair proteins including MSH2, MSH3, and MLH1, whose activity paradoxically promotes rather than prevents repeat expansion at the *HTT* locus.[17,18,19,20] This somatic expansion may drive repeat length across the pathogenic threshold even when the inherited allele falls below it, resulting in mutant huntingtin accumulation and selective striatal neurodegeneration.[1,2,9] Transgenic and knock-in models support this mechanism, demonstrating that artificially introduced expanded CAG repeats recapitulate HD neuropathology in non-human systems. The suggests that the underlying vulnerability to repeat expansion is not unique to humans; only the naturally evolved repeat length that brings human alleles close to the pathogenic threshold appears to be.[4,19,20]

## DISCUSSION

The *HTT* gene is a large gene spanning approximately 180 kilobases on chromosome 4 that encodes the huntingtin protein, a protein with over 3,144 amino acids and a molecular weight of approximately 350 kDa.[7] The huntingtin protein is ubiquitously expressed throughout the body, with particularly high expression levels in the brain and testes,[8] and is responsible for a diverse range of critical cellular processes. These include embryonic development, where HTT is essential for neurulation and gastrulation, as evidenced by the embryonic lethality observed in *HTT* knockout mouse models;[9] axonal transport, where HTT acts as a scaffolding protein facilitating the movement of vesicles and organelles along microtubules and the regulation of brain-derived neurotrophic factor (BDNF) production and transport, which is critical for the survival and maintenance of striatal neurons.[10]

The *HTT* gene is highly evolutionarily conserved across complex multicellular eukaryotes, reflecting its fundamental biological importance. Orthologues of *HTT* have been identified in organisms ranging from invertebrates such as *Drosophila melanogaster* and *Caenorhabditis elegans* to all vertebrate classes,

including fish, amphibians, reptiles, birds, and mammals.[8] However, the gene shows considerably less conservation in simpler eukaryotes such as yeast (*Saccharomyces cerevisiae*), which lack a true *HTT* homologue,[11] suggesting that many of HTT's functions could have evolved alongside the increasing complexity of multicellular nervous systems.

Although the *HTT* gene is evolutionarily conserved across vertebrate taxa, Huntington's disease is a fundamentally human-specific condition. A critical distinction lies in the length and stability of the CAG trinucleotide repeat tract within exon 1 of the *HTT* gene. In healthy humans, CAG repeat lengths typically range from 10-35 repeats, with alleles exceeding 40 repeats invariably causing HD.[12] In contrast, non-human primates and other mammals harbour significantly shorter and more constrained CAG repeat tracts. Chimpanzees (*Pan troglodytes*), our closest living relatives, sharing approximately 98.7% genomic identity with humans,[13] possess CAG repeat lengths ranging from approximately 14–20 repeats.[6] Similarly, Ma's Night Monkey (*Aotus nancymaae*) exhibits average repeat lengths of approximately 11, Sumatran orangutans (*Pongo abelii*) exhibit average repeat lengths of approximately 10, and more distantly related species such as rats (*Rattus norvegicus*) carry tracts of approximately 8 repeats, while mice (*Mus musculus*) and grey mouse lemurs (*Microcebus murinus*) carry considerably shorter tracts of approximately 7 repeats (Table 1).[14] Across all non-human species examined to date, CAG repeat lengths within the *HTT* gene appear to be both shorter and more evolutionarily stable than those observed in humans, suggesting that the human *HTT* locus occupies a uniquely precarious position at or near the threshold of pathological instability.

| **Common Name** | **Species Name** | **PolyQ Repeats** | **UniProt ID** |
|---|---|---|---|
| Human | *Homo sapiens* | 21 | P42858 |
| Olive baboon | *Papio anubis* | 13 | A0A096ML42 |
| Golden snub-nosed monkey | *Rhinopithecus roxellana* | 11 | A0A2K6QU14 |
| Ma's Night Monkey | *Aotus nancymaae* | 11 | A0A2K5E1N6 |
| Chimpanzee | *Pan troglodytes* | 11 | A0A2I3RLD9 |
| Green Monkey | *Chlorocebus sabaeus* | 10 | A0A0D9RTK1 |
| Sumatran orangutan | *Pongo abelii* | 10 | H2PCR6 |
| Rat | *Rattus norvegicus* | 8 | P51111 |
| Mouse | *Mus musculus* | 7 | P42859 |
| Grey Mouse Lemur | *Microcebus murinus* | 7 | A0A8B7EEX2 |

**Table 1:** Polyglutamine (PolyQ) repeat lengths for the huntingtin (HTT) protein across 10 representative mammalian species. The table includes the common name, species name, PolyQ repeat length, and UniProt accession ID for each species and is ordered by descending PolyQ repeat length.

Despite the widespread presence of the *HTT* gene across vertebrates, no naturally occurring case of Huntington's disease has ever been documented in any non-human species under wild or captive conditions.[15] The absence of spontaneous HD in these species suggests that the pathological CAG repeat expansions characteristic of human HD do not arise naturally in non-human populations, and that even if such expansions were artificially introduced, additional human-specific biological factors may be required for full disease manifestation.[16]

One mechanism that may underlie the human-specific propensity for HD is somatic instability of the CAG repeat tract, specifically the progressive, tissue-specific expansion of repeat length that occurs in post-mitotic neurons over the course of an individual's lifetime.[17] In humans, somatic expansion is particularly pronounced in the striatum, the brain region most affected in HD, where repeat lengths can increase by dozens of units beyond the inherited germline length. This somatic expansion is thought to accelerate neurodegeneration by driving repeat lengths further into pathological ranges within vulnerable neurons.[18] Comparative studies suggest that somatic instability of this magnitude is either absent or greatly attenuated in non-human primates and rodents, potentially due to differences in DNA mismatch repair (MMR) activity, base excision repair (BER) pathway efficiency, and the chromatin environment surrounding the *HTT* repeat. In particular, human-specific variants or expression levels of MMR proteins such as MSH2, MSH3, and MLH1, which paradoxically promote rather than prevent repeat expansion, may contribute disproportionately to somatic instability in the human brain.[19] MSH3, in particular, has been identified as a key driver of CAG repeat expansion in human striatal neurons, with genome-wide association studies in HD patients linking MSH3 polymorphisms to earlier age of onset.[20] This suggests that the human MMR machinery has evolved or diverged in a manner that renders it uniquely permissive to repeat expansion at the HTT locus, a property that may not be shared to the same degree in non-human primates or rodents.

From an evolutionary perspective, it has been proposed that the gradual lengthening of the CAG repeat tract in the human *HTT* lineage may have been positively selected because of beneficial effects on neuronal development, cognitive function, or BDNF signalling, inadvertently pushing human repeat lengths closer to the instability threshold.[21] Comparative genomic analyses suggest that mean CAG repeat lengths in the HTT gene have increased progressively across the primate lineage from New World monkeys to Old World monkeys, apes, and finally humans,[22] consistent with a directional evolutionary trend towards longer repeats in the human lineage. This evolutionary lengthening, while potentially conferring selective advantages in the context of brain development, may have simultaneously created a latent vulnerability to pathological repeat expansion that is unique to *Homo sapiens*.

This review is subject to several limitations. The comparative genomic literature on *HTT* biology in non-human species remains sparse, meaning that some conclusions are necessarily inferential rather than

directly supported by empirical evidence. The species-level CAG repeat data summarised here are derived from studies with relatively limited sample sizes, and broader surveys across a wider range of primate taxa would strengthen the evolutionary trends described. Furthermore, although a systematic literature search and study selection process were employed, this review remains subject to potential publication and selection bias inherent in the available literature. Consequently, the conclusions drawn are dependent on the quality and availability of existing studies.

Future research should prioritise comparative studies of MMR protein expression and activity, particularly that of MSH3, across human and non-human primate brain tissues to determine whether differences in DNA repair machinery are sufficient to account for the disparity in somatic instability observed between species. Comparative analyses of the chromatin environment surrounding the *HTT* CAG repeat across multiple species would further clarify whether differences in repeat accessibility contribute to expansion rates. Longitudinal studies investigating somatic mosaicism in non-human primates with experimentally lengthened *HTT* CAG repeat tracts could also provide valuable mechanistic insight. Finally, determining whether the proposed cognitive or developmental advantages associated with longer CAG repeat tracts in humans can be functionally validated would strengthen the evolutionary hypothesis presented in this review.

## CONCLUSION

This review explores potential reasons why Huntington's disease remains a condition that occurs almost exclusively in humans despite the widespread conservation of the *HTT* gene across vertebrates. The observation that CAG repeat lengths in the *HTT* gene have increased progressively across the primate lineage, culminating in the longest and most unstable CAG repeat tracts in Homo sapiens, suggests that human neurological evolution may have come at a biological cost. Furthermore, evidence that somatic instability is influenced by DNA mismatch repair proteins such as MSH3, MSH2, and MLH1 provides a possible explanation for why repeat expansion is not simply a consequence of inheriting a long CAG repeat, but also an ongoing, tissue-specific process that may accelerate neurodegeneration over an individual's lifetime. Collectively, the evidence synthesised in this review provides an evolutionary and molecular framework for understanding why Huntington's disease appears to be uniquely human and highlights promising directions for future research into the mechanisms underlying disease susceptibility and progression.

Comparative *HTT* gene structure and CAG repeat dynamics across species were examined, revealing a general trend toward longer CAG repeat tracts in humans relative to non-human primates and rodent model organisms. The potential mechanisms underlying human-specific somatic instability, including differences in mismatch repair (MMR) pathway activity and the chromatin environment surrounding the *HTT* locus, were explored, and the evolutionary trajectory of *HTT* repeat lengthening in the human lineage was evaluated as a possible contributor to human susceptibility to Huntington's disease. Where the objectives were only partially fulfilled, this primarily reflects limitations in the existing literature

rather than deficiencies in the analytical framework. In particular, the molecular mechanisms by which somatic expansion is attenuated in non-human primates remain incompletely characterized, and comparative data on MMR protein activity across species remain limited.

Huntington's disease serves as a reminder that the biological processes underlying human brain development may also carry an inherent vulnerability. Understanding why *Homo sapiens* alone bears the burden of this disease is not merely an exercise in academic inquiry; it provides an opportunity to examine the evolutionary trade-offs that shaped the human brain and lays a foundation for developing therapeutic strategies that are as specific to human biology as the disease itself.

## ACKNOWLEDGMENTS

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