

How is the HTT mutation expressed differently in primate species as compared to Homo sapiens?

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Abstract: This lab explores the evolutionary history of the HTT (huntingtin) gene using the Basic Local Alignment Search Tool (BLAST) which allows for comparing DNA sequences present in different species. The HTT gene provides instructions for creating the huntingtin protein, which is crucial for normal brain function. A mutation in this gene is the cause of Huntington's disease. The DNA sequence comparison will also show the effects of certain mutations in the HTT gene on organisms in similar or different ways. A cladogram and other visuals will be included as evidence to support the conclusion.

Keywords: Genetic disorder; Mutations; Biological organisms

1. Introduction

The HTT gene produces the huntingtin protein, which is essential for normal neural development and function. This gene is located on chromosome 4. Huntingtin plays a critical role in intracellular transport, signaling, and cell survival, particularly in neurons. Its function is crucial for maintaining healthy brain activity since neural communication is a key evolutionary advantage that enables complex sensory processing and cognitive abilities. Under normal conditions, the HTT gene interacts with various cellular components to regulate processes such as gene expression and vesicle trafficking or movements.

Mutations in the HTT gene, particularly the CAG trinucleotide expansion, causes Huntington's disease, which is a neurodegenerative disorder that has symptoms ranging from progressive motor dysfunction to cognitive decline. The mutant huntingtin protein produced may cause neuronal damage and even cell death.

This study will compare HTT gene sequences across various primate species to identify those with the closest genetic similarity to humans. The goal is to better understand the evolutionary relationships and conservations of the HTT gene by exploring variations among different primate species.

2. Procedure

Using the National Library of Medicine's database, the mRNA nucleotide sequence of Homo Sapiens HTT gene was found using the FASTA function. After this research was completed, the mRNA sequence was then copied into the Basic Local Alignment Search Tool (BLAST). BLAST was then proceeded to be used to find other species' HTT gene that had similarities with the Homo sapiens HTT gene. The percentage similarity between Homo sapiens and other primate species is illustrated in Table 1 and Figure 2. Figure 2, which is a cladogram, is helpful in visualizing the evolutionary history of the HTT gene, which could aim towards answering the question, "how is the HTT mutation expressed differently in primate species as compared to Homo sapiens?"

Table 1: Table of the common name, scientific name, order, and percent identity for the HTT gene of an organism as found in NCBI's BLAST.

Common Name	Scientific Name	Order	Percent Identity
Human	<i>Homo sapien</i>	Primate	100.00%
Western lowland gorilla	<i>Gorilla gorilla gorilla</i>	Primate	99.26%
Chimpanzee	<i>Pan troglodytes</i>	Primate	98.96%
Bonobo	<i>Pan paniscus</i>	Primate	98.66%
Bornean orangutan	<i>Pongo pygmaeus</i>	Primate	98.33%
Sumatran orangutan	<i>Pongo abelii</i>	Primate	98.07%
Tibetan macaque	<i>Macaca thibetana</i>	Primate	96.27%
Common marmoset	<i>Callithrix jacchus</i>	Primate	94.68%

Figure 2: Cladogram illustrating the evolutionary history of the HTT gene according to their percent identity of different primate species with the *Homo sapiens* HTT gene given by NCBI's BLAST.

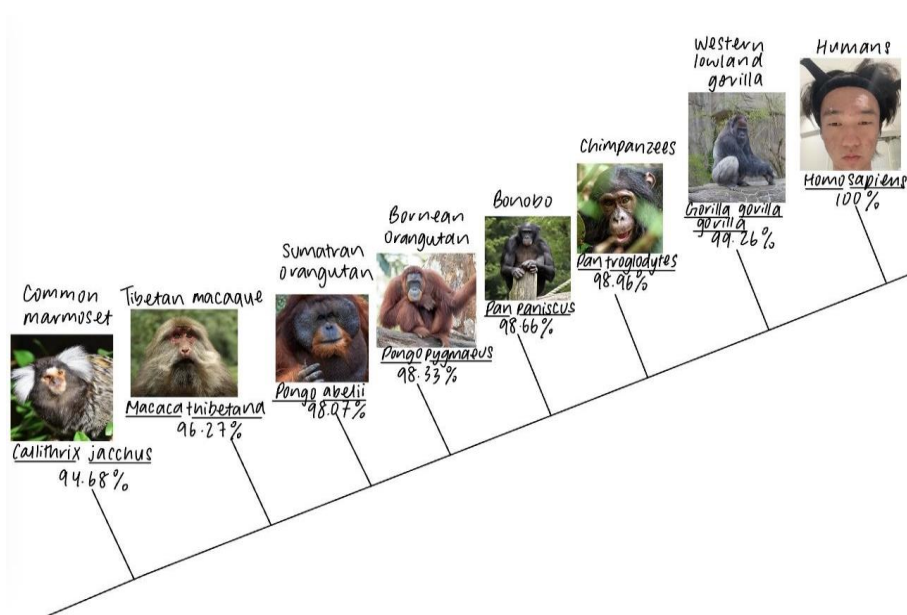


Figure 3: The development of nerve cells under normal vs. mutated HTT gene.

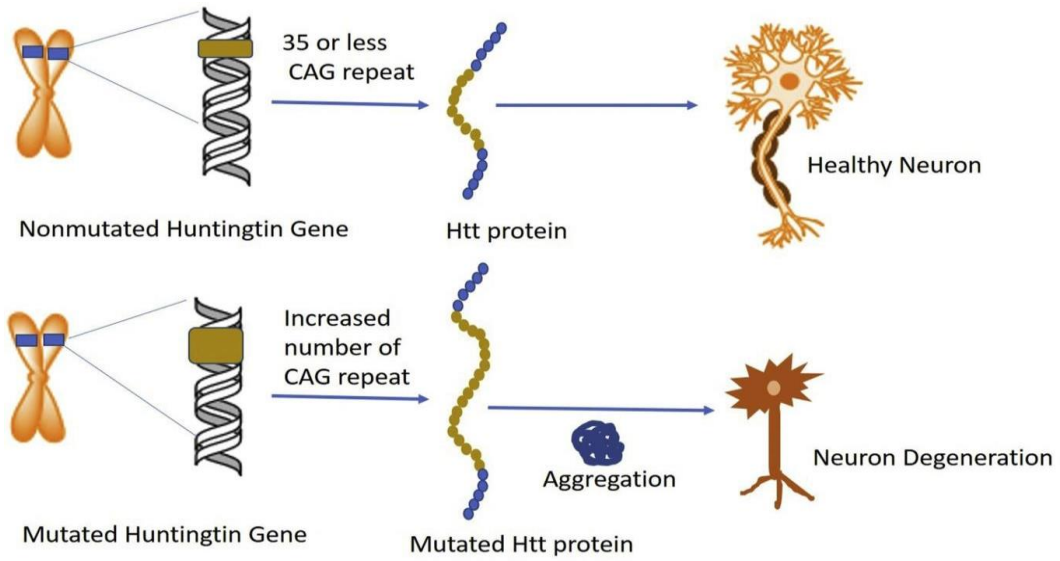


Figure 4: Location of the HTT gene on chromosome 4.

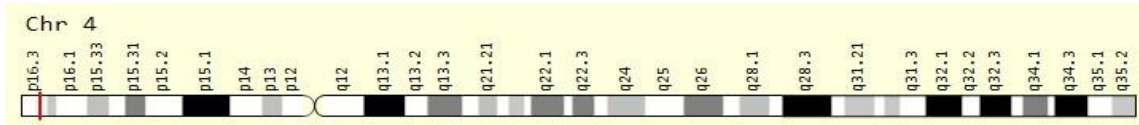


Figure 5: Bar graph depicting the percent similarity of primate species' HTT gene to Homo sapiens.

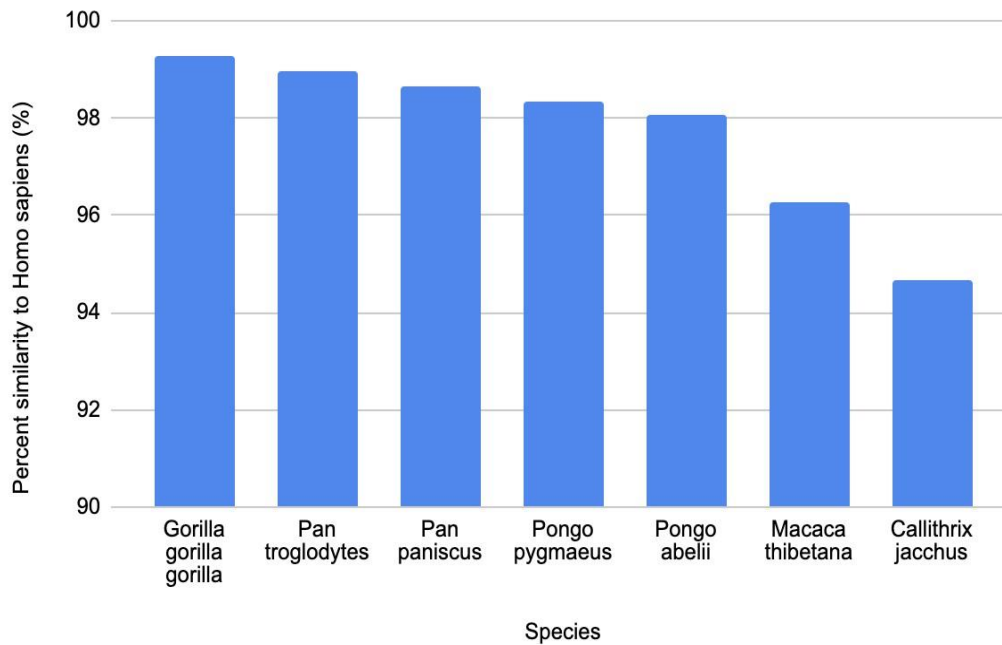


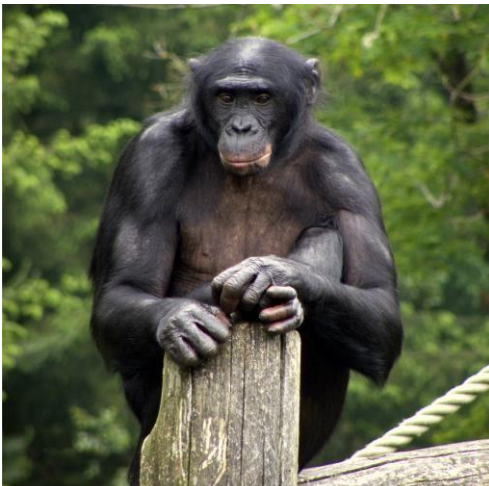
Figure 6: Gorilla gorilla gorilla
(https://en.wikipedia.org/wiki/Western_lowland_gorilla)



Figure 7: Pan troglodytes
(<https://www.britannica.com/animal/chimpanzee>)



Figure 8: Pan paniscus
(<https://en.wikipedia.org/wiki/Bonobo>)



3. Discussion

3.1 What is the function of the HTT protein produced from the HTT gene in humans and other primates?

The HTT protein, produced from the HTT gene on chromosome 4 (Fig. 4), is essential for normal development and is highly active in the brain. It functions in neurons by participating in chemical signaling, transporting materials within the cells, protecting the cell from apoptosis (programmed cell death), and binding to other proteins and structures. The healthy HTT protein also plays a key role in axonal transport (the process where motor proteins actively move various organelles and vesicles along the axons of nerve cells) by interacting with motor proteins to facilitate vesicle and organelle trafficking. Additionally, it supports gene regulation and selective autophagy, helping to maintain neuronal health and survival.

3.2 What effects does a mutated HTT gene have on humans and other primates?

A mutated HTT gene, characterized by an abnormally expanded CAG repeat, produces a mutant huntingtin protein that disrupts the normal neurodevelopment which leads to the Huntington's disease (HD) in humans and other primate species. This mutation causes progressive neurodegeneration, causing a progressive loss of nerve cells particularly in the striatum, resulting in motor dysfunction (involuntary, jerky movements and muscle spasms), cognitive decline (memory problems, difficulty with executive functions, and impaired attention), and psychiatric symptoms (depression, anxiety, and irritability). In primate species, the effect of HD is more pronounced due to their closer genetic similarity to humans than any other biological orders. Specifically, mutant HTT gene induces severe neurological phenotypes such as dystonia and chorea, which closely resemble human HD symptoms. The mutant protein also impairs cellular processes such as the neurometabolic function and protein degradation, contributing to neuronal vulnerability and even death, as shown in Figure 3.

3.3 Which primate species share a high degree of similarity with *Homo sapiens'* HTT gene? What can be concluded about the evolutionary relationship between these organisms?

According to NCBI BLAST's results demonstrated in Table 1 and the resulting bar graph depicted in Figure 5, only different primate species were given to have a high degree of similarity with the *Homo sapiens* HTT gene. The primate species presented in the cladogram in Figure 2 uses data from Table 1 to show 7 primate species that share over 90% identity with the human HTT gene, which reflects how closely these species are related to each other genetically. The species closer to *Homo sapiens* in the cladogram (Fig. 2), such as *Gorilla gorilla gorilla*, have a higher percent identity than species further away from *Homo sapiens*, such as *Callithrix jacchus*. Compared to *Gorilla gorilla gorilla's* percent identity of 99.26%, *Callithrix jacchus* only have a percent identity of 94.68%, which is significantly lower than that of *Gorilla gorilla gorilla* (Fig. 5).

Although Huntington's disease (HD) naturally only occurs in humans, researchers have developed animal models of the disease in several other groups, such as large mammals and invertebrates, to study its mechanisms and potential treatments. However, HD is still more prevalent in other primate species and humans due to a combination of factors related to their similar brain structures, shared evolutionary history, and the nature of the genetic mutation causing this disease, which is the evolutionary expansion of CAG repeats. Moreover, in humans and other primate species, the brain regions affected by HD, like the striatum, have similar structures and functions, making them more susceptible to the effects of the mutant Huntingtin protein. Thus, the mutational bias toward longer CAG repeats and similarity in brain structures is especially pronounced in humans and other primate species, explaining the higher prevalence of HD in these groups without requiring natural selection to account for it.

3.4 Do other species with the mutated HTT gene experience Huntington's disease symptoms?

Huntington's disease (HD) symptoms generally develop between ages 30 to 50 in humans and progress slowly over several years. Early symptoms typically include difficulty concentrating, memory problems, mood changes (depression, anxiety, and irritability), and small involuntary movements such as jerking or twitching known as chorea. Furthermore, people may exhibit clumsiness and have trouble with organization. As the disease advances, symptoms may worsen to include muscle stiffness, slower movements, difficulty speaking, weight loss, and more severe mood changes. In late stages, individuals often lose the ability to walk, talk, care for themselves, and cognitive decline could lead to dementia.

Considering that the primate species listed in Table 1 have a high degree of HTT gene similarity to *Homo sapiens*, including *Gorilla gorilla gorilla* (Figure. 6), *Pan troglodytes* (Figure. 7), and *Pan paniscus* (Figure. 8), it is thus reasonable to conclude that they do experience similar Huntington's disease symptoms such as motor impairments. However, there are limited research and documentation of Huntington's disease symptoms of *Gorilla gorilla gorilla*, *Pan troglodytes*, and *Pan paniscus*, but the symptoms of transgenic primate species that are created by scientists through genetic modification have been under study. Transgenic primate species such as the Rhesus macaques exhibit many parallels such as motor impairments, mood changes, and cognitive decline. Neuropathologically, affected primates show brain atrophy, particularly in the striatum, like human patients. Unlike rodent models, primate species display a more complete spectrum of HD symptoms, making them closer analogues for studying disease progression and testing therapies. Nonetheless, some subtle differences remain, and no animal model can perfectly replicate the full human HD phenotype.

4. Conclusion:

This study employs the Basic Local Alignment Search Tool (BLAST) to elucidate the evolutionary history of the huntingtin (HTT) gene through cross-species DNA sequence comparison. The HTT gene encodes the huntingtin protein, which is vital for normal brain function, and mutations within it are implicated in Huntington's disease. Analyzing sequence alignments will illustrate the phenotypic consequences of specific HTT mutations across different organisms. The conclusions drawn will be supported by evidence including a cladogram and supplementary graphical representations.

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