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Huntington's disease

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Abstract

Huntington's disease (HD) is the most common inherited neurodegenerative disorder, clinically characterized by a triad of abnormalities: uncontrollable hyperkinesia (chorea), progressive cognitive decline, and emotional disturbances. The molecular basis for its pathogenesis is a mutation in the HTT gene, resulting in an abnormal expansion of the polyglutamine (polyQ) tract within the huntingtin (Htt) protein. This mutation imparts one or more toxic functions to the mutant Htt, which initiate a cascade of pathological processes culminating in selective neurodegeneration.

A critical link in the pathogenesis is that the polyQ expansion makes the Htt protein susceptible to misfolding and aggregation. Experimental data suggest that strategies aimed at mitigating the consequences of protein misfolding or facilitating the removal of aggregated forms can slow disease progression in HD models. In this article, HD is considered a classic conformational disease in which inherited polyglutamine mutations trigger a proteotoxic cascade. The accumulation of abnormal Htt overloads the cellular chaperone and proteostasis network, causing other metastable proteins to also adopt abnormal conformations. The resulting complex phenotype, caused not only by the toxicity of the mutant protein but also by the secondary loss of function of critical proteins, underlies the mechanisms leading to neurodegeneration.

Background

Genetic factors that determine the onset of symptoms and disease progression.

With the discovery of *HTT*, the clinical features of HD could be better defined by investigating genotype-phenotype relationships with greater specificity. A major focus of these early studies was on understanding the relationship between the age when an individual first develops neurological symptoms and the length of the triplet repeat[1,2,3]. Alleles of *HTT* with fewer than 35 CAGs were found to pose no risk for causing HD. Individuals harboring alleles with between 36–40 CAGs may or may not develop HD symptoms; those that do tend to become symptomatic late in life. However, those with alleles containing expansions greater than 40 CAGs repeats will eventually develop symptoms of HD if they live long enough. Curiously, individuals who harbor two HD-causing alleles (i.e., homozygous for mutant *HTT*) appear to develop symptoms about the same age as people with a single allele and the same CAG expansion. However, homozygosity for the CAG mutation has been reported to lead to a more severe clinical course[4].

Interestingly, there is a striking and significant negative relationship between the length of the CAG expansion and the age of symptom onset; the longer the CAG stretch, the earlier symptoms typically appear . The most common HD alleles contain 40–50 polyQ. In that range, 50–70% of age of symptom onset appears to be explained by the length of the polyQ stretch, the remainder is determined by other modifying genes and environmental influences[5]. At longer polyQ stretches, an even greater proportion of age of symptom onset is explained by the

length of the polyQ stretch. Length of the polyQ stretch also appears to influence the progression of pathology, although the link between disease progression and the length of the polyQ stretch appears to be weaker than for age of symptom onset [6,7].

The ability to correlate the length of the CAG expansion with the clinical phenotype has revealed the molecular basis of genetic anticipation [8,9]. Anticipation in Huntington's disease refers to the enigmatic phenomenon in which inheritance of the mutant HTT allele through the male germline often results in a more severe clinical course than inheritance through the female germline. On average, children with Huntington's disease developed symptoms 8 years earlier than their fathers [10].

The length of the CAG sequence also influences the types of symptoms. The most common Huntington's disease alleles (40–50 CAGs) typically cause classic symptoms that appear in middle age. The most prominent symptoms are excessive, uncontrollable jerky movements called chorea and gait disturbances. Some patients experience dystonia, an increase in muscle tone. Neuropsychiatric symptoms are common, particularly depression and anxiety. Some patients report obsessive-compulsive symptoms and cognitive impairment. Executive function deficits appear early, and global dementia often develops. Unusually long CAG sequences (>50) manifest with such a wide range of symptoms that the syndrome is called juvenile Huntington's disease (JHD), reflecting the earlier onset of the disease.[11]

Having established that CAG repeat expansion is the cause of Huntington's disease, researchers turned to studying the mechanism by which it causes neurodegeneration. The first question was whether neurodegeneration caused by CAG repeat expansion occurs at the level of the nucleic acids they contain (DNA and mRNA) or through the polyglutamine expansion they encode in the HTT protein[12].

CAG expansions can mediate neurodegeneration through abnormal polyglutamine expansions. Recently, an inducible transgenic mouse model of Huntington's disease was created with the first exon of the HTT gene (HTT ex1) containing a CAG expansion. In this model, induction of HTT ex1 resulted in behavioral and pathological abnormalities, which could be reversed by removing the inducing agent and allowing HTT ex1 levels to decrease[13]. This result rules out a DNA-based mechanism of neurodegeneration. Perhaps the most compelling result was obtained serendipitously several years earlier. Hayden and colleagues created a transgenic mouse that constitutively expressed a human transcript encoding the human Huntington's disease gene.[14] However, an unintended stop codon resulted in the HTT transcript producing no protein. The animal showed no signs of the disease-associated phenotype, suggesting that CAG expansion at the DNA or mRNA level was insufficient to cause neurodegeneration.[12]

Other researchers created a transgenic mouse constitutively expressing the human Huntington's disease gene but replaced the pure CAG repeat with a mixture of CAG and CAA codons encoding glutamine.[15] This mixture did not affect the HTT protein; the polyglutamine region was identical to the region encoded by the pure CAG repeat. However, the length of the CAG repeat was less likely to change during breeding. This mouse, expressing HTT with a polyglutamine repeat but lacking a pure CAG repeat, exhibited behavioral and pathological features of neurodegeneration reminiscent of Huntington's disease. The mixture of CAA and CAG codons is important for another reason as well. mRNAs containing pure triplet repeats form double-stranded hairpins stabilized by intrastrand base pairing. The use of alternating CAA and CAG codons disrupts hairpin formation. Because hairpin RNA formation has been proposed as a mechanism of toxicity mediated by triplet repeats contained in mRNA, the persistence of the phenotype despite manipulation aimed at reducing mRNA hairpin formation is consistent with the conclusion that neurodegeneration mediated by CAG expansions results predominantly from the production of polyglutamine-containing proteins rather than from mRNA-mediated effects. These results strongly suggest proteotoxicity, but some mRNA-mediated toxicity cannot be excluded [16].

Conclusion

Analysis of the genetic factors determining the onset and progression of Huntington's disease (HD) convincingly demonstrates that the length of the CAG repeat in the *HTT* gene is a central determinant of the clinical phenotype, but not the only one. It has been established that alleles with fewer than 36 repeats carry no risk of developing the disease, while expansions of more than 40 repeats exhibit full penetrance. A key finding is the inverse correlation between the length of the polyglutamine (polyQ) tract and the age of onset: the longer the CAG block, the earlier the onset of symptoms. Moreover, the genetic effect is most pronounced for the age of disease onset, while the influence on the rate of disease progression is less clear and is likely modulated to a greater extent by other factors.

An important clinical consequence of repeat length variability is the phenomenon of genetic anticipation, mediated by CAG repeat instability during transmission through the male germline. Furthermore, the length of the CAG block determines not only the time of onset but also the spectrum of symptoms: from classic chorea with moderate expansion sizes (40–50 CAGs) to a severe juvenile phenotype with a wide range of motor, cognitive, and mental disorders with ultra-long repeats (>50 CAGs).

A crucial step in understanding the pathogenesis was elucidating the mechanism by which CAG expansion causes neurodegeneration. Results from experiments in transgenic models, including models with inducible expression and with replacement of pure CAG repeats with mixed CAG/CAA codons, allowed us to draw several fundamental conclusions. First, the reversibility of the phenotype upon cessation of mutant protein expression rules out irreversible changes at the DNA level as the primary mechanism. Second, the persistence of neurodegenerative manifestations in mice expressing a protein with a polyQ tract but lacking a pure CAG repeat in mRNA (and, therefore, the ability to form toxic hairpins) supports protein toxicity as the primary pathogenic mechanism.

Thus, the combined data presented allow us to conclude that Huntington's disease is a classic conformational disorder in which the primary trigger of neurodegeneration is toxicity from

the mutant huntingtin protein with an abnormally expanded polyglutamine tract. Although the contribution of mRNA-mediated effects cannot be completely excluded, the main directions of pathogenesis—from the genetic determination of clinical heterogeneity to the implementation of the proteotoxic cascade—convincingly demonstrate that the central link in the development of the disease is a violation of proteostasis caused by the expansion of the CAG repeat at the protein level.

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