Are neuronal intranuclear inclusions the common neuropathology of triplet-repeat disorders with polyglutamine-repeat expansions?

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Neuronal intranuclear inclusions have been found in the brain of a transgenic mouse model of Huntington’s disease and in necropsy brain tissue of patients with Huntington’s disease. We suggest that neuronal intranuclear inclusions are the common neuropathology for all inherited diseases caused by expansion of polyglutamine repeats. We also suggest that patients with a pathological diagnosis of neuronal intranuclear hyaline inclusion disease may also have polyglutamine repeat expansions.

The onset of neurological signs in a transgenic animal model of Huntington's disease is preceded by the appearance of huntingtin protein in neuronal nuclei. The protein is identified by electron microscopy as a characteristic neuronal intracellular inclusion (NII). We have found these structures in neuronal nuclei in the cerebral cortex and caudate or putamen of necropsy brain tissue from patients with Huntington’s disease, and believe that disruption of the neuronal nucleus by NIs may be the pathogenic mechanism in seven other neurodegenerative diseases caused by expansion of polyglutamine repeats.

Previous reports have identified patients with a wide range of neurological symptoms accompanied by a neuropathological diagnosis of neuronal intranuclear hyaline inclusion disease, established by the presence of NIs, identical in ultrastructural appearance to those we have seen in Huntington’s disease. We suggest that many of these patients may have inherited disease due to polyglutamine repeat expansion.

Inherited neurodegenerative disorders caused by polyglutamine-tract expansion

Molecular genetic studies have identified eight neurodegenerative diseases caused by inheritance of the expanded trinucleotide repeat, CAG: Huntington’s disease;1–3 dentatorubropallido-Luysian atrophy;2,3 spinobulbar muscular atrophy or Kennedy’s disease;4–6 spinocerebellar ataxia type 1,7–9 type 2,10,11 type 3 (or Machado Joseph disease),11 type 6,12 and now type 7.13

In each case the expansion of a CAG-repeat sequence in DNA results in the translation of an extended glutamine sequence within the corresponding protein. With the exception of spinobulbar muscular atrophy (androgen receptor) and spinocerebellar ataxia type 6 (alpha subunit of a Purkinje-cell-specific calcium channel), the proteins are of ubiquitous expression and of unknown function. They have been named huntingtin (dentatorubropallido-Luysian atrophy), atrophin (Huntington’s disease), and ataxins 1–7 (spinocerebellar ataxia types 1–7). Each disease is characterised by a unique pattern or neuron death within the central nervous system. However, the juvenile forms of these diseases, characterised by inheritance of large polyglutamine expansions, are invariably accompanied by a more extensive neuropathology than the adult-onset forms.14 For example, juvenile-onset Huntington’s disease is frequently accompanied by loss of cerebellar...
Neuronal intranuclear inclusions in transgenic mice

Transgenic mice expressing exon 1 of the human Huntington’s-disease gene containing an expanded CAG repeat derived from a patient with juvenile-onset Huntington’s disease develop many of the clinical features characteristic of this disease. Within the brains of these transgenic mice, before the onset of neurological signs, the transgene protein containing an expanded polyglutamine repeat appears in the nucleus and forms a characteristic intranuclear inclusion (figure). The presence of this inclusion leads to morphological changes within the nucleus. The nuclear membrane develops prominent invaginations accompanied by an apparent increase in the density of nuclear pores. The NII is additionally strongly immunoreactive with antibodies to ubiquitin. These observations in transgenic mice prompted us to analyse the distribution of huntingtin protein within the brains of patients with Huntington’s disease. Antibodies that recognise the N-terminal of huntingtin immunolabel NIIIs, whereas antibodies to C-terminal portions of the protein do not. Antibodies to ubiquitin also recognise NIIIs. Similar structures have occasionally been seen in necropsy or biopsy samples of cerebral cortex or caudate nucleus from patients with Huntington’s disease, although their relevance to the mechanism of the disease was not appreciated. Intranuclear inclusions containing a protein with an expanded polyglutamine repeat have been seen in the brains of patients with spinocerebellar ataxia type 3, dentatorubropallidoluysian atrophy (M Becher and C A Ross personal communication), as well as in Purkinje cells in the cerebellum of patients with spinocerebellar ataxia type 1 and mice transgenic for this mutation, which suggests that neuronal dysfunction is due to the mutant protein within the nucleus. Schrezing and colleagues showed that the expansion of a polyglutamine sequence within a truncated huntingtin protein leads to in-vitro and in-vivo formation of fibrils with a β-pleated sheet (amyloid-like) structures that are insoluble. The insolubility of the mutated protein seems to be enhanced by cleavage of an n-terminal fragment containing the polyglutamine sequence. Antibodies that recognise this n-terminal fragment immunolabel NIIIs in the brains of patients with Huntington’s disease, whereas antibodies directed to more central sequences in the protein do not. It remains to be established if the mutant proteins involved in the other triplet-repeat expansion diseases similarly form amyloid-like insoluble nuclear fibrils.

Neuronal intranuclear hyaline inclusion disease

Neuropathological investigations over the past 35 years have identified 30 patients with neuronal intranuclear hyaline inclusion disease (full details of all published papers are available from the authors on request) who during their lives had various neurological disorders, notably ataxia, chorea, rigidity, and dyskinesia—similar to those seen in juvenile-onset or adult-onset spinocerebellar ataxies, dentatorubropallidoluysian atrophy, and Huntington’s disease. The NIIs in the brains of these cases are identical in ultrastructural appearance to those seen in transgenic mice with Huntington’s disease and in cases of Huntington’s disease and spinocerebellar ataxia type 3. Many of these reports describe cases of neuronal intranuclear hyaline inclusion disease with juvenile onset, although several are of mid-life onset and some have a clear familiar incidence. The molecular basis for the neuropathological changes reported is not understood. We suggest that these patients may have inherited a disease due to expansion of a polyglutamine repeat. This mutation may be within one of the already identified genes with CAG-repeat expansion or may be a new mutation. Molecular methods can be readily used to investigate these possibilities.

Hypothesis

Several proteins (huntingtin, atrophin, androgen receptor, and ataxins), as a result of an increase in size of their intrinsic polyglutamine sequences, are transported into the nucleus of neurons where they accumulate as insoluble amyloid-like fibrils that form NIIs. These NIIs may be the neuropathological basis for all inherited polyglutamine-repeat expansion disorders. The neuropathological diagnosis of neuronal intranuclear hyaline inclusion disease in many patients with progressive neurodegenerative disease may also be related to the inheritance of an expanded polyglutamine repeat.

Testing the hypothesis

The hypothesis can be tested by investigation of the molecular, genetic, and neuropathological characteristics of transgenic mouse models, patients with polyglutamine-repeat expansion disease, and with neuronal intranuclear hyaline inclusion disease. We thank A B Young, A R Lieberman, and M Goedert for their helpful comments.

References


HYPOTHESIS