

Huntington disease

A molecular-to-morphology approach

Molecular genetics • neuropathology • clinicopathologic correlation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

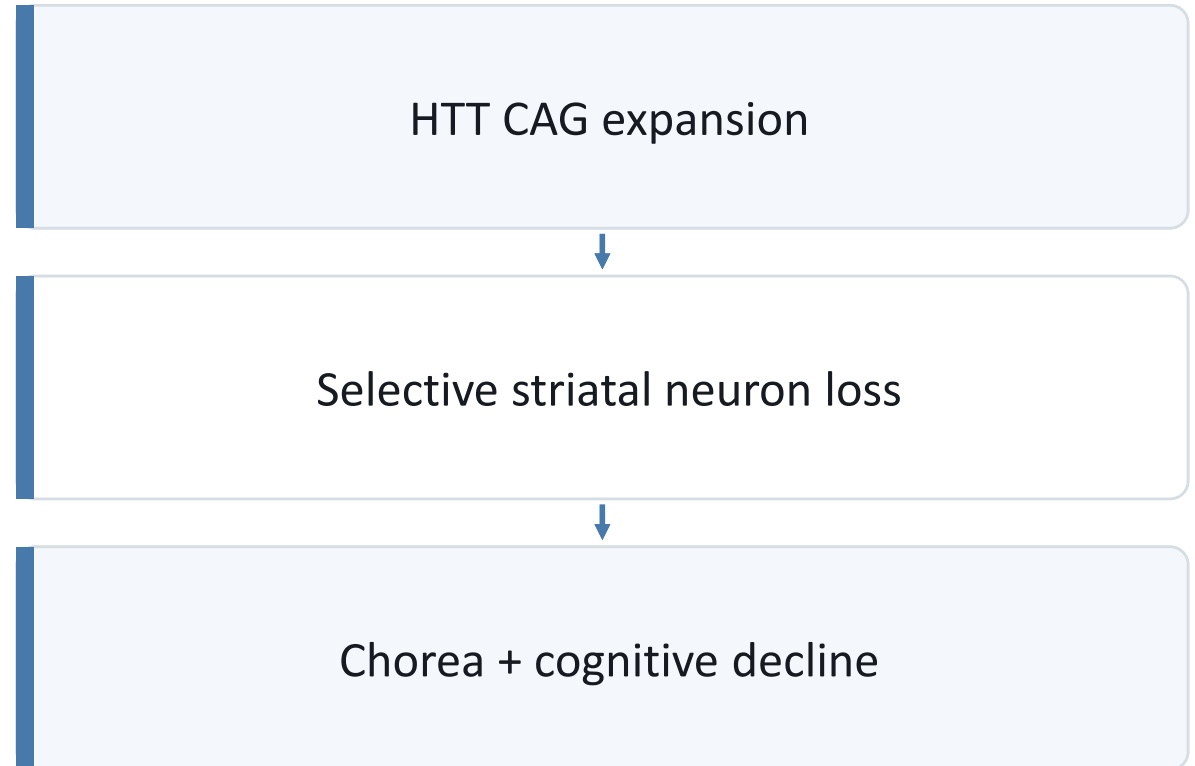
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Learning objectives

- Trace the HTT CAG expansion from inheritance to neuronal dysfunction.
- Recognize characteristic striatal atrophy and microscopic degeneration.
- Connect movement, cognitive and affective manifestations to pathology.
- Explain the implications and limitations of predictive genetic testing.

The defining clinicopathologic syndrome

- Autosomal dominant neurodegeneration, most conspicuous in the striatum.
- A progressive movement disorder accompanied by cognitive decline.
- Chorea is characteristic, but later motor impairment can become hypokinetic.



Three connected dimensions of disease

Gene

HTT CAG-repeat expansion

Tissue

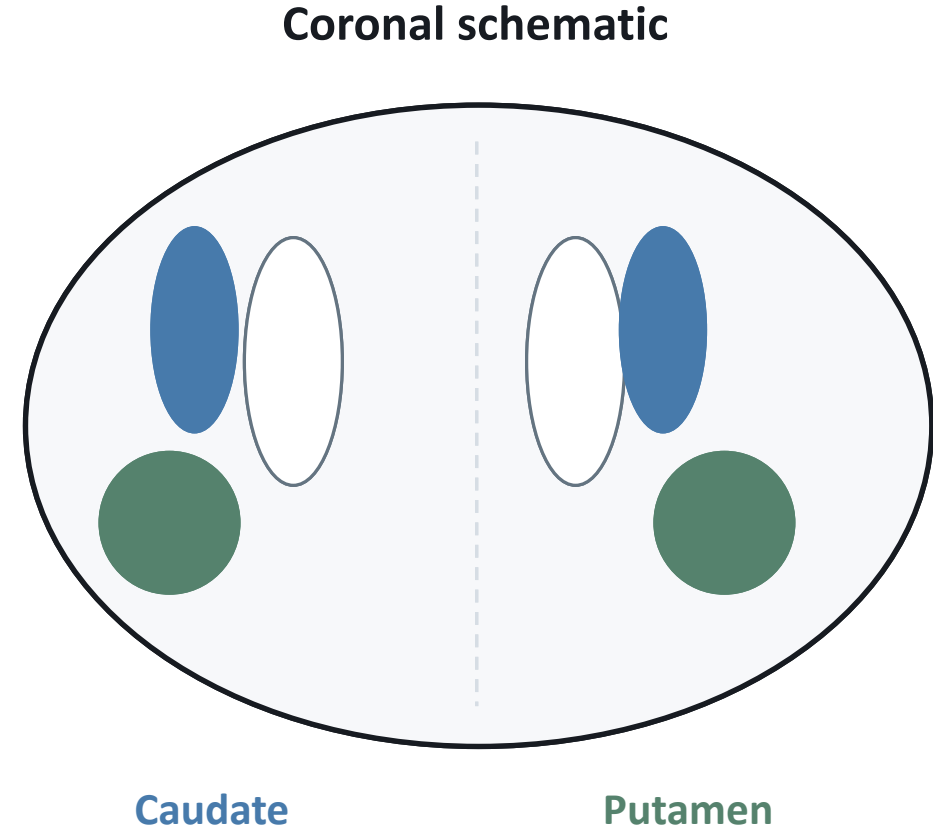
Caudate and putamen
degeneration

Phenotype

Motor, cognitive and
affective deterioration

The striatum is the primary anatomic target

- Caudate nucleus and putamen constitute the dorsal striatum.
- Profound neuronal loss particularly involves the caudate.
- Involvement of frontal cortex provides an additional correlate of cognitive change.



Schematic (not a specimen)

Striatal dysfunction explains hyperkinesia

- Striatal neurons normally help restrain motor output.
- Their loss reduces this inhibitory influence.
- The clinical consequence is increased, involuntary movement.

Medium spiny neuron loss



Reduced motor suppression



Excess involuntary movement

The motor phenotype evolves over time

- Early movement is typically jerky, hyperkinetic and choreiform.
- Writhing or dystonic components may coexist.
- Bradykinesia and rigidity can emerge later in the course.

Early chorea / hyperkinesia



Variable dystonia or writhing

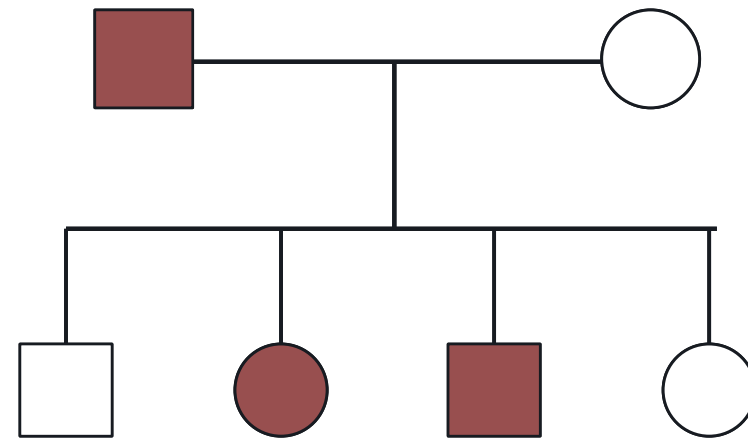


Later bradykinesia / rigidity

The disease is autosomal dominant

- A pathogenic HTT expansion can transmit disease across generations.
- One affected heterozygous parent can transmit the allele to offspring.
- Anticipation modifies age at onset across some generations.

Autosomal dominant transmission



Affected carrier

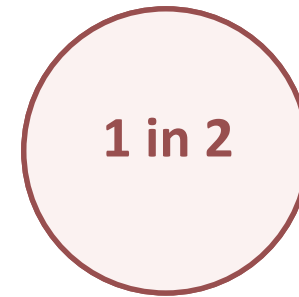
Unaffected

Illustrative pedigree, not patient data

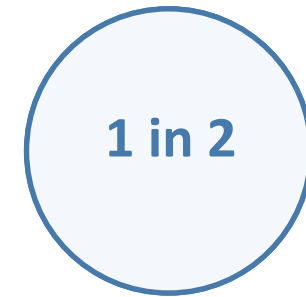
Pedigree reasoning: Recurrence risk

- Autosomal dominant transmission gives each child of a heterozygous carrier a 1-in-2 inheritance probability.
- Transmission probability does not predict age at onset.
- Phenotypically unaffected relatives may carry an expansion before symptoms develop.

Each pregnancy



Inherits allele



Does not inherit

Risk is not an age-at-onset prediction

HTT maps to chromosome 4p16.3

- The HTT gene encodes huntingtin, a large 348-kDa protein.
- The unstable repeat lies in the first exon.
- The corresponding polyglutamine tract lies near the protein N-terminus.

HTT • chromosome 4p16.3



CAG repeats

Coding DNA

The causal DNA sequence is a CAG repeat

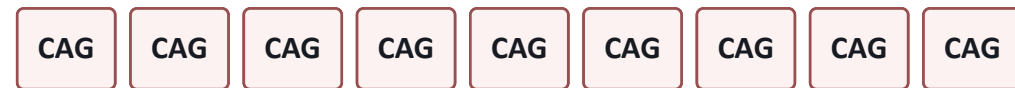
- CAG is a protein-coding trinucleotide repeat.
- Each CAG codon specifies glutamine.
- Expansion therefore lengthens the polyglutamine sequence in huntingtin.

CAG = glutamine codon

Unexpanded tract



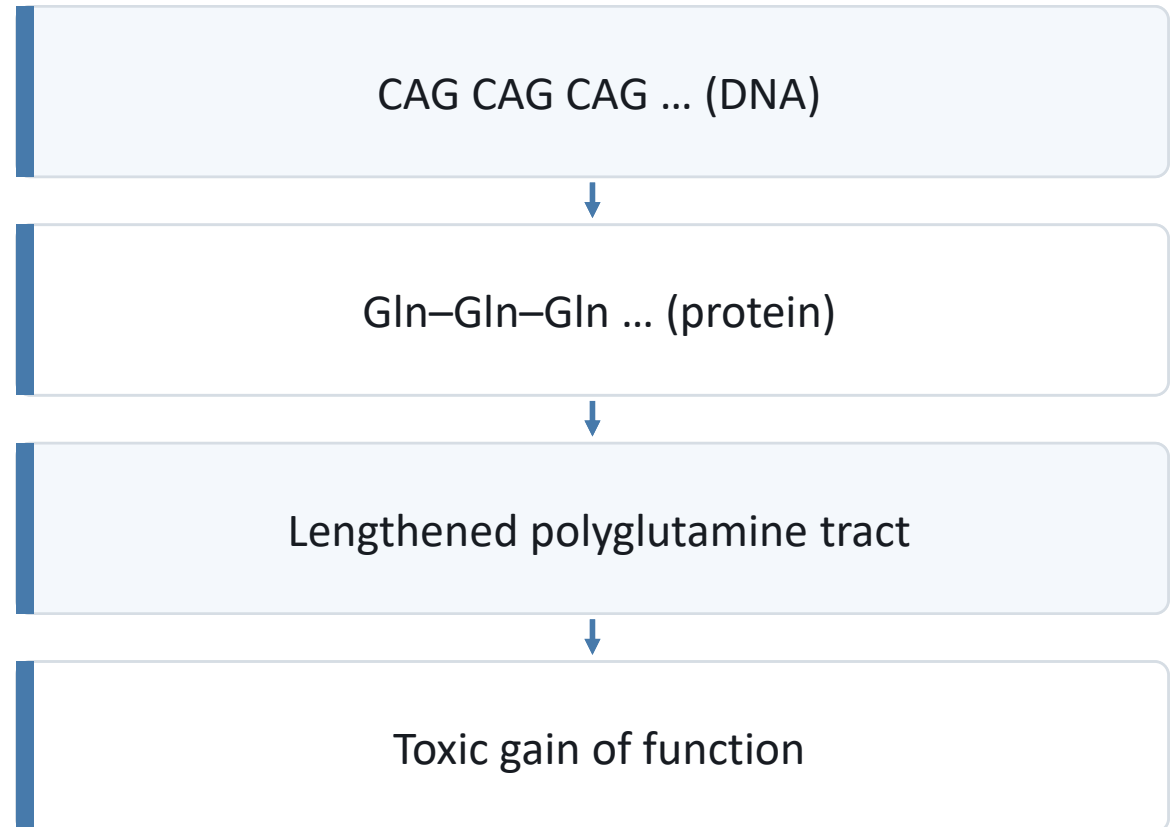
Expanded tract



Schematic only: Number of boxes is not a diagnostic cutoff

Expansion changes the encoded protein

- DNA repeat expansion alters the translated polyglutamine tract.
- The effect is a protein-structure-linked toxic gain of function.
- This distinguishes HD from repeat disorders caused primarily by gene silencing.



Repeat counts require precise interpretation

Unexpanded HTT

Normal-range repeat tract

No disease-causing expanded polyQ tract

Expanded HTT

Lengthened polyglutamine region

Pathogenicity / penetrance depend on repeat category

Repeat length and onset are inversely related

- Larger expanded repeats are associated with earlier symptom onset.
- Repeat count is informative, not an exact personal onset clock.
- A qualitative relationship is established without assigning individual predictions.

More CAG repeats

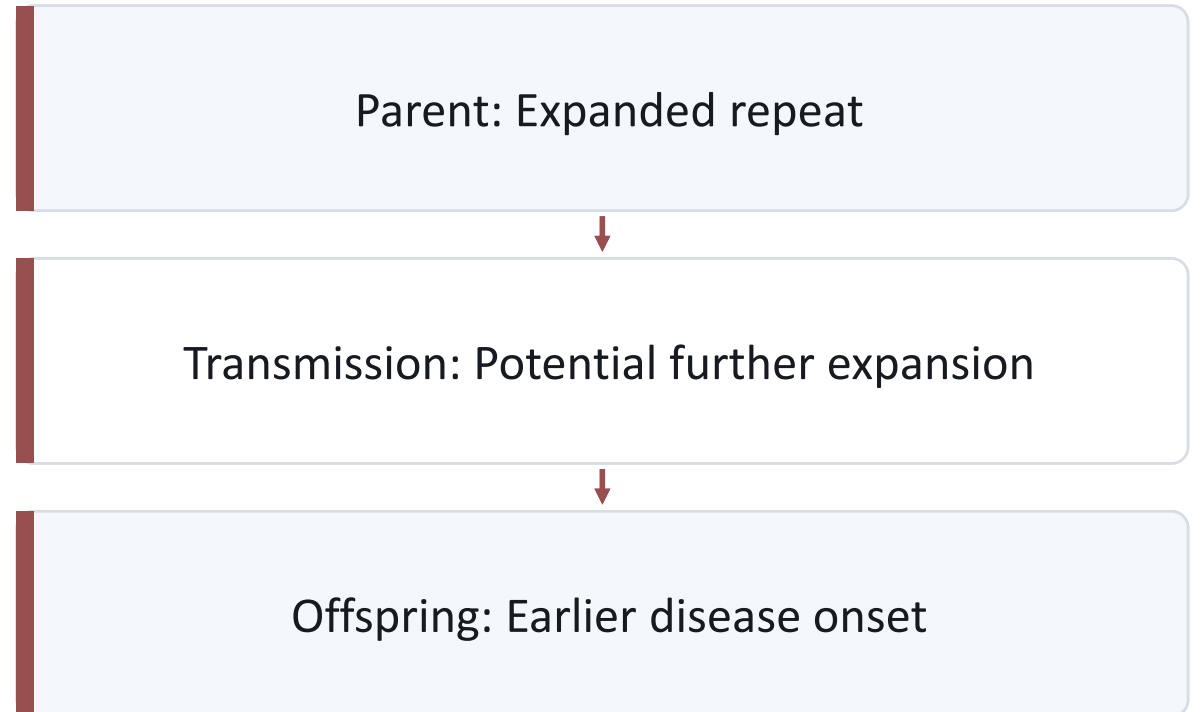


Earlier typical onset

Association $\neq$ exact prediction

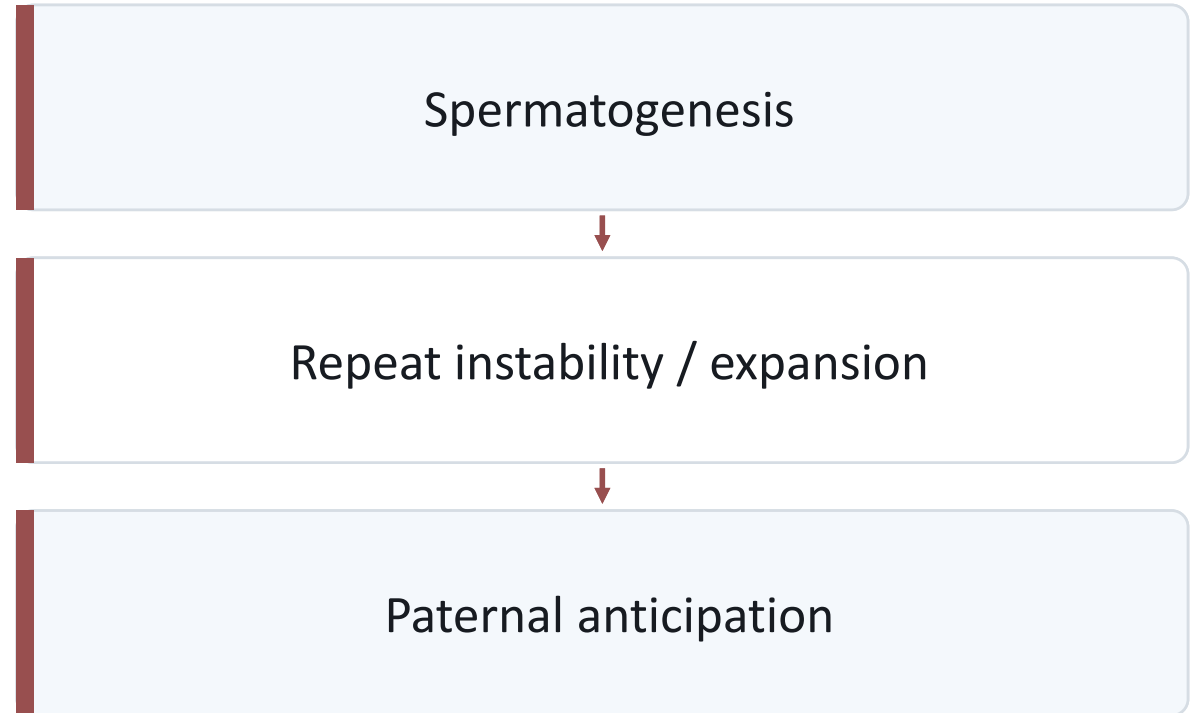
Anticipation is a generational phenomenon

- Repeat number can increase during transmission.
- Greater expansion can shift onset to a younger generation.
- HD is an example of genetic anticipation.



Paternal transmission is especially relevant

- Repeat expansion can occur during spermatogenesis.
- Paternal transmission is linked to anticipation in the Robbins description.
- An unaffected father with a mild expansion can have an affected offspring after further expansion.



An isolated presentation need not be nongenetic

- No truly nongenetic sporadic form of HD.
- Apparently negative family histories may reflect death before onset or unrecognized disease.
- Nonpaternity and paternal repeat expansion are additional explanations identified by the text.

Negative or unclear family history



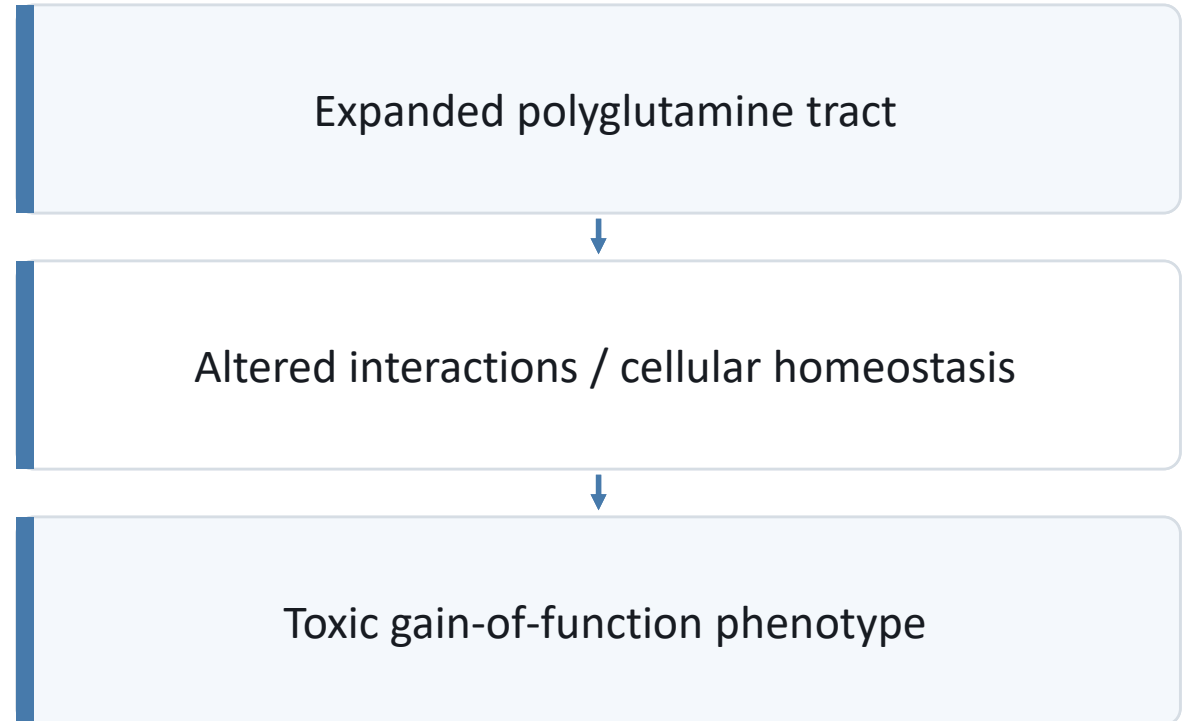
Premature parental death / nonrecognition



Investigate inherited HTT expansion

HTT expansion acts through toxic gain of function

- Expansion confers deleterious properties on huntingtin.
- This is not presented as simple loss of normal protein function.
- Suppressing mutant HTT expression is consequently investigated as a therapeutic strategy.



Normal huntingtin function remains incompletely defined

- The normal protein's biologic role as incompletely understood.
- Pathogenic interpretation centers on mutant huntingtin toxicity.
- A molecular diagnosis does not settle every downstream injury mechanism.

Broad expression, selective neuronal injury

- Huntingtin is expressed widely in tissues.
- The dominant destructive effect occurs in selected central nervous system populations.
- Striatal vulnerability therefore requires more explanation than expression alone.

Systemic expression

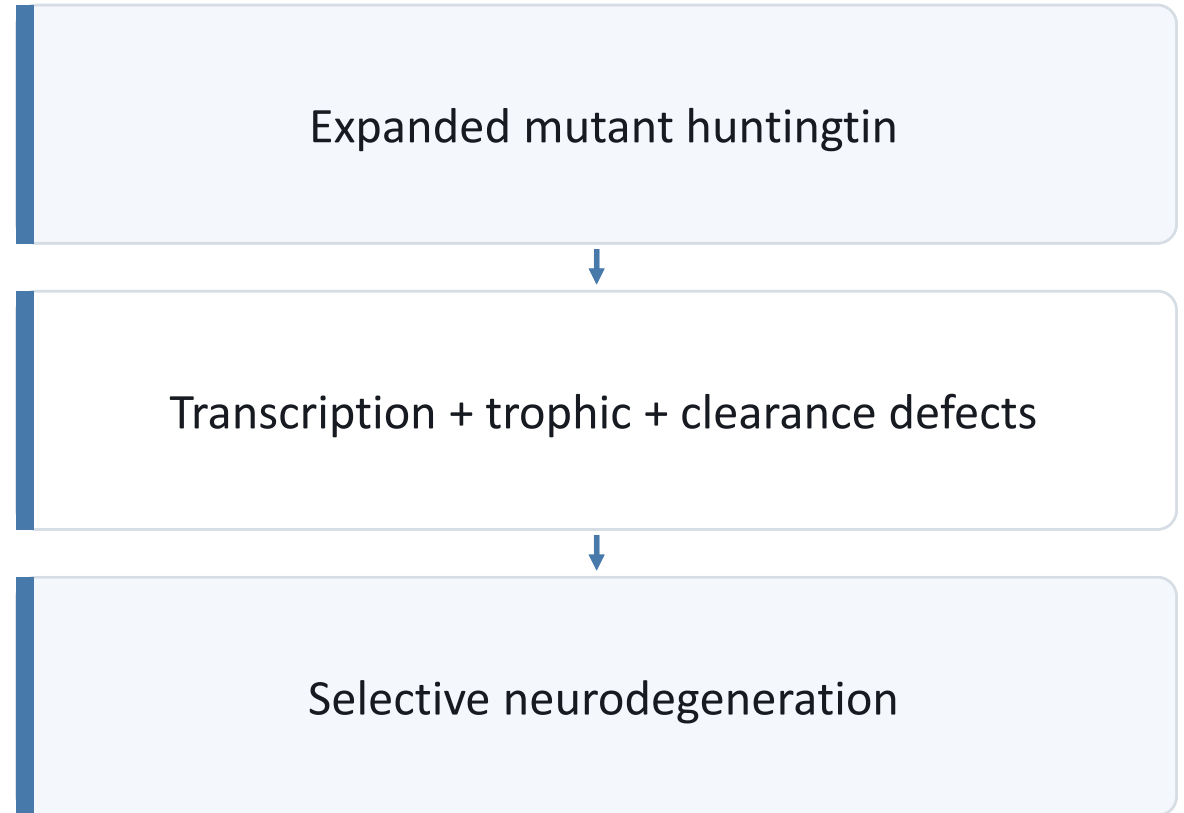
Normal and mutant huntingtin expressed across tissues

Regional vulnerability

Particularly severe CNS injury

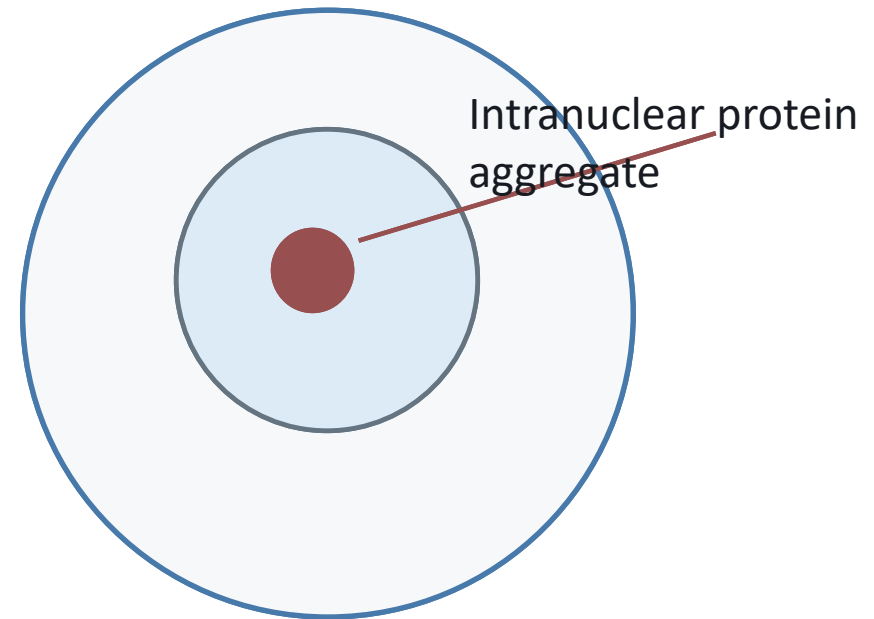
HD pathogenesis comprises parallel pathways

- Mutant huntingtin perturbs transcriptional regulation and oxidative-stress responses.
- Altered BDNF expression and protein clearance may amplify neuronal vulnerability.
- Aggregation and possible transfer between cells complicate the mechanistic model.



Neuronal inclusions are a pathologic hallmark

- Aggregated mutant huntingtin forms neuronal inclusions, including intranuclear deposits.
- These inclusions are observed in affected striatal and cortical neurons.
- Visible aggregates do not necessarily identify the most toxic molecular species.



Neuron / nucleus diagram

Schematic (not a specimen)

Inclusion burden is not synonymous with toxicity

- Experimental observations challenge a directly toxic role for inclusions.
- Some inclusion-bearing striatal neurons survive longer.
- Sequestration of smaller toxic species is proposed as one possible explanation.

Diffusible abnormal huntingtin species



Aggregation into inclusion



Possible sequestration; Net toxicity uncertain

Transcriptional dysregulation is implicated

- Mutant huntingtin can associate with transcriptional regulators.
- Interference with regulation may alter neuronal stress-response programs.
- The pathway is implicated, not presented as the sole demonstrated cause of cell death.

Mutant huntingtin ↔ transcription factors



Altered gene regulatory activity



Reduced protective response

Mitochondrial protective programs may weaken

- Interacting transcription factors participate in mitochondrial biogenesis.
- Reduced protective transcriptional activity may impair stress resilience.
- This provides a mechanistic bridge to oxidative vulnerability.

Transcriptional regulator interactions



Reduced mitochondrial biogenesis program



Lower resistance to cellular stress

Oxidative stress may accentuate degeneration

- Reduced activity of protective transcription factors increases susceptibility to oxidative injury.
- Oxidative stress is one contributing model of injury, not a complete explanation.
- The causal network may contain interacting downstream processes.

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graph TD; A[Less protective transcriptional activity] --> B[Greater susceptibility to oxidative stress]
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Less protective transcriptional activity

Greater susceptibility to oxidative stress

Reduced BDNF expression is a candidate mechanism

- Brain-derived neurotrophic factor is a neuronal growth/survival-related factor.
- Reduced expression is implicated in HD pathogenesis.
- It fits a model of declining support to vulnerable neurons.

Mutant huntingtin-associated dysregulation



Lower expression of BDNF



Potential loss of neuronal support

Protein quality-control pathways are disturbed

- Proteasomal degradation and autophagic pathways are reported as disrupted.
- Defective clearance can increase persistence of abnormal huntingtin species.
- These systems interact with, rather than replace, other pathogenic mechanisms.

Protein disposal systems

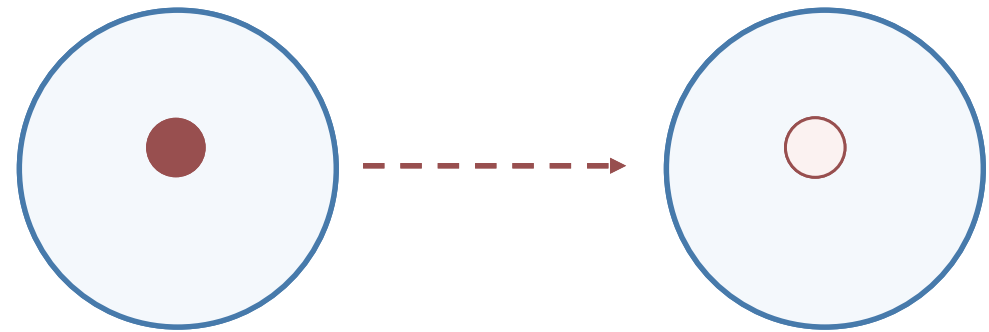
Proteasomal degradation

Autophagic degradation

Both pathways may be disrupted in HD

Prion-like transfer remains an emerging hypothesis

- Aggregated huntingtin may transfer between cells.
- The text describes this as emerging evidence of possible prion-like spread.
- Do not equate this hypothesis with transmissible human prion disease.



Possible intercellular transfer

Investigational mechanism, not infectious HD

Schematic (not a specimen)

Distinguish observation from mechanistic inference

Directly described findings

Expanded HTT CAG repeat

Striatal neuronal degeneration

Neuronal huntingtin aggregates

Proposed contributors

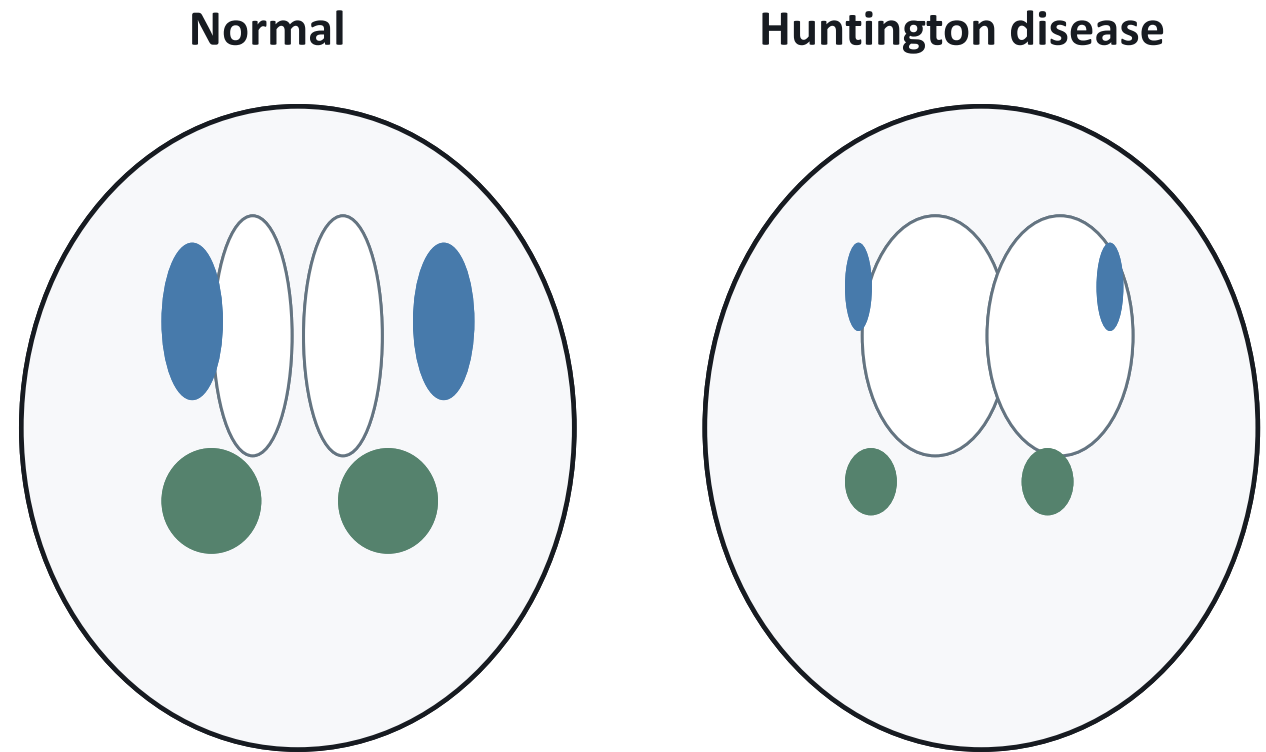
Transcriptional disruption / oxidative stress

BDNF and proteostasis changes

Possible cell-to-cell aggregate transfer

Gross examination reveals striking striatal atrophy

- The brain is small, with conspicuous loss of caudate and putamen volume.
- Ventricular enlargement accompanies surrounding tissue loss.
- Frontal atrophy is frequent; Broader cortical atrophy is less uniform.

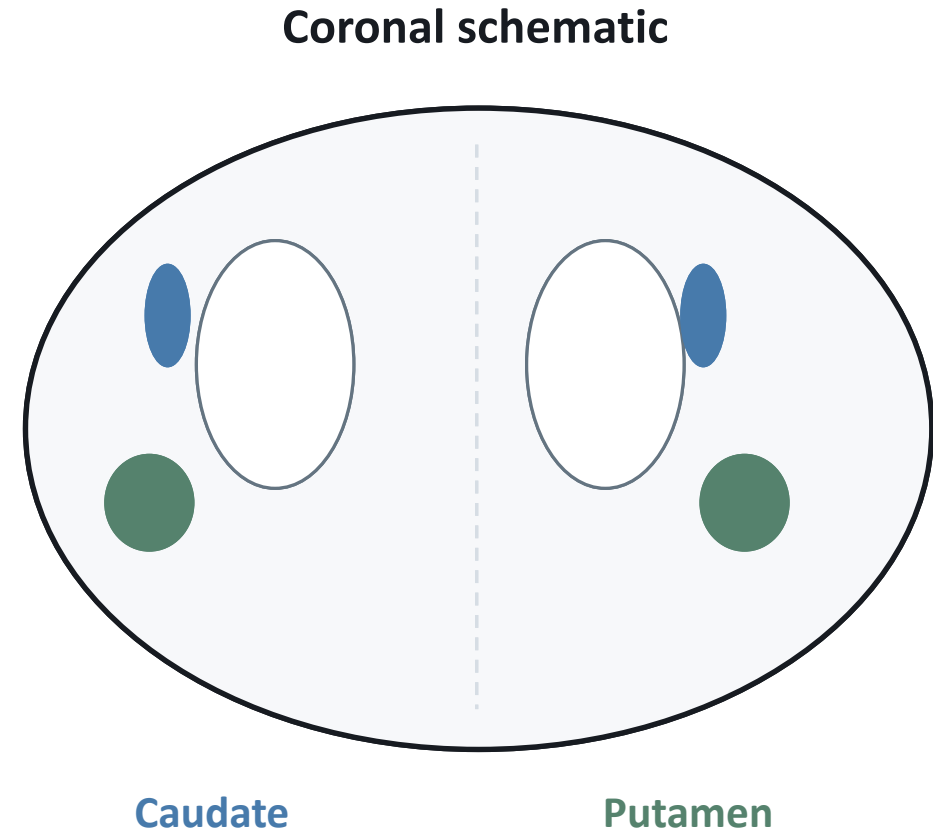


Volume loss → relative ventricular enlargement

Schematic (not a specimen)

Caudate atrophy is a defining gross clue

- The caudate is particularly vulnerable among striatal structures.
- Volume loss alters the walls neighboring the lateral ventricles.
- A coronal-section comparison is a useful teaching approach.



Schematic (not a specimen)

Putaminal degeneration accompanies caudate loss

- The dorsal striatum consists of both caudate and putamen.
- Putaminal neuronal loss contributes to basal ganglia dysfunction.
- The spatial pattern of injury is not necessarily identical to the caudate.

Caudate

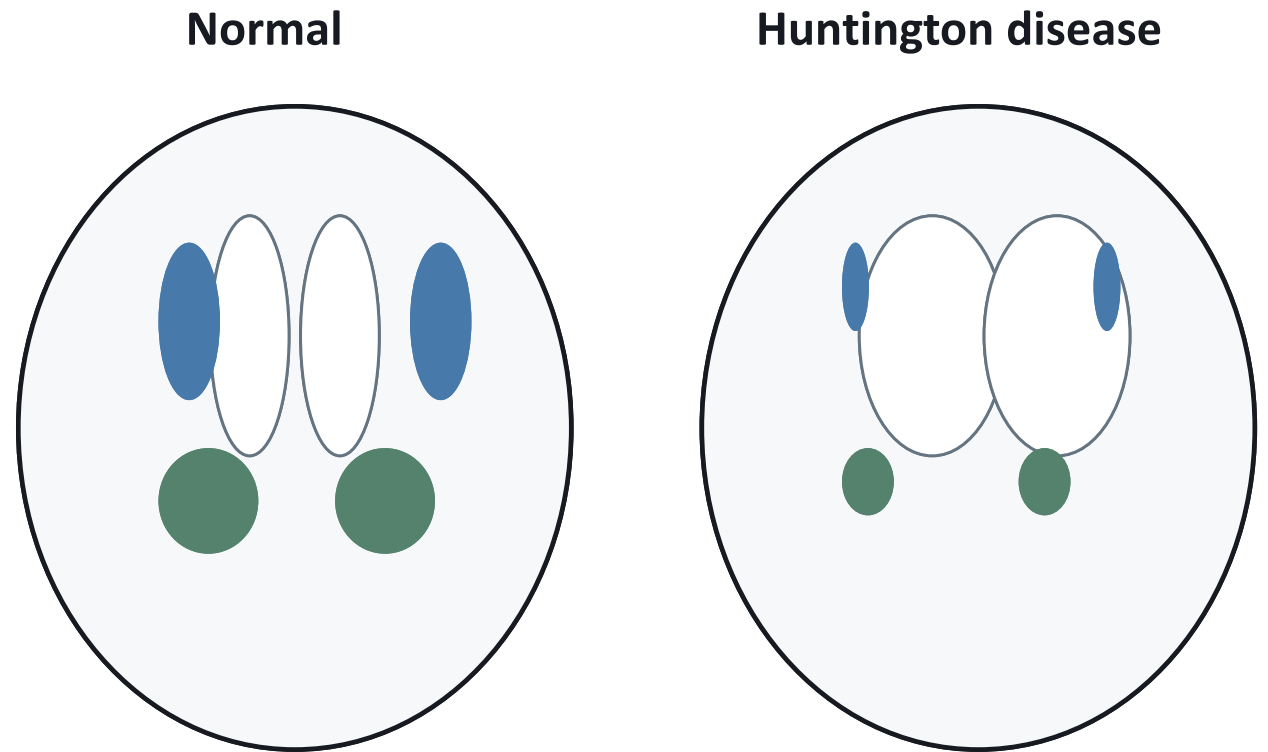
Caudate
degeneration

Putamen

Putaminal
degeneration

Ventricles enlarge as tissue volume declines

- Dilation of lateral and third ventricles is reported.
- This is ex-vacuo enlargement associated with adjacent parenchymal atrophy.
- Ventricular size is a morphologic correlate, not a stand-alone molecular diagnosis.

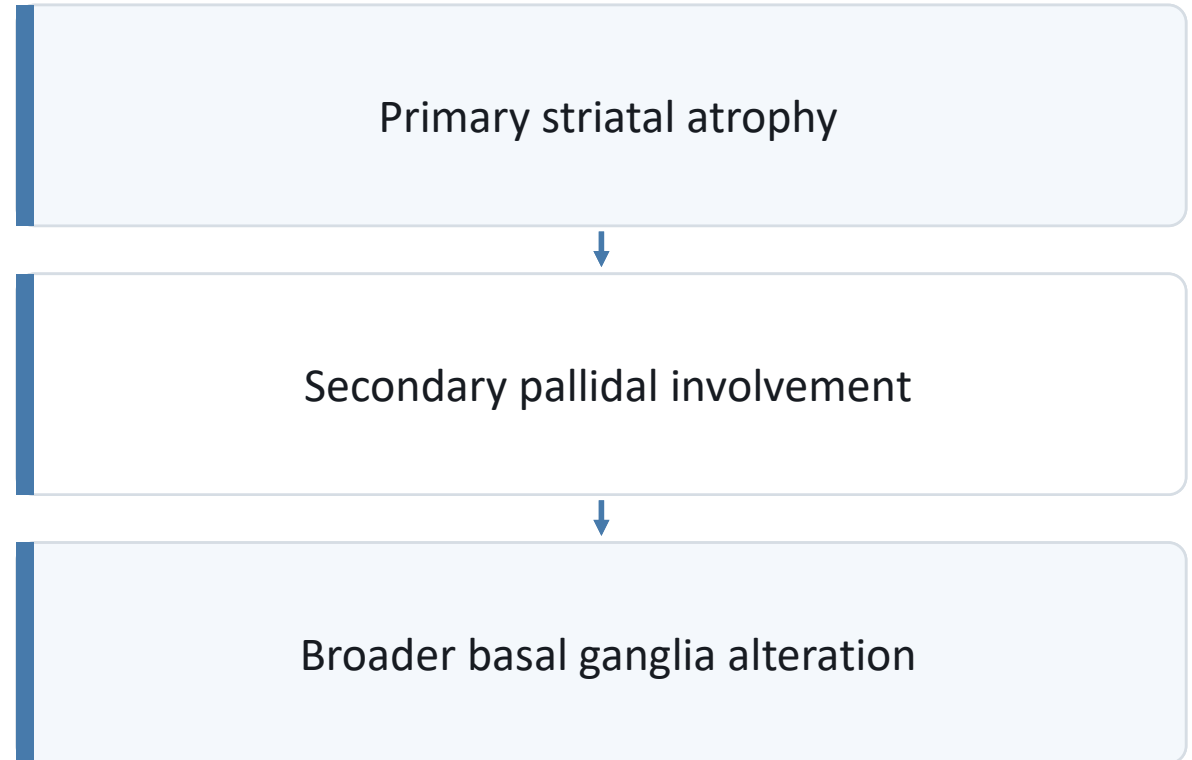


Volume loss → relative ventricular enlargement

Schematic (not a specimen)

Globus pallidus can atrophy secondarily

- The pallidum may become atrophic in advanced disease.
- Its involvement is described as secondary to major striatal degeneration.
- Do not confuse the primary striatal lesion with secondary circuit changes.



Frontal cortical atrophy is frequent

- Atrophy is often seen in frontal lobes.
- Parietal involvement occurs less frequently.
- More diffuse cortical atrophy can occur, but is not universal.

Frequent

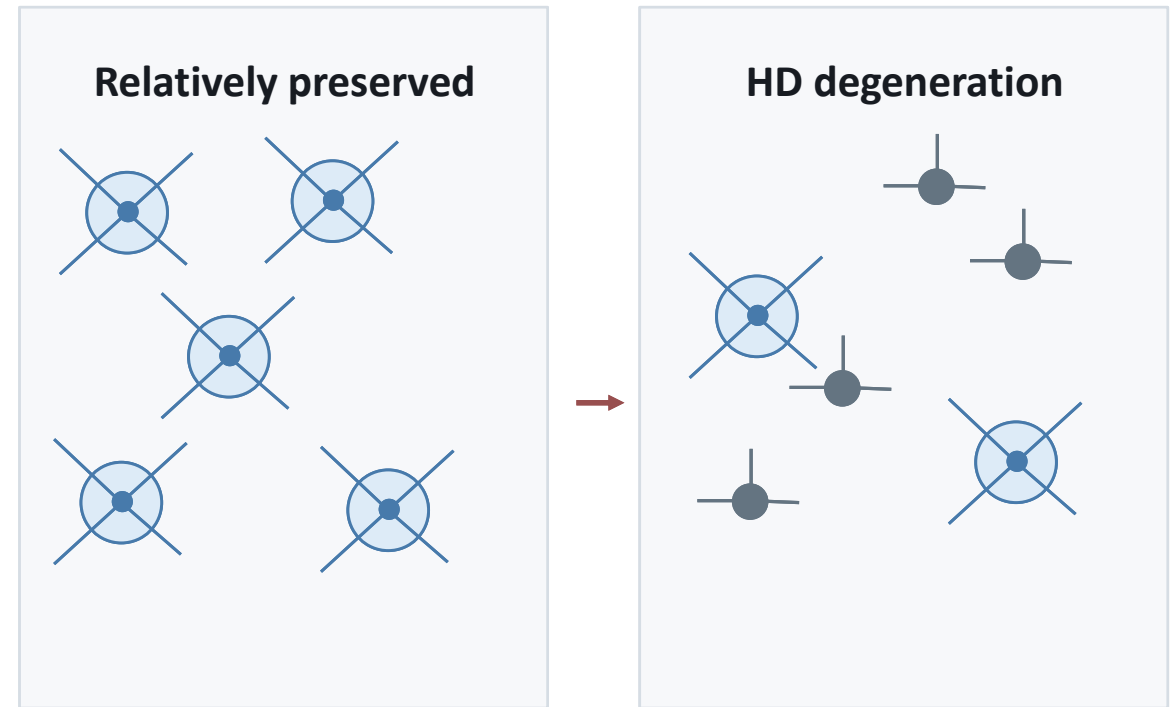
Frontal atrophy
often described

Variable

Parietal / diffuse
cortical changes less
frequent

Microscopy: Profound loss of striatal neurons

- Neuronal depletion is a principal microscopic lesion.
- The most conspicuous changes occur in the caudate.
- Fibrillary gliosis accompanies the degenerative process.

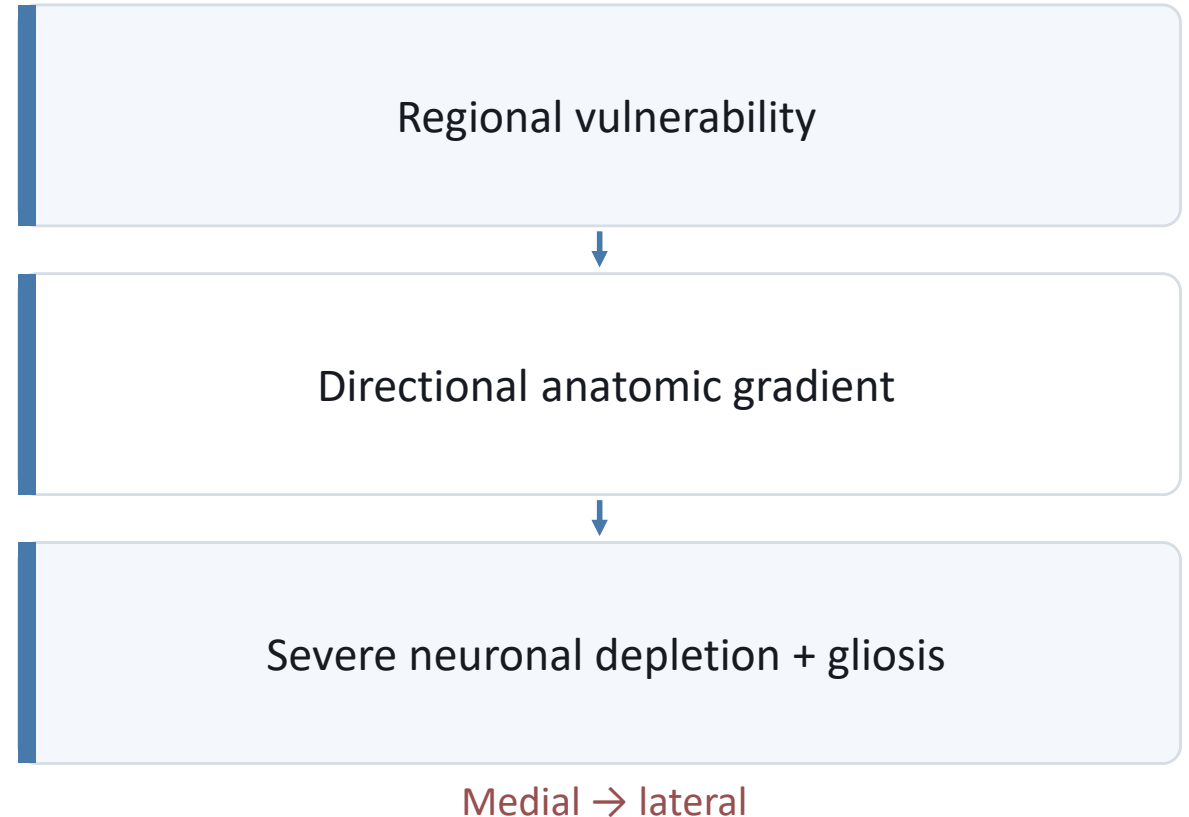


Neuron loss and reactive gliia (conceptual)

Schematic (not a specimen)

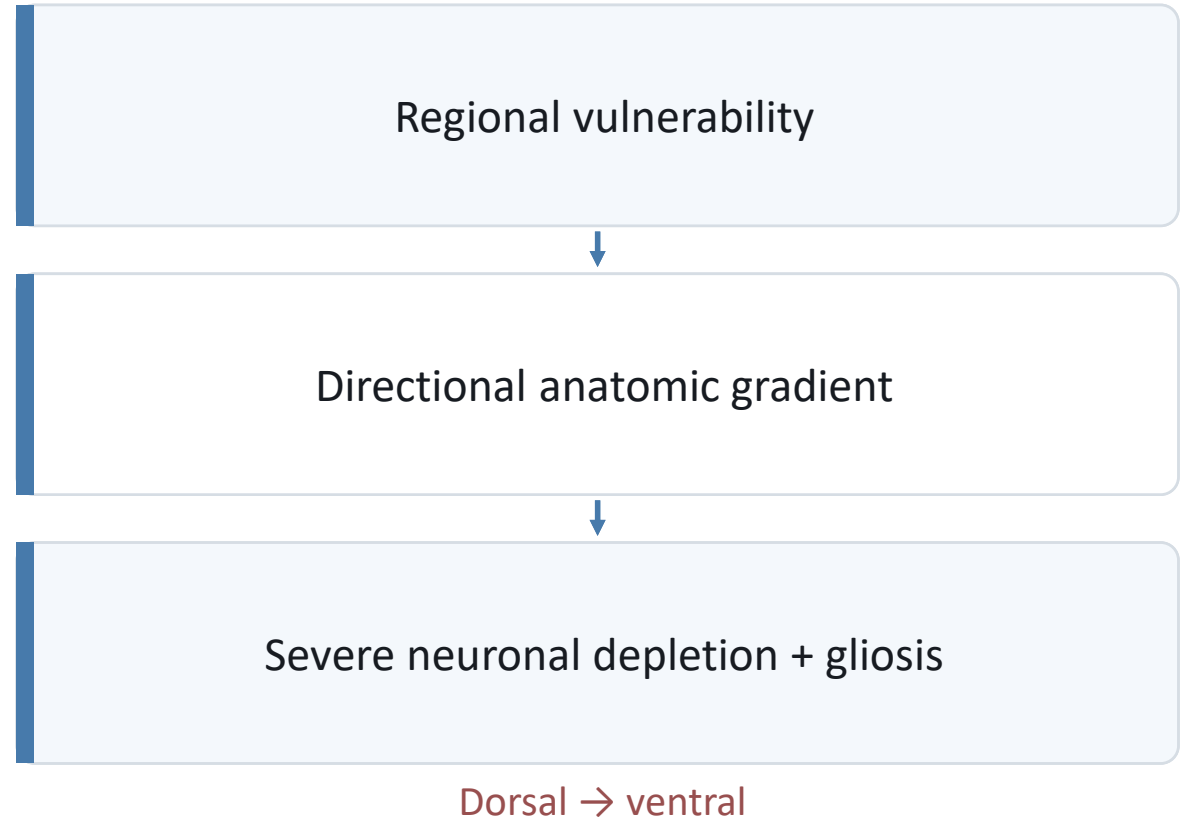
Caudate injury has regional predilection

- The caudate tail and areas close to the ventricle show particularly marked changes.
- Progression is described in a medial-to-lateral direction.
- This anatomic gradient is distinct from the timeline of clinical symptoms.



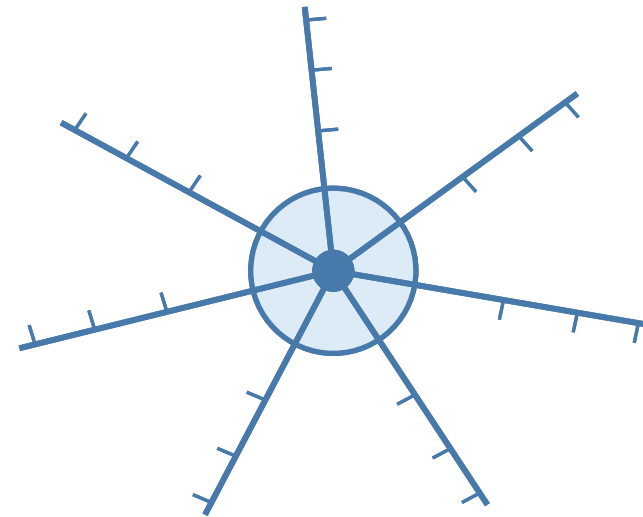
Putaminal changes follow a spatial gradient

- Degeneration in the putamen is described from dorsal to ventral.
- This differs from the medial-to-lateral pattern in the caudate.
- Precise anatomic location matters in neuropathologic descriptions.



Medium spiny neurons are especially vulnerable

- Medium-sized, spiny striatal neurons are preferentially affected.
- They provide inhibitory signaling within motor circuits.
- Preferential neuronal loss offers a cellular basis for the motor phenotype.



Schematic medium spiny neuron

Schematic (not a specimen)

Affected neurons use GABA and neuropeptides

- The principal inhibitory transmitter identified is γ -aminobutyric acid (GABA).
- Enkephalin, dynorphin and substance P are also associated with these neurons.
- Loss of these neurons disrupts the functional output of striatal circuits.

GABA

Primary inhibitory transmitter

Enkephalin

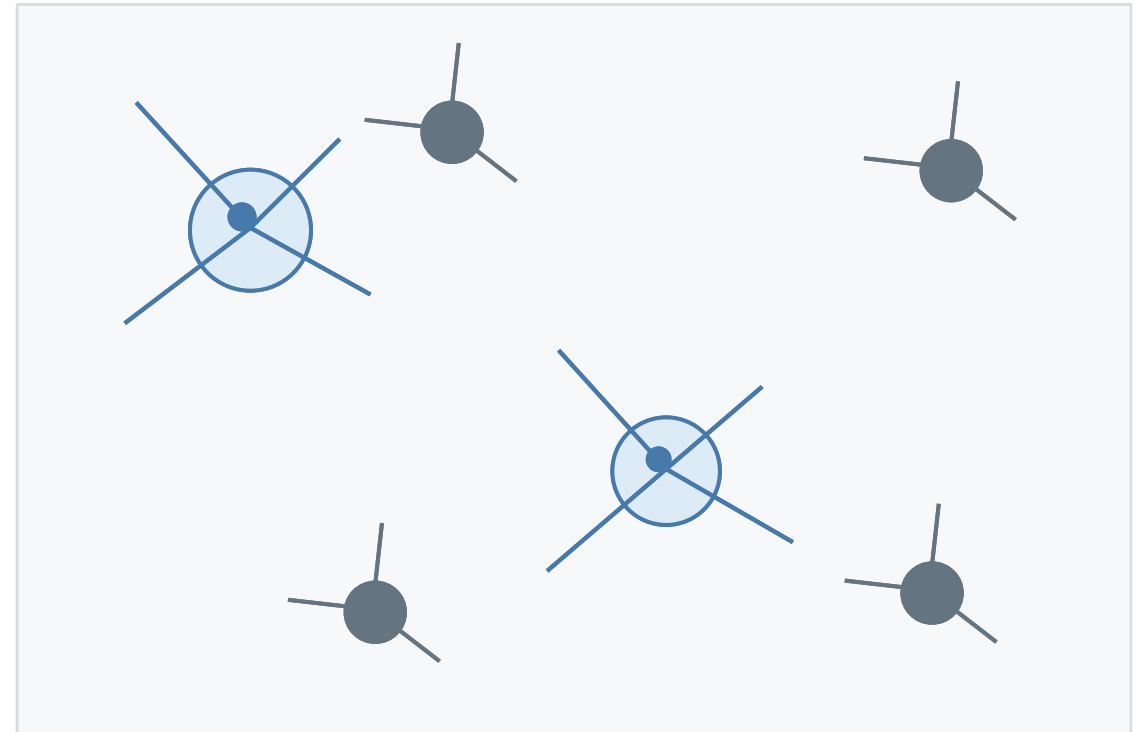
Associated peptide

**Dynorphin /
substance P**

Associated peptides

Reactive gliosis exceeds simple background change

- Fibrillary gliosis is prominent at sites of neuronal loss.
- The reaction is more extensive than usual for comparable neuronal loss,.
- Gliosis is a secondary tissue response, not a disease-specific molecular assay.



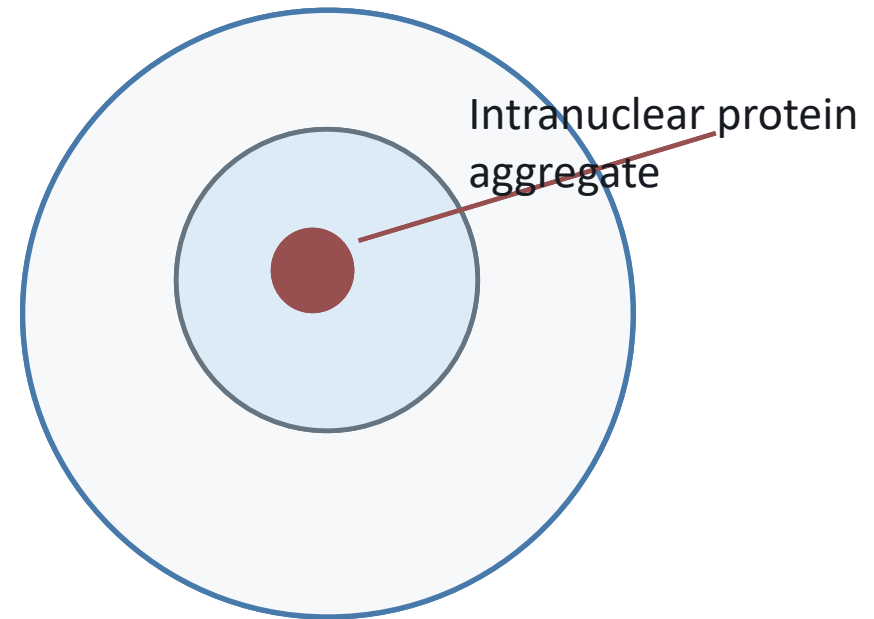
Surviving neurons

Reactive glia

Schematic (not a specimen)

Huntingtin aggregates localize to affected regions

- Protein inclusions are detectable in striatum and cerebral cortex.
- The published textbook figure uses ubiquitin immunohistochemistry to highlight an intranuclear inclusion.
- No authentic textbook photomicrograph is reproduced in this presentation.



Neuron / nucleus diagram

Schematic (not a specimen)

Integrating morphology and phenotype

- Striatal loss weakens the motor-suppressing influence of basal ganglia circuits.
- Cortical neuronal loss contributes to progressive cognitive dysfunction.
- Different manifestations can therefore emerge from one molecular cause.

Striatal neuron loss → hyperkinesia



Cortical neuron loss → cognitive change



Progression → combined disabilities

Adult onset is most typical

- Initial manifestations are most commonly observed in the fourth or fifth decade.
- Age at onset varies with expanded CAG length.
- This typical age distribution does not substitute for a molecular definition.

Typical onset

Fourth–fifth decades

Variation depends in part on repeat length

Chorea is a recognizable motor manifestation

- Movements are involuntary, brief, jerky and hyperkinetic.
- Different body regions may be affected.
- Chorea reflects disordered motor control rather than increased voluntary strength.

Loss of striatal inhibitory neurons



Failure to dampen movement



Irregular involuntary jerks

Choreoathetosis includes a writhing component

- Writhing movements of the extremities.
- Jerky and flowing involuntary movements may coexist.
- The phenotype must be distinguished clinically from tremor or isolated rigidity.

Chorea

Brief, irregular, jerky movements

Athetotic component

Writhing movements of extremities

Rigidity and bradykinesia may appear later

- Hyperkinetic manifestations dominate the classic description.
- Later disease may feature slow movement and increased muscle tone.
- The phase of illness changes what the clinician observes.

Early chorea / hyperkinesia



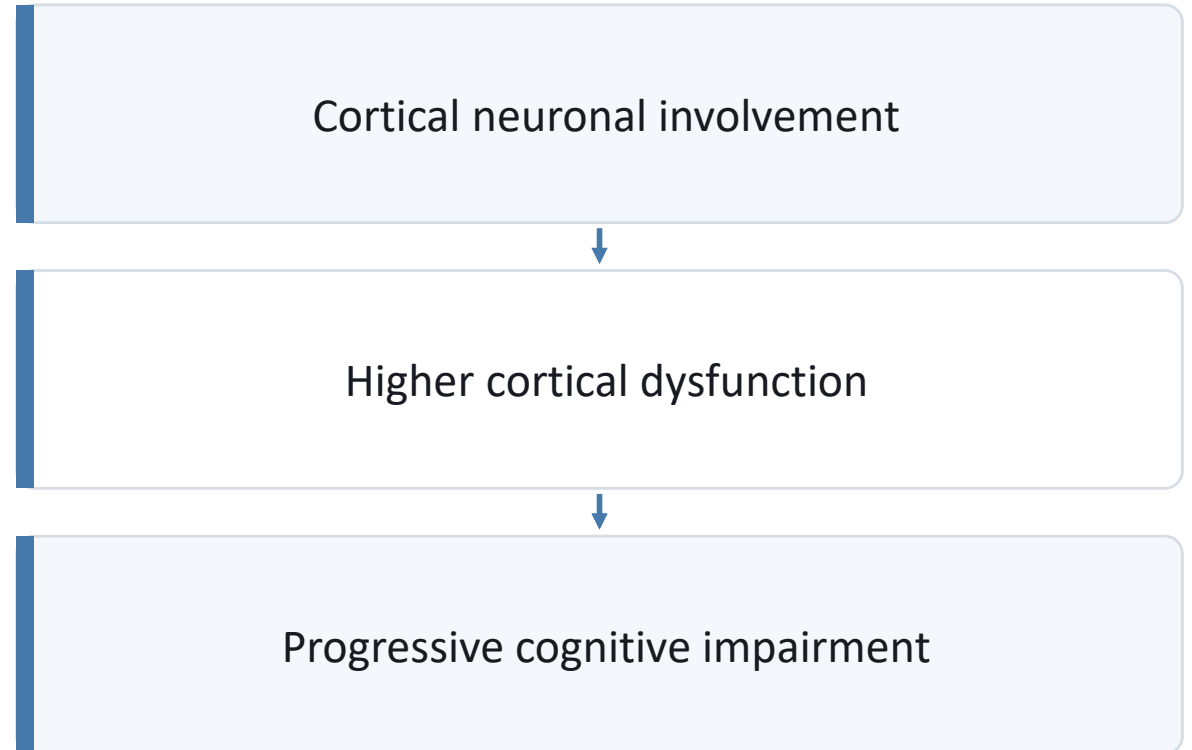
Variable dystonia or writhing



Later bradykinesia / rigidity

Cognitive dysfunction has a cortical correlate

- Degeneration extends beyond the striatum in many patients.
- Cortical neuronal loss is implicated in cognitive decline.
- The pathologic process is therefore not exclusively a movement disorder.



Early neurobehavioral symptoms may be subtle

- Forgetfulness may appear early.
- Cognitive and affective disturbances can accompany motor symptoms.
- Neurologic assessment should not focus only on involuntary movements.

Memory: Forgetfulness

Cognition: Higher cortical dysfunction

Affect: Emotional / behavioral changes

Progression can culminate in severe dementia

- Cognitive deficits intensify during the course.
- Severe dementia may develop in advanced disease.
- Behavioral and cognitive changes are central components of the illness.

Early forgetfulness



Progressive cognitive and affective decline



Severe dementia in advanced illness

Motor manifestations often precede cognition

- That motor symptoms commonly precede cognitive impairment.
- The sequence is not a rigid diagnostic requirement.
- A history of progressive change across multiple domains is informative.

Movement disorder often first



Cognitive and affective impairment progresses



Combined late-stage disability

The clinical course is relentlessly progressive

- The textbook gives an average disease course of about 15 years.
- Progression affects movement, cognition and functional capacity.
- The quoted duration is a population-level summary, not a personal prognosis.

Initial movement / neurobehavioral changes



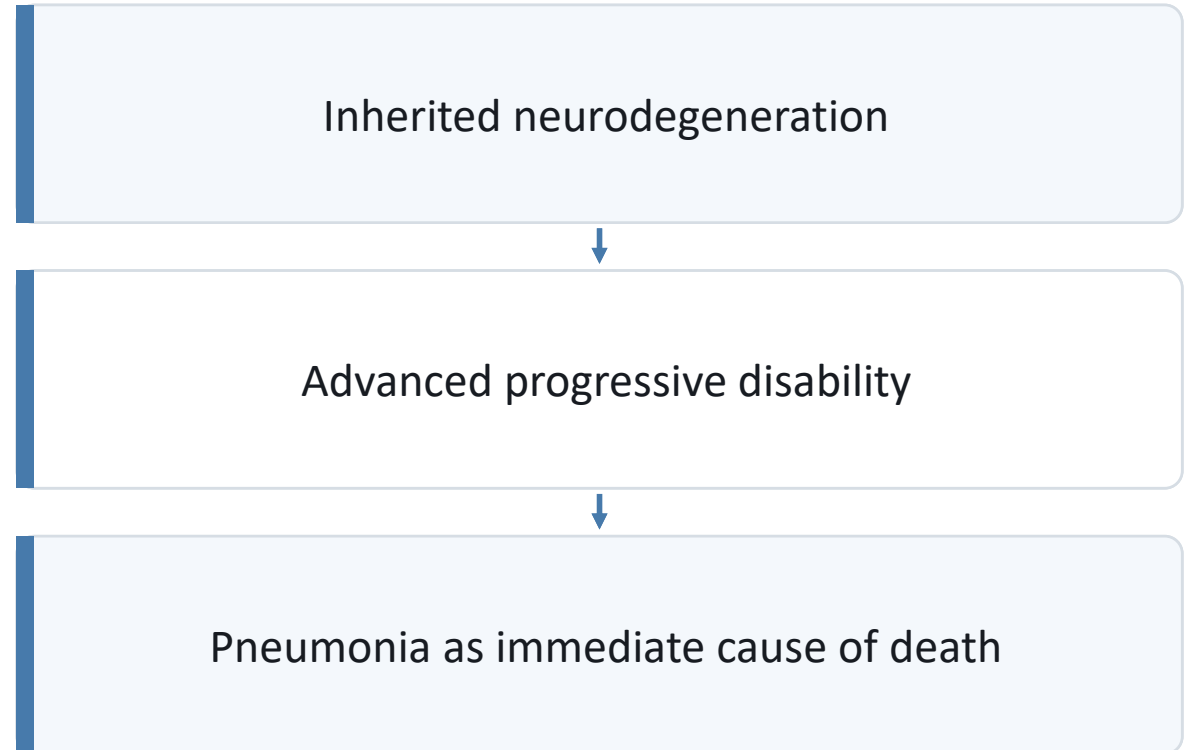
Progression across neurologic domains



Advanced disability and complications

Pneumonia is a major terminal complication

- Pneumonia is identified as the most common immediate cause of death.
- It often occurs during advanced disease.
- The terminal event should be distinguished from the underlying inherited neurodegeneration.



Psychiatric safety is clinically consequential

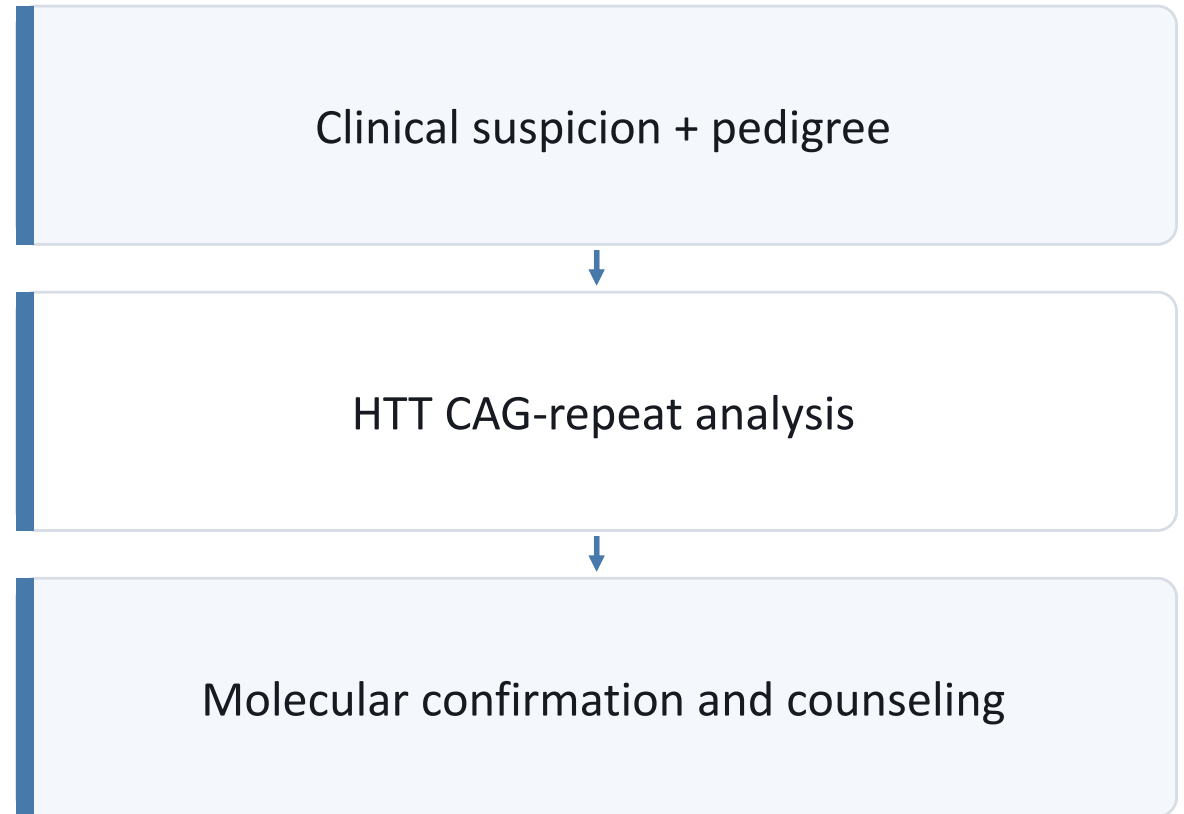
- Elevated suicide risk in HD.
- Affective dysfunction deserves attention throughout the disease course.
- Discuss risk without reducing the illness to a psychiatric stereotype.

Affective dysfunction + elevated suicide risk

Clinical vigilance is necessary throughout disease

Genetic testing establishes the molecular lesion

- A test targeting the HTT CAG-repeat expansion can identify a disease-associated allele.
- Phenotypic assessment and family history still provide clinical context.
- Interpretation of borderline categories and predictive testing requires specialized counseling.



Testing an unaffected relative is different

- Presymptomatic identification may provide genetic information before clinical manifestations.
- The result may have major personal and family consequences.
- The textbook explicitly raises ethical concerns about routine predictive screening.

Asymptomatic at-risk adult



Informed choice + counseling



Potential genetic knowledge; Uncertain onset

Counseling must address genetic uncertainty

- Autosomal dominant inheritance and anticipation alter family discussions.
- Repeat size is associated with onset but does not fix an exact future date.
- Autonomy and informed decision-making are critical in predictive testing.

Transmission risk



Meaning and limits of repeat result



Voluntary informed decision

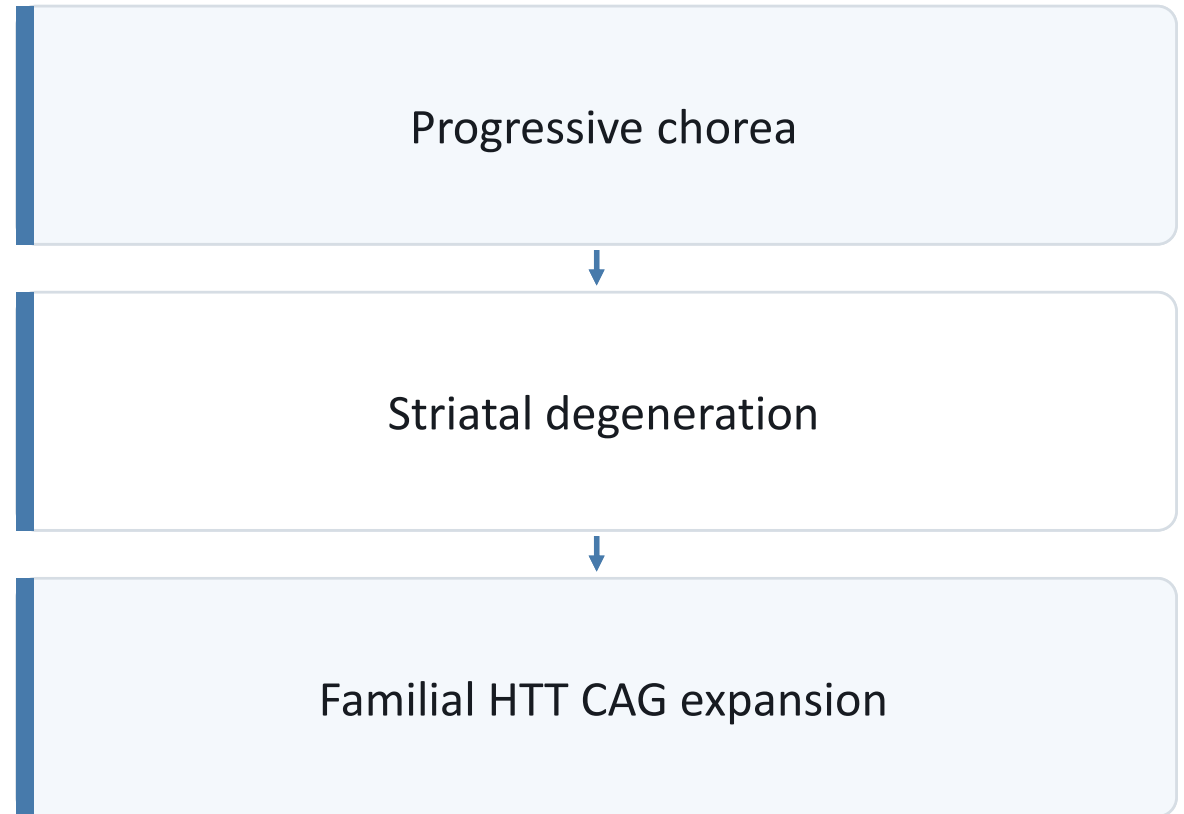
Case: Progressive involuntary movements

- A 44-year-old develops progressive generalized jerky movements.
- Family members describe increasing forgetfulness and personality change.
- A parent had an incompletely characterized progressive neurologic illness.

Which anatomic structure and molecular lesion best unify the findings?

Case reasoning: Phenotype to genotype

- Chorea suggests disinhibition of motor output from striatal damage.
- Cognitive and affective changes suggest additional cortical involvement.
- An inherited HTT CAG expansion unifies the motor, familial and cognitive features.



Case: A healthy adult requests prediction

- An asymptomatic adult has a parent with genetically confirmed HD.
- The adult requests a test predicting precisely when symptoms will develop.
- The question includes medical, psychological and familial dimensions.

What can a repeat-expansion result establish—and what can it not?

Predictive testing: Answer the right question

- Genetic testing may identify an HTT repeat expansion.
- Repeat length cannot provide a precise individual onset date.
- Pretest counseling and respect for the person's decision are essential.

Allele categorization



No exact onset prediction



Counseling-centered decision-making

Distinguishing HD from another degeneration

Huntington disease

HTT CAG polyglutamine expansion

Striatal neuronal degeneration

Chorea with cognitive and affective decline

Multiple system atrophy

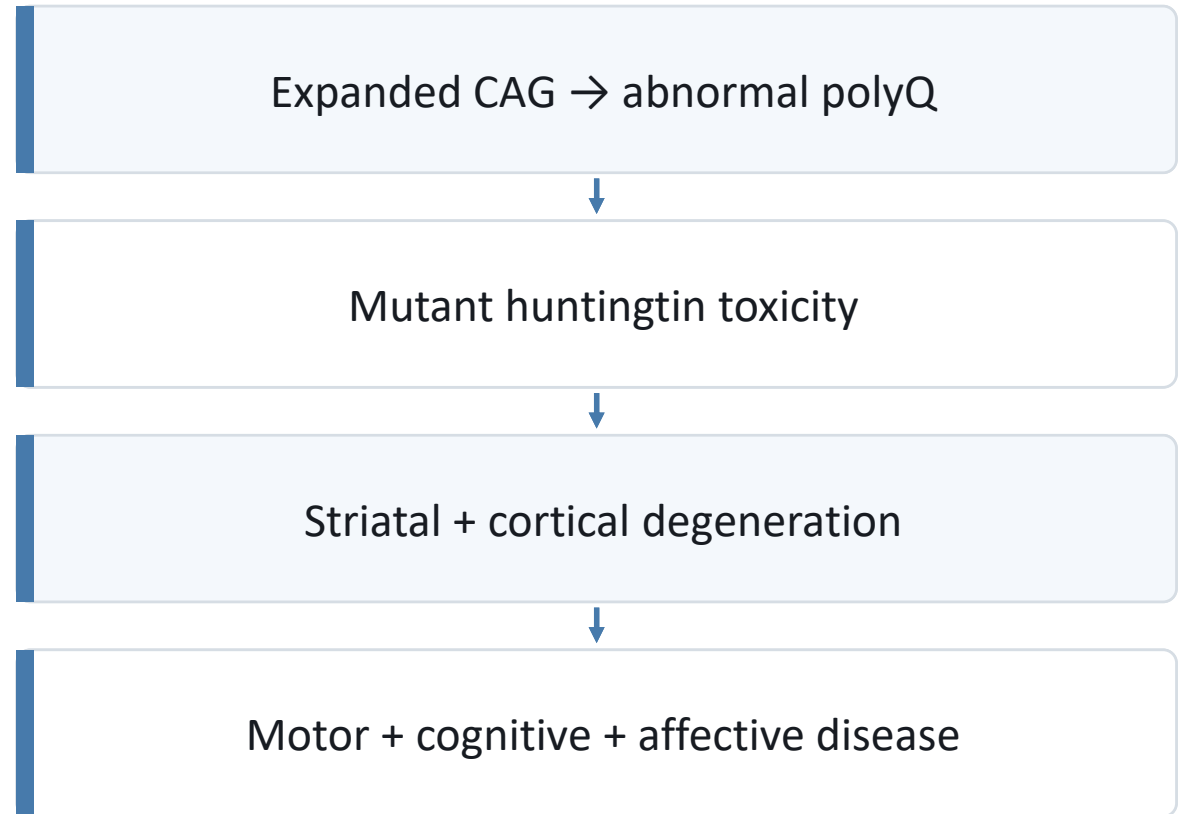
Oligodendroglial α -synuclein inclusions

Striatonigral / autonomic / cerebellar systems

Parkinsonism, autonomic failure or ataxia

Integrating the disease in one causal model

- HTT CAG expansion → mutant huntingtin toxic gain of function.
- Multiple cellular stress pathways → selective striatal / cortical degeneration.
- Caudate–putamen atrophy → chorea; Cortical involvement → cognitive change.



References and interpretive boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Content follows the Huntington disease section and the general repeat-expansion discussion.
- Morphology illustrations are original editable schematics—not clinical photographs or textbook figures.