

Neurodegenerative Diseases

Pathology of selective neuronal loss and protein accumulation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

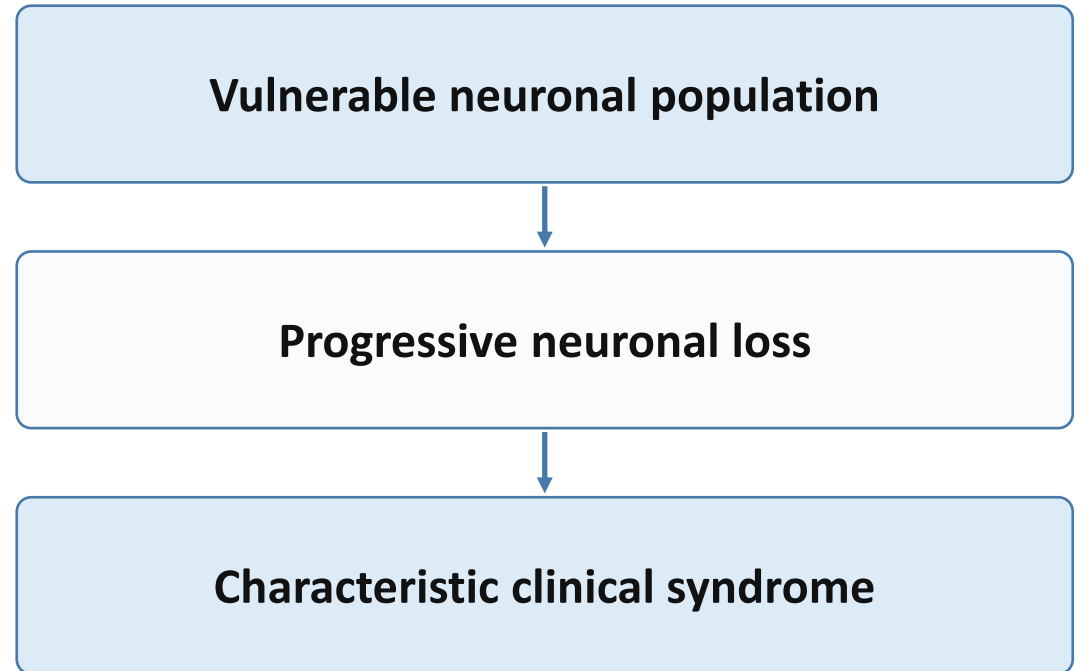
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Learning objectives

- Explain selective degeneration of neural systems and its clinical consequences.
- Distinguish protein misfolding, aggregation, and impaired clearance.
- Classify disorders by phenotype, neuroanatomy, and aggregate identity.
- Relate representative pathological inclusions to major disease groups.

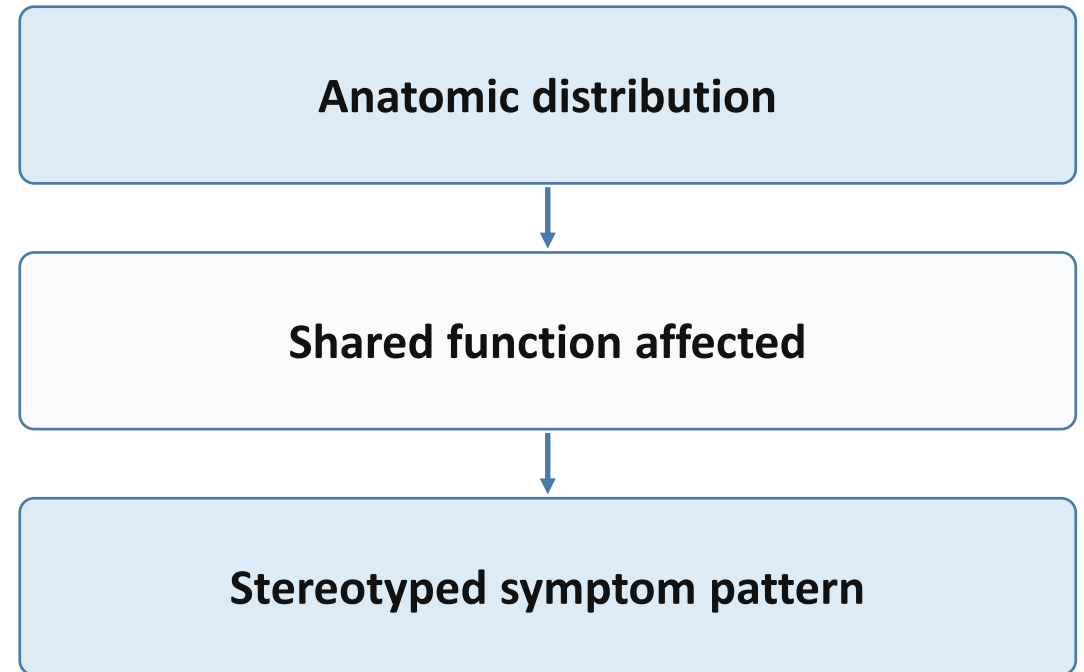
Selective neuronal loss defines the group

- Neurodegeneration involves progressive loss of populations of neurons.
- Vulnerable neuronal populations commonly share related functions.
- The distribution of neuronal loss helps determine presenting symptoms.

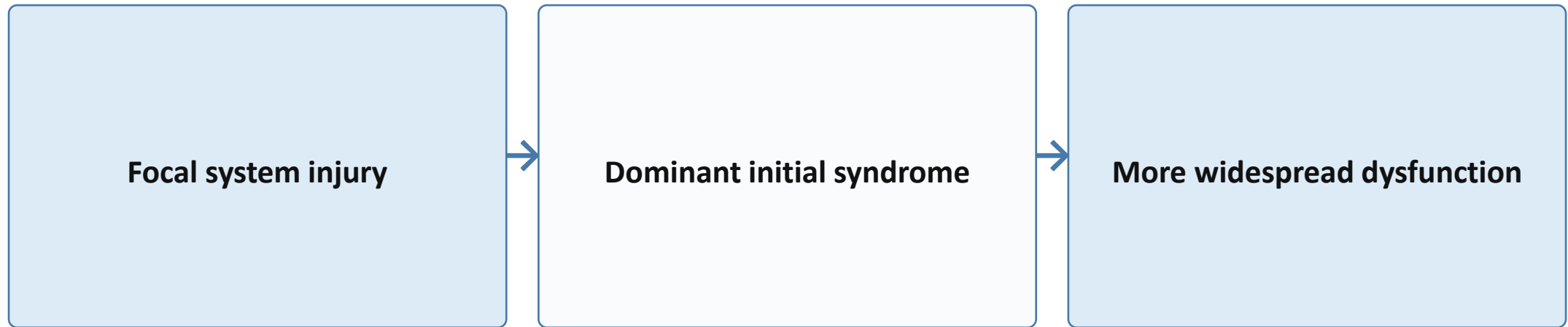


Disease patterns reflect neural systems

- Involvement is not uniformly distributed throughout the CNS.
- Each syndrome typically targets a recognizable network or circuit.
- Localization is clinically informative, but not uniquely diagnostic.



Progression and presentation are distinct



Gradual tissue damage may precede the first recognizable symptom. • A recognizable presenting phenotype reflects the initially affected system. • Additional systems may become involved as disease progresses.

Major clinical entry points

Cognitive / behavioral

Movement

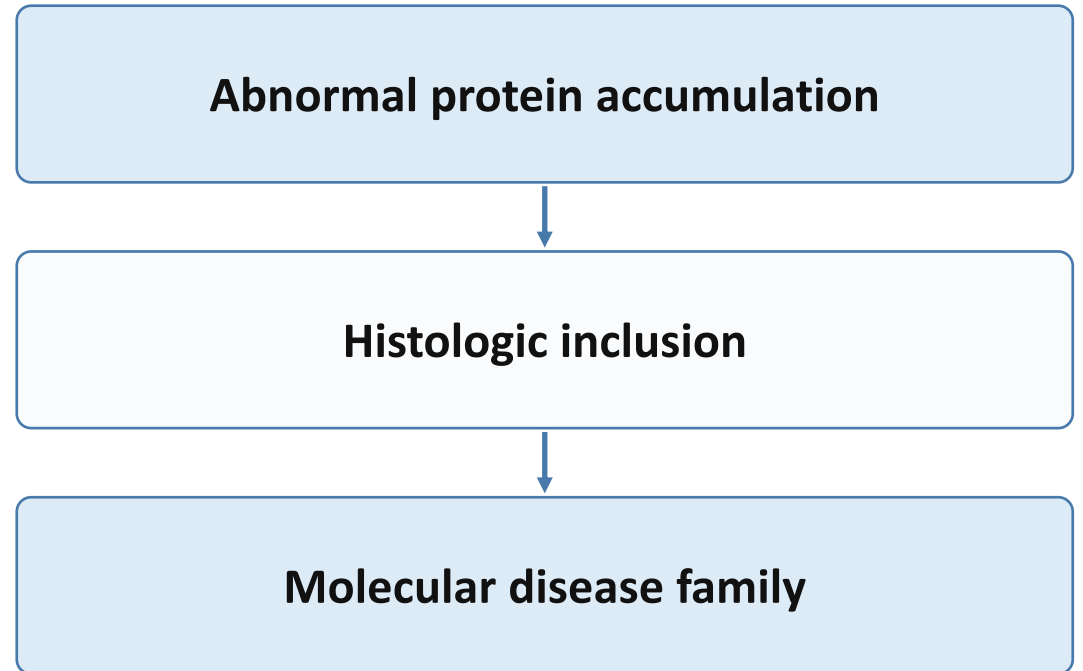
**Cerebellar /
autonomic**

Motor neuron

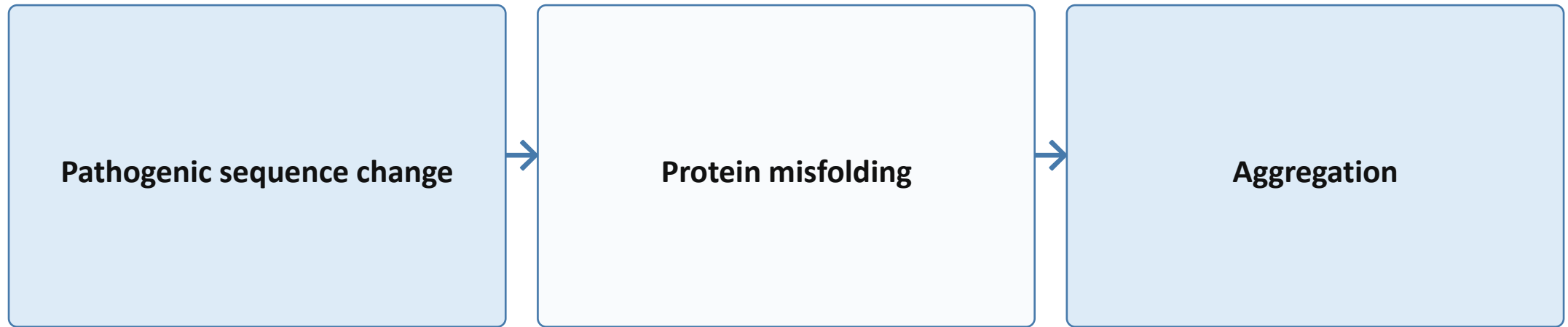
Cognitive decline and dementia • Behavior or language impairment • Hypokinetic or hyperkinetic movement disorders

Protein aggregation is a unifying process

- Many neurodegenerative diseases accumulate abnormal protein aggregates.
- These conditions are sometimes grouped as proteinopathies.
- Aggregate identity and regional distribution help distinguish disease families.

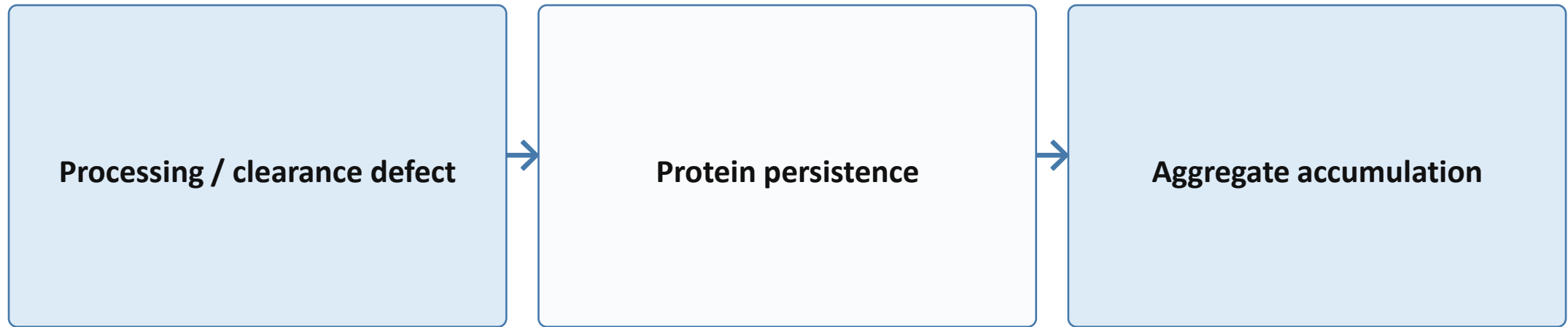


Altered protein conformation can initiate aggregation



Inherited mutations may alter the conformation of an affected protein. • Some altered proteins become prone to misfolding and accumulation. • Huntingtin with expanded polyglutamine repeats is one example.

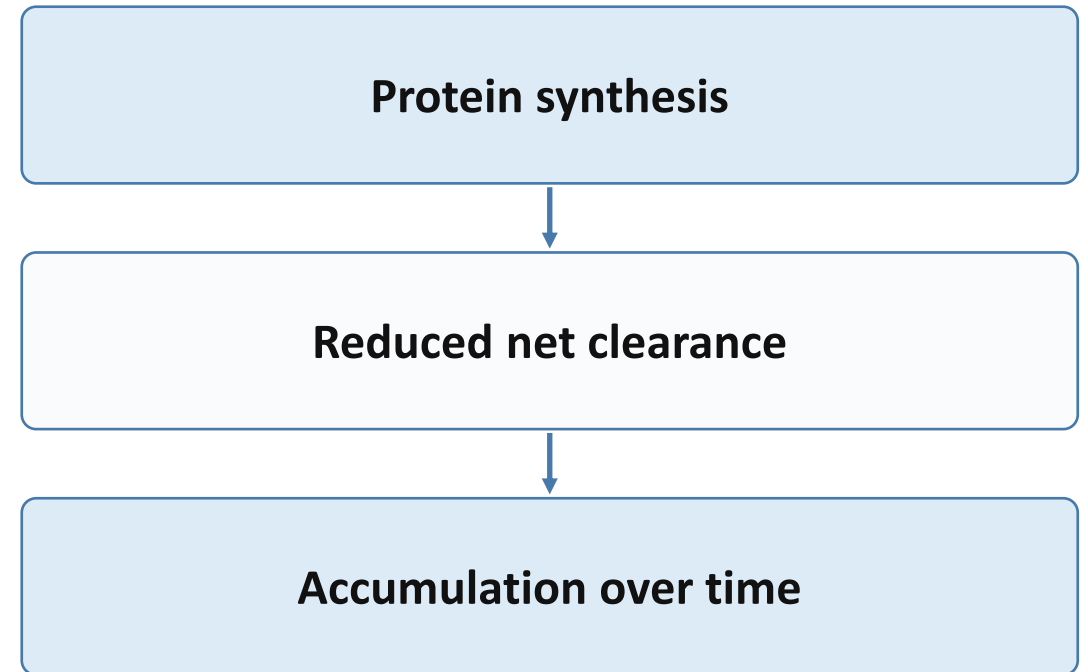
Defective protein handling is another route



Mutations may instead disrupt processing of otherwise normal proteins. • Mutations may also interfere with clearance pathways. • The result can be excessive retention of aggregation-prone proteins.

Synthesis–clearance imbalance can be acquired

- Proteins are continually produced and removed within cells.
- An imbalance can permit gradual accumulation without a specific change in the protein sequence.
- Genetic, environmental, and unknown influences may contribute.

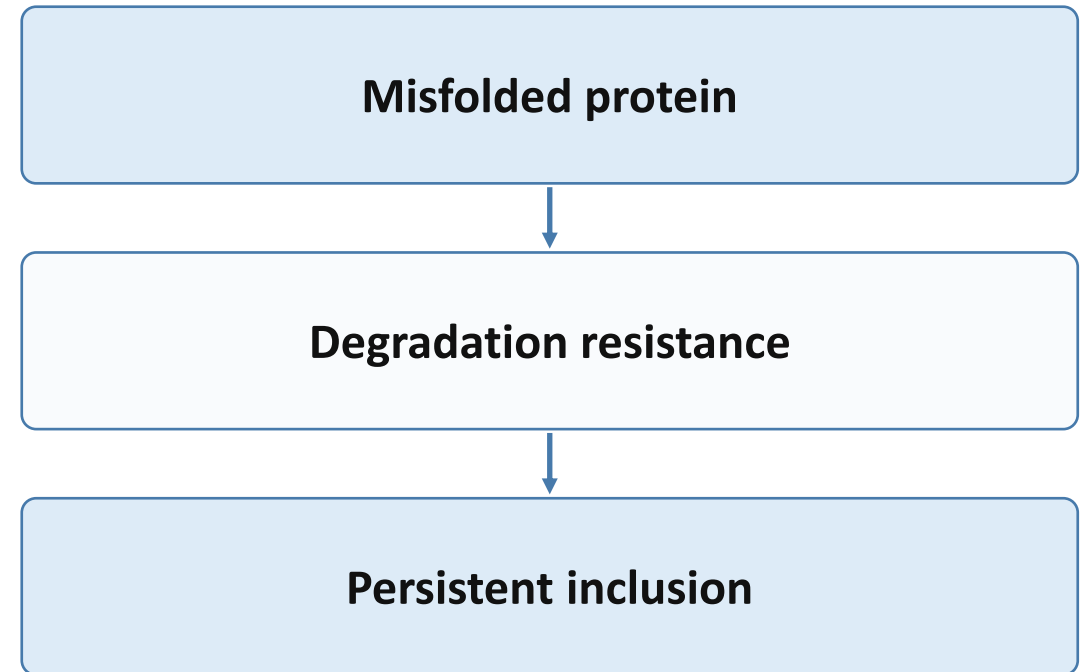


Three routes converge on the same endpoint

Entry mechanism	Shared endpoint
Altered protein conformation	Aggregated protein
Defective processing / clearance	Aggregated protein
Synthesis–clearance imbalance	Aggregated protein

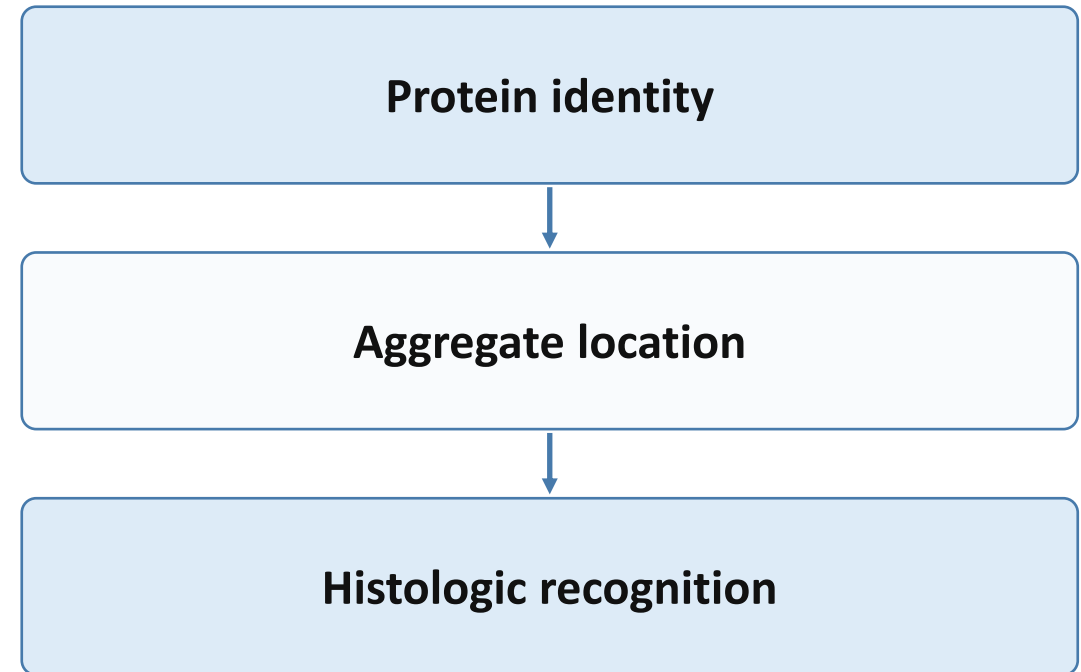
Aggregates are often resistant to degradation

- Accumulated proteins may persist despite normal degradation mechanisms.
- Intracellular deposition commonly occurs in abnormal locations.
- The resulting structures can be recognized as microscopic inclusions.

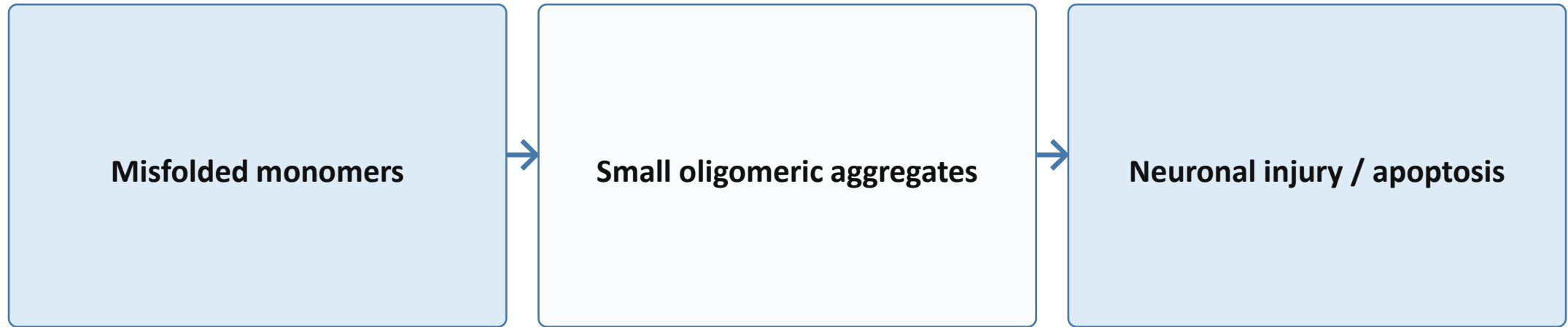


Inclusions provide pathological signatures

- An inclusion is an observable deposit of aggregated cellular material.
- Different disorders have characteristic proteins and inclusion patterns.
- The deposit is often a diagnostic hallmark rather than a complete explanation of toxicity.



Soluble oligomers may contribute to toxicity



Small aggregates of misfolded protein may injure neurons. • an association with activation of apoptosis.
• Visible end-stage inclusions should not automatically be assumed to be the sole toxic species.

Aggregation can deplete normal protein function

Mechanism	Potential effect
Toxic gain of function	Injury from abnormal aggregate species
Loss of normal function	Functional protein unavailable

Two injury mechanisms can coexist

Aggregate-related injury

Misfolded species → neuronal stress

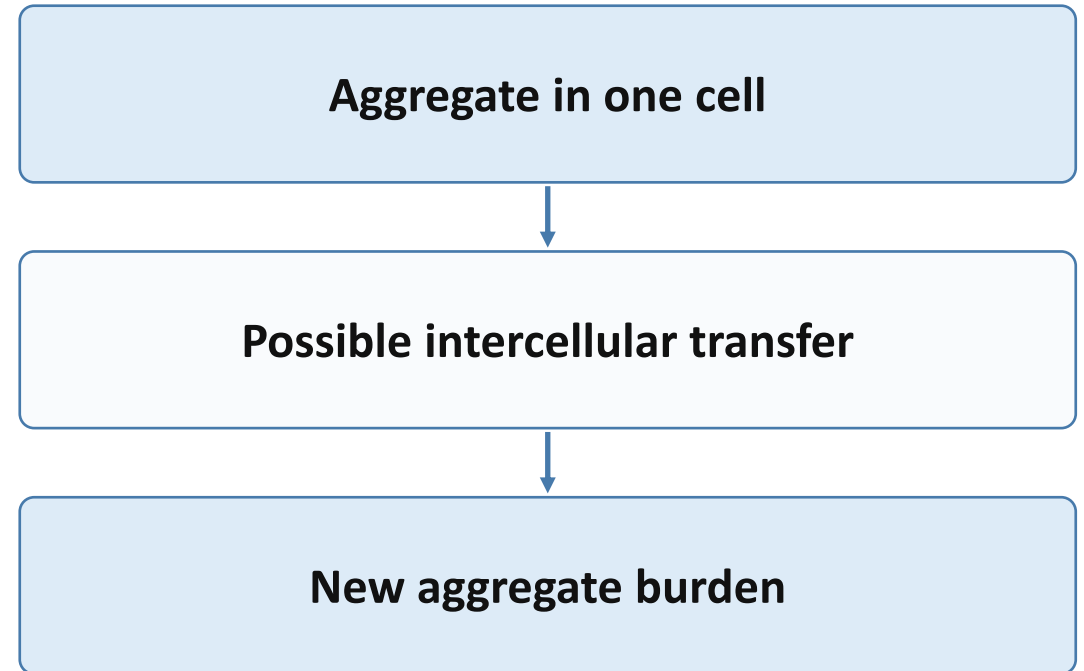
Loss of normal function

Functional protein → aggregate pool

Misfolded protein species may trigger cellular death pathways. • Sequestration may reduce availability of functional protein. • The relative contribution varies across disease mechanisms.

Cell-to-cell spread is a qualified hypothesis

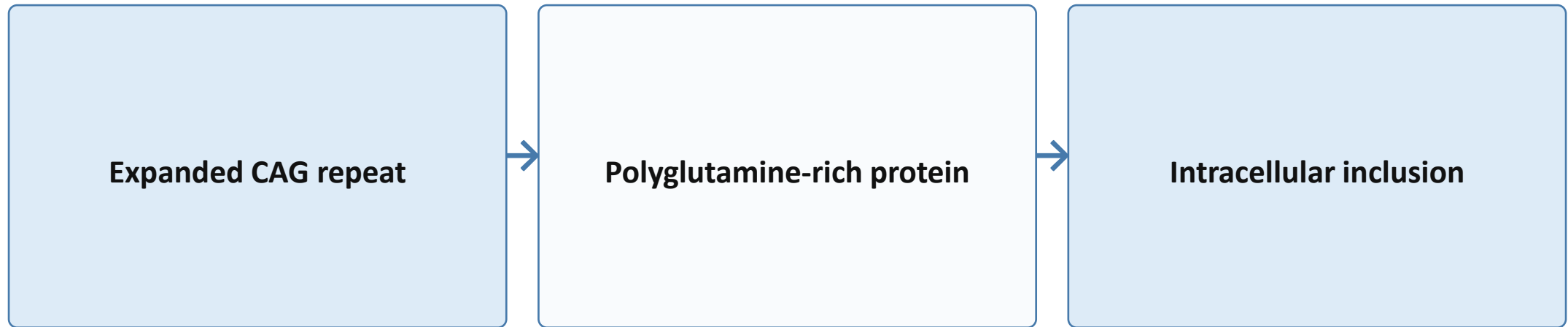
- Disease-associated aggregates have been observed to spread between cells in experimental settings.
- Much supporting evidence comes from animal studies.
- Prion disease provides a clear pathogenic example; Broader generalization requires caution.



Protein origins differ across diseases

Illustrative disease	Protein origin
Huntington disease	Mutant huntingtin with polyglutamine expansion
Alzheimer disease	Amyloid- β from precursor processing
Parkinson disease	Aggregation of α -synuclein

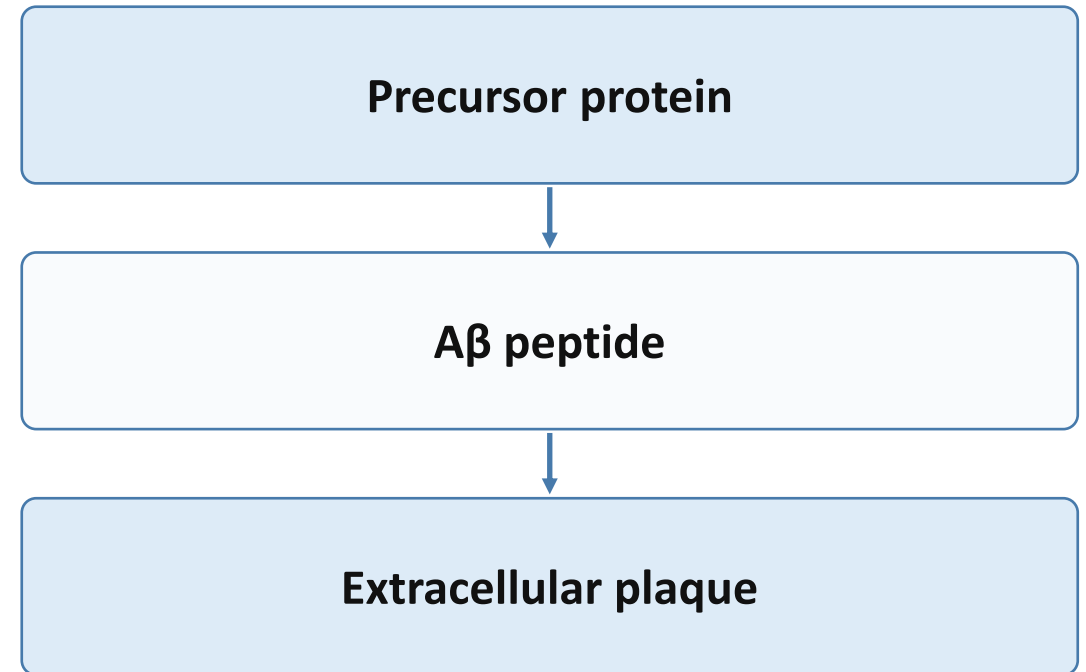
Polyglutamine expansions favor aggregation



An expanded repeat changes the encoded polyglutamine tract. • Huntingtin is a disease-defining example. • Related polyglutamine proteins accumulate in several ataxias and motor neuron disorders.

Amyloid- β is derived from a precursor

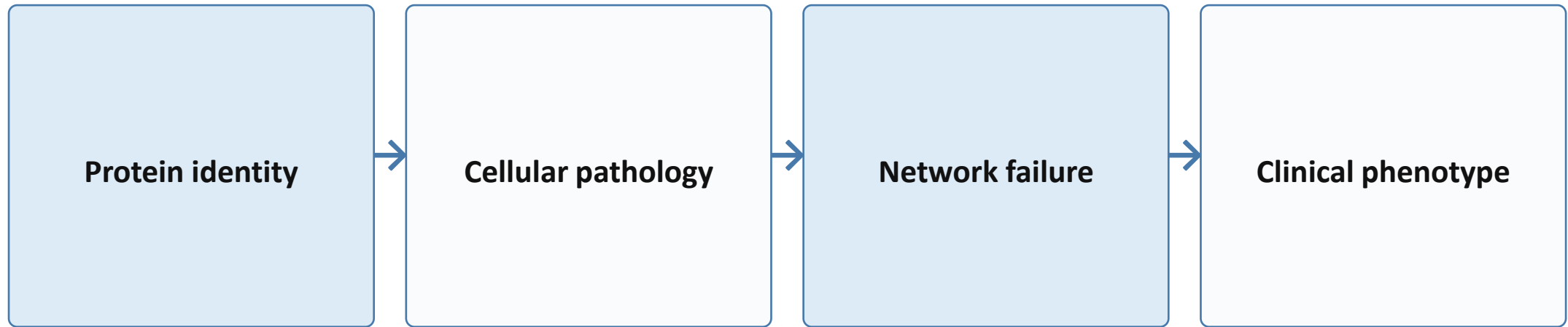
- Amyloid- β (A β) is a peptide cleaved from a larger protein.
- Its aggregation is central to the pathological signature of Alzheimer disease.
- Alzheimer disease also features tau-containing neurofibrillary tangles.



α -Synuclein is a major aggregate protein

Condition	Characteristic inclusion location
Parkinson / Lewy body spectrum	Neuronal Lewy bodies
Multiple system atrophy	Oligodendroglial cytoplasmic inclusions

Biology and histology must be linked

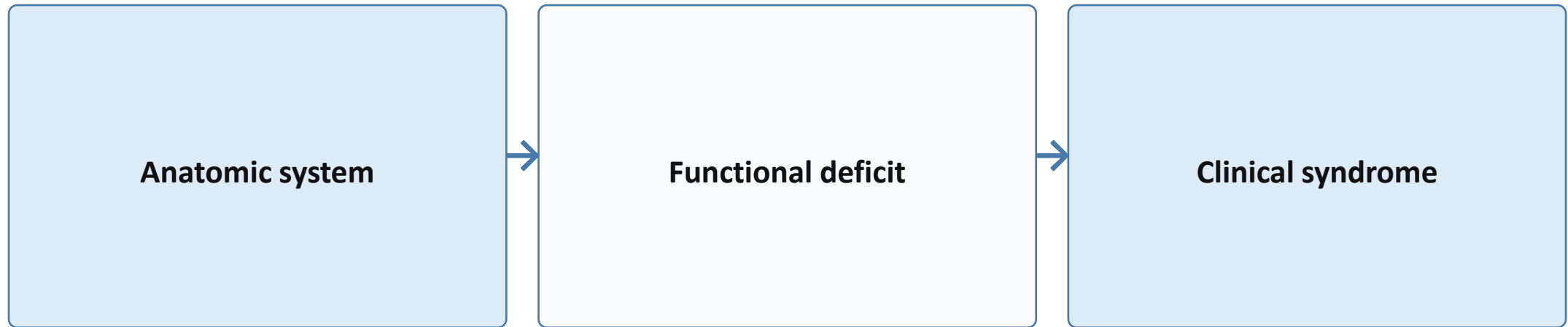


An aggregate protein suggests a molecular mechanism. • Its microscopic location provides the pathologic pattern. • The affected neural system explains the dominant clinical deficits.

Two complementary classification systems

Symptom / anatomy	Pathology / molecule
Dementia, parkinsonism, ataxia	A β , tau, α -synuclein
Behavior / language deficits	TDP-43, FUS
Motor neuron weakness	SOD1, TDP-43, FUS

Clinical classifications emphasize location



Neocortical damage can present with cognitive impairment. • Striatonigral dysfunction may present with parkinsonism. • Motor neuron dysfunction can cause progressive weakness.

Molecular classes emphasize deposit identity

Tau

α -Synuclein

TDP-43 / FUS

PrP / polyglutamine

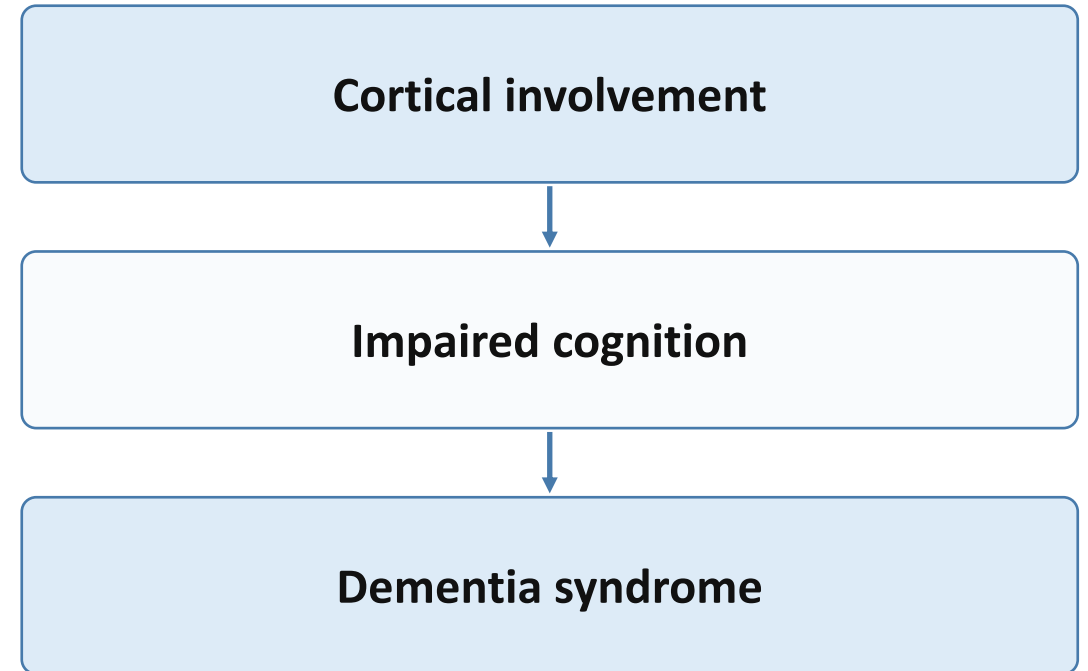
Tauopathies are linked by tau-positive abnormalities. • Synucleinopathies contain disease-associated α -synuclein deposits. • Other major protein families include A β , TDP-43, FUS, PrP, and polyglutamine proteins.

Topography and molecular class can cross

Clinical syndrome	Different molecular associations
Dementia	A β /tau; FTLD proteins; prion protein
Parkinsonism	α -Synuclein; tau
Motor neuron disease	TDP-43; SOD1; FUS

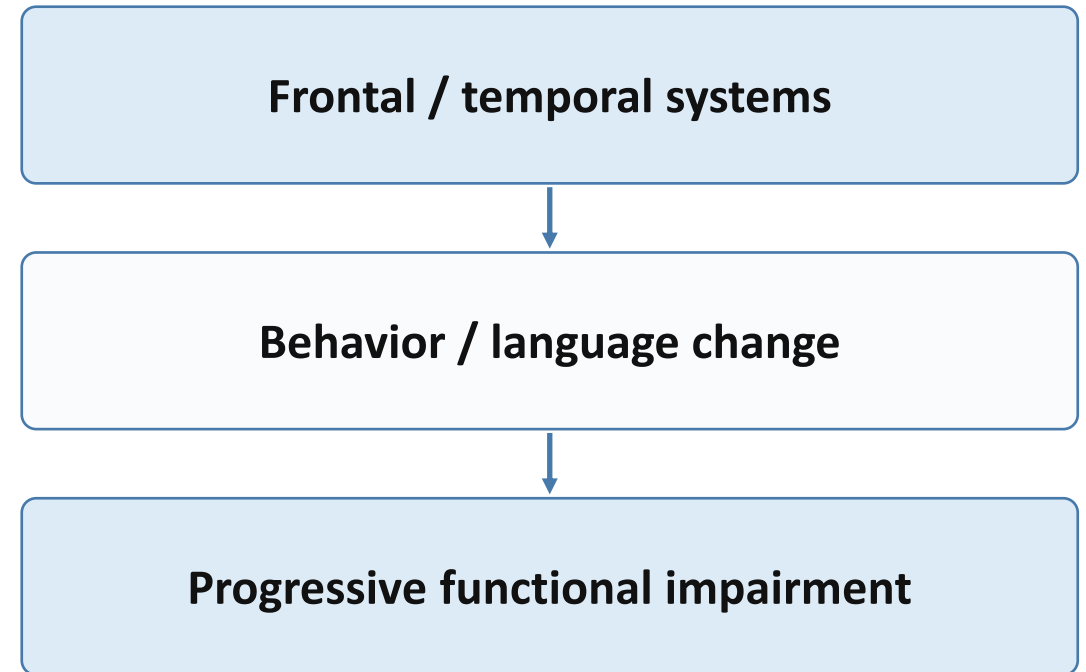
Cognitive-predominant neurodegeneration

- Higher cortical dysfunction is a common presentation.
- Alzheimer disease is typically associated with progressive cognitive decline.
- Prion disease provides an example of unusually rapid progression.



Behavioral and language syndromes

- Frontal and temporal lobe dysfunction alters behavior or language.
- These deficits can precede substantial memory impairment in FTLD.
- The molecular substrate of FTLD is heterogeneous.



Hypokinetic movement disorders

- Parkinson disease is associated with loss of substantia nigra dopaminergic neurons.
- Slowness of movement, rigidity, and tremor occur in the clinical syndrome.
- Similar clinical motor deficits can arise through several distinct diseases.

Nigrostriatal circuit dysfunction



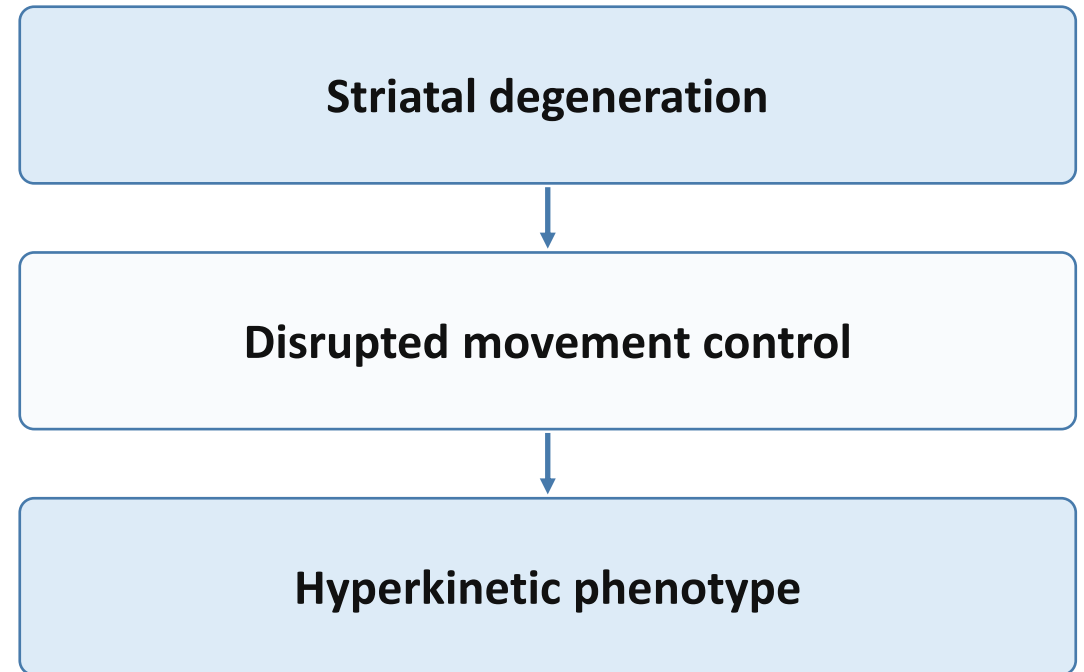
Impaired movement initiation



Parkinsonian syndrome

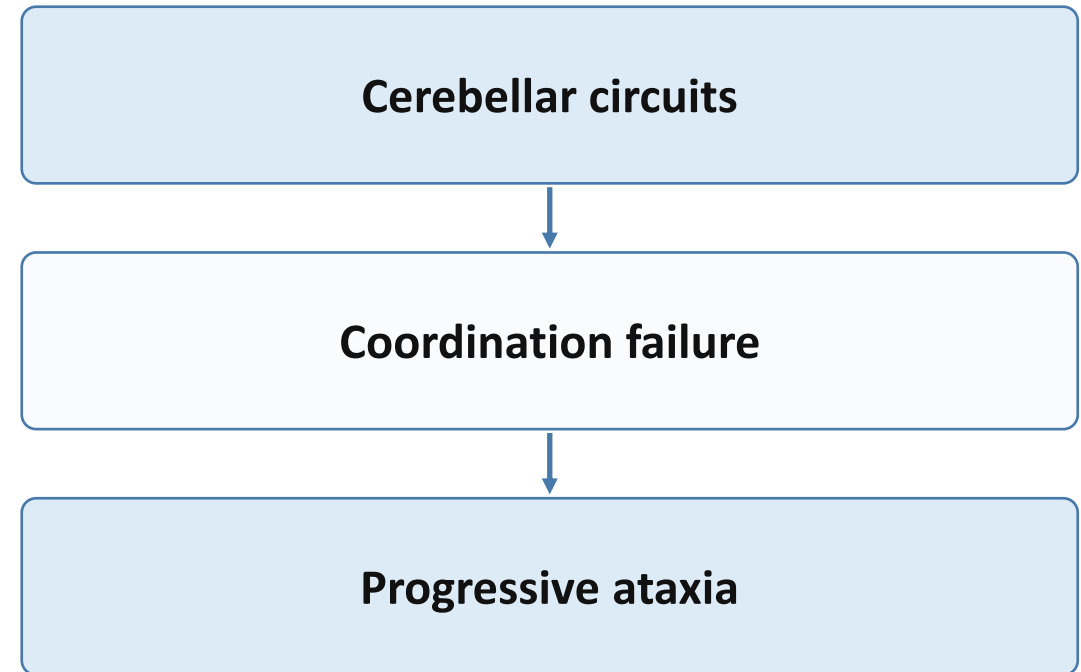
Hyperkinetic movement disorders

- Huntington disease typically presents with hyperkinetic movement abnormalities.
- The striatum is a major site of degeneration.
- An inherited expansion in HTT provides a molecular anchor for diagnosis.



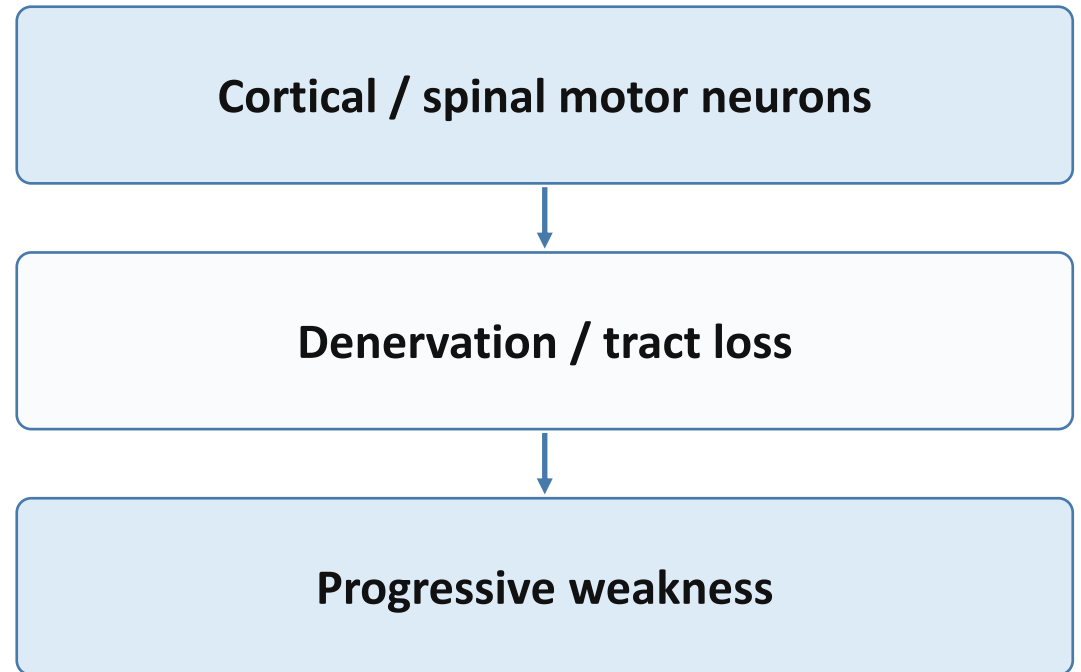
Cerebellar and spinocerebellar syndromes

- Degeneration of cerebellar pathways often produces progressive ataxia.
- Several inherited spinocerebellar ataxias involve repeat expansions.
- The clinical category is molecularly heterogeneous.



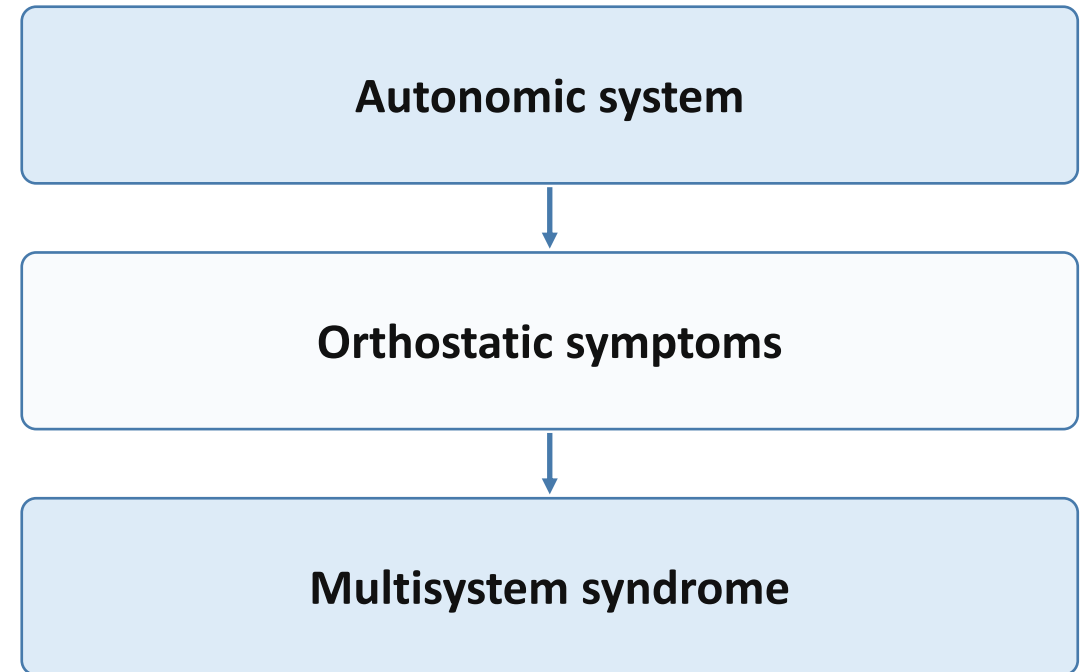
Motor neuron–predominant syndromes

- ALS affects both upper and lower motor neuron systems.
- Weakness develops through progressive denervation and motor pathway damage.
- Pathology may include distinct disease-linked protein inclusions.

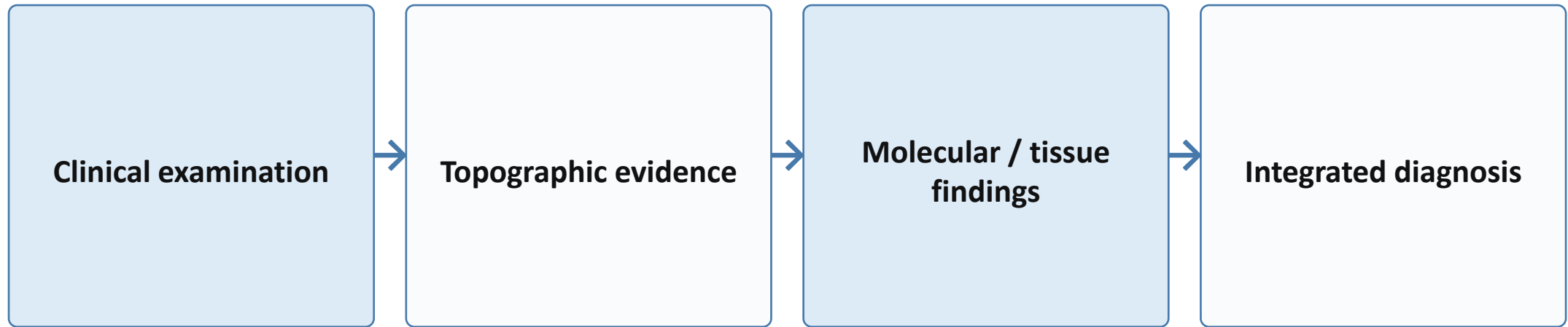


Autonomic involvement identifies another axis

- Multiple system atrophy often involves autonomic circuits.
- Orthostatic hypotension is an important clinical manifestation.
- Parkinsonism and/or cerebellar ataxia may accompany autonomic dysfunction.



Clinical syndrome does not define the deposit



A similar movement phenotype may reflect different aggregates. • Identical proteins may appear in anatomically different syndromes. • Final interpretation integrates clinical and pathological evidence.

Major proteinopathy families

Molecule	Illustrative disease group
A β + tau	Alzheimer disease
Tau	FTLD-tau; PSP; CBD
α -Synuclein	PD / DLB; MSA
TDP-43 / FUS	FTLD; ALS

Prion proteinopathy is mechanistically distinctive



Misfolded PrP can promote conformational conversion of additional PrP. • Propagation of the altered conformation explains transmissibility. • Prion diseases classically produce spongiform neural tissue change.

Tau appears across distinct syndromes

Alzheimer disease

FTLD-tau

PSP

CBD

Tau occurs in Alzheimer neurofibrillary tangles. • Tau also characterizes PSP, corticobasal degeneration, and some FTLD. • A common protein does not imply identical lesion distribution or symptoms.

Synucleinopathies differ by cellular compartment

Neuronal inclusions	Oligodendroglial inclusions
PD / dementia with Lewy bodies	MSA
Lewy bodies	Glial cytoplasmic inclusions

TDP-43 and FUS link clinical categories

FTLD phenotype

Shared protein pathology

ALS phenotype

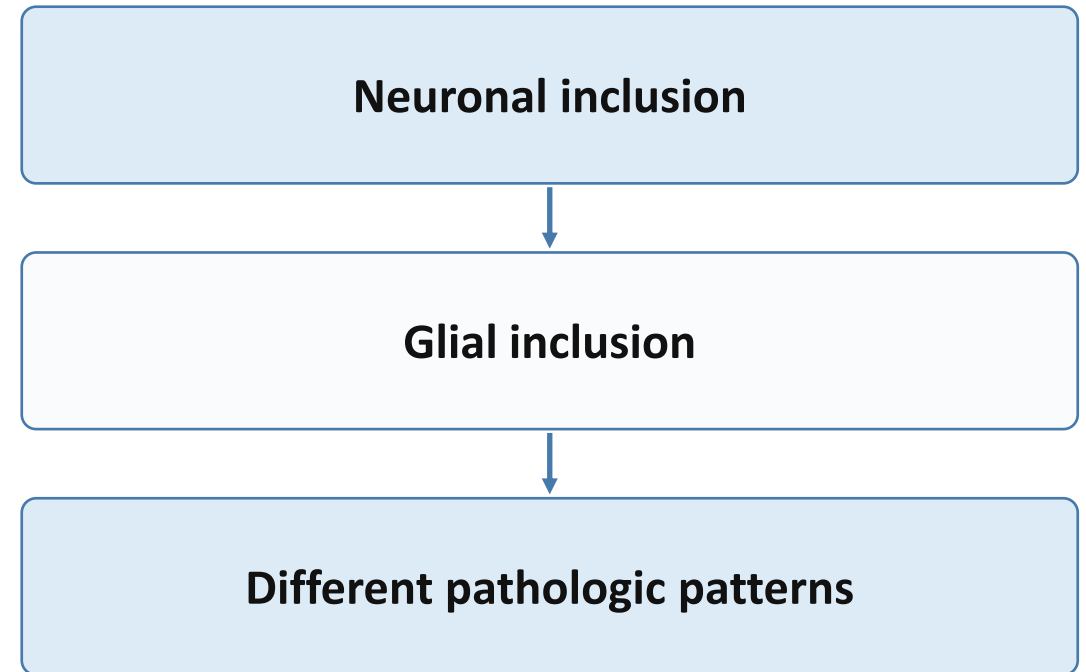
Both proteins occur in some FTLD disorders. • Both also occur in subsets of ALS. • This molecular overlap supports an FTLD–motor neuron disease spectrum.

Polyglutamine disorders share a mutation motif

Disorder	Expanded protein
Huntington disease	Huntingtin
Selected SCAs	Several distinct proteins
Spinal and bulbar muscular atrophy	Androgen receptor

Neuron versus glia: Localization matters

- Many diseases feature neuronal inclusions.
- MSA prominently contains α -synuclein inclusions in oligodendrocytes.
- The affected cell type changes interpretation of apparently similar aggregates.

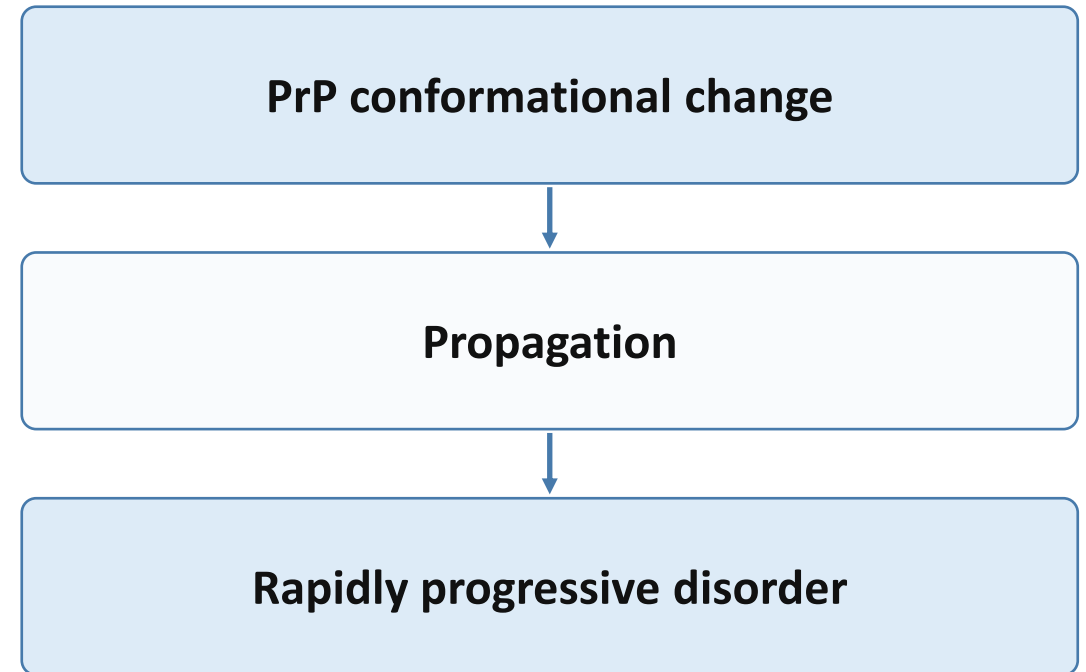


Microscopic structures have distinct names

Pattern	Illustrative association
Plaques / tangles	Alzheimer disease
Lewy bodies	Parkinson / Lewy body spectrum
Spongiform change	Prion disease

Prion disease: Rapid clinical course

- Prion disorders can be sporadic, familial, or acquired.
- Rapidly progressive dementia is a key clinical pattern.
- Misfolded PrP is central to pathogenesis.



Prion disease: Spongiform morphology

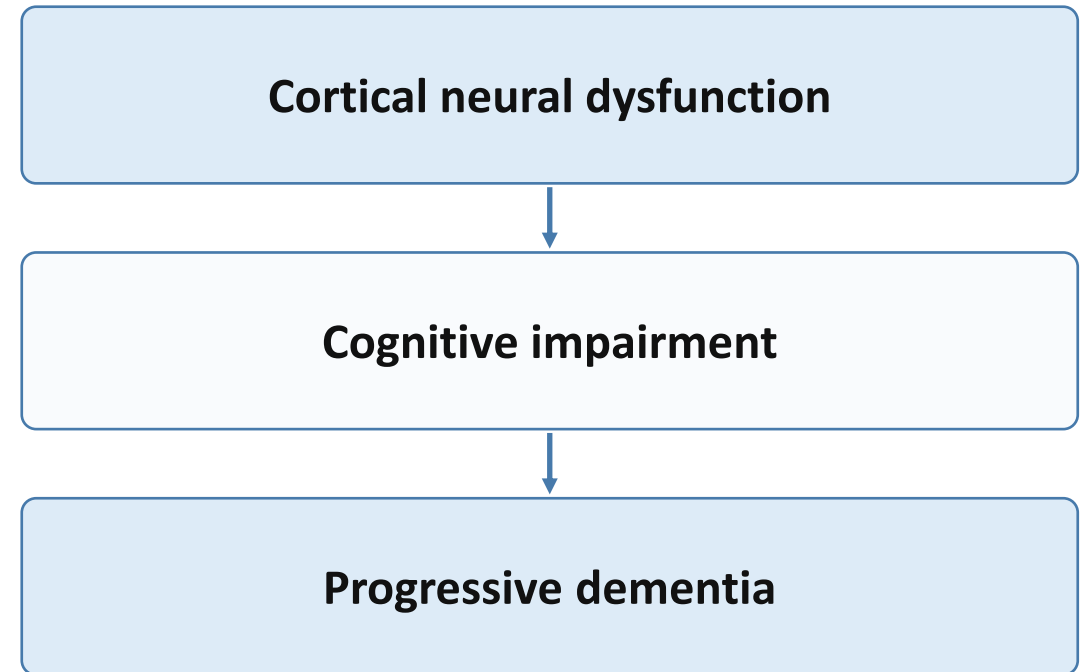
- Microscopic tissue shows vacuoles within gray matter neuropil.
- Neuronal loss and reactive gliosis may occur in advanced disease.
- Inflammation is characteristically absent in the described pattern.

Alzheimer disease: Dual protein signature

Lesion	Principal protein
Amyloid plaque	A β
Neurofibrillary tangle	Tau

Alzheimer disease: Clinical–anatomic link

- Insidious higher cognitive impairment is characteristic.
- The neocortex is critical to the progressive dementia syndrome.
- AD is distinguished from rapidly progressive prion-associated dementia by clinical course.

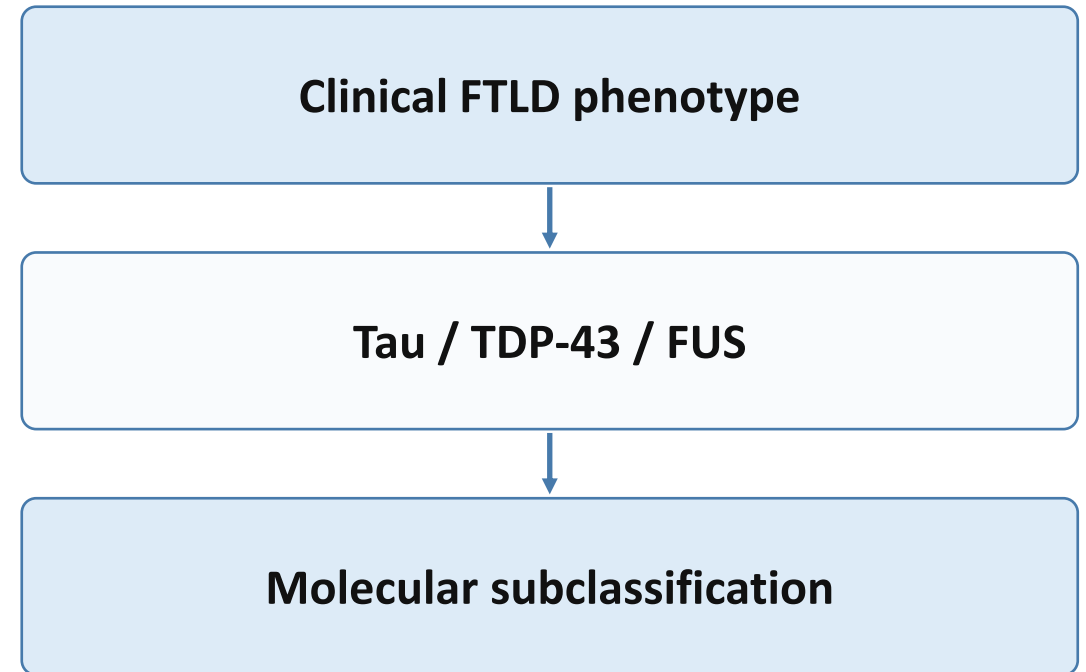


FTLD: Predominantly frontal–temporal degeneration

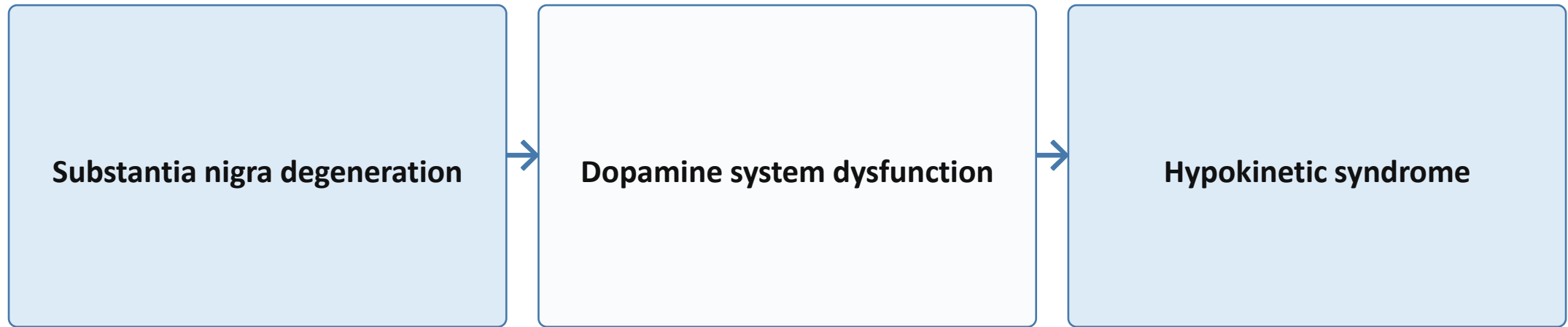
Anatomic pattern	Molecular possibilities
Frontal / temporal degeneration	Tau
Behavior / language impairment	TDP-43 or FUS

FTLD: One syndrome, multiple proteins

- A shared clinical family encompasses heterogeneous pathology.
- Molecular categories cannot be assigned from symptoms alone.
- Motor neuron disease can coexist in part of the FTLD spectrum.



Parkinson disease: Selective nigral injury



Loss of dopaminergic neurons in substantia nigra drives hypokinetic abnormalities. • Typical features include slowed movement, rigidity, tremor, and altered gait. • Parkinsonism describes a syndrome, not a single histological diagnosis.

Parkinson disease: Lewy body association

Parkinsonian group	Molecular pattern
PD / DLB spectrum	α -Synuclein Lewy bodies
PSP / CBD	Tau
MSA	Glial α -synuclein

Dementia with Lewy bodies

- Diffuse Lewy body deposition includes cortex and brainstem.
- Fluctuating cognitive impairment and visual hallucinations are described features.
- Clinical and pathological boundaries with PD dementia can overlap.

Widespread neuronal Lewy bodies



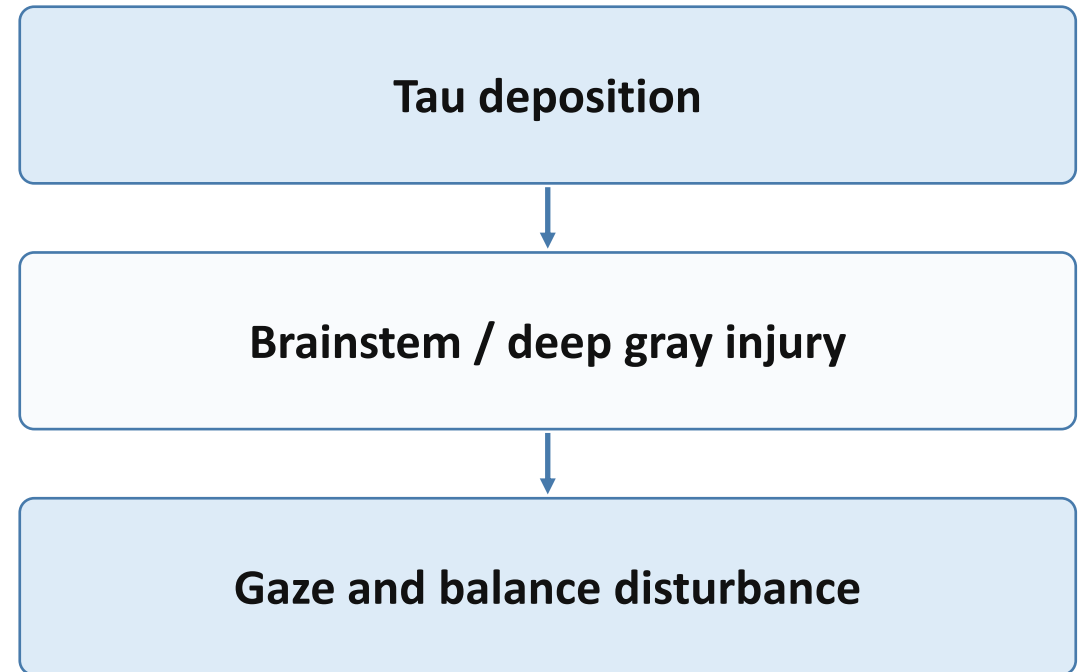
Cortical dysfunction



Dementia phenotype

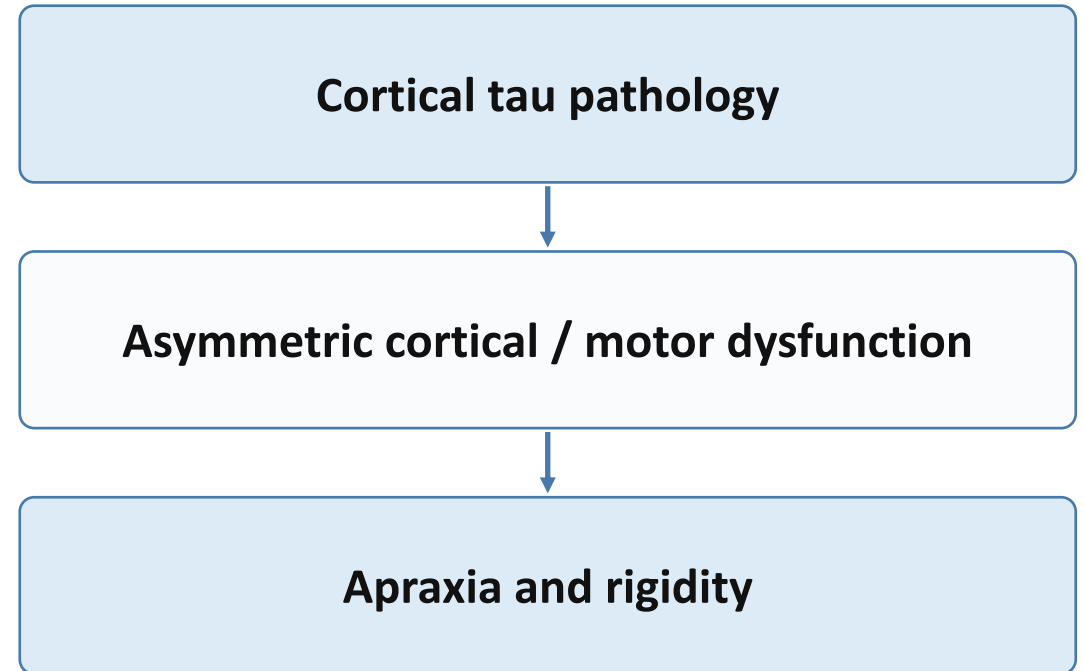
Progressive supranuclear palsy

- PSP is a tauopathy with parkinsonism.
- Postural instability, falls, and voluntary eye movement abnormalities are typical.
- Tau inclusions affect neurons and glia, prominently in deep regions and brainstem.



Corticobasal degeneration

- CBD belongs to the tauopathy group.
- Asymmetric motor impairment, rigidity, and apraxia are important clues.
- The cerebral cortex is particularly affected by the disease process.



Multiple system atrophy: Unusual glial pathology

MSA	Lewy body spectrum
Oligodendroglial α -synuclein	Neuronal α -synuclein
White matter tract pathology prominent	Lewy body neuronal pathology prominent

Multiple system atrophy: Three circuits

Striatonigral

Parkinsonism

Olivopontocerebellar

Ataxia

Autonomic

Autonomic failure

Striatonigral involvement contributes to parkinsonism. • Olivopontocerebellar involvement contributes to ataxia. • Autonomic system involvement contributes to orthostatic dysfunction.

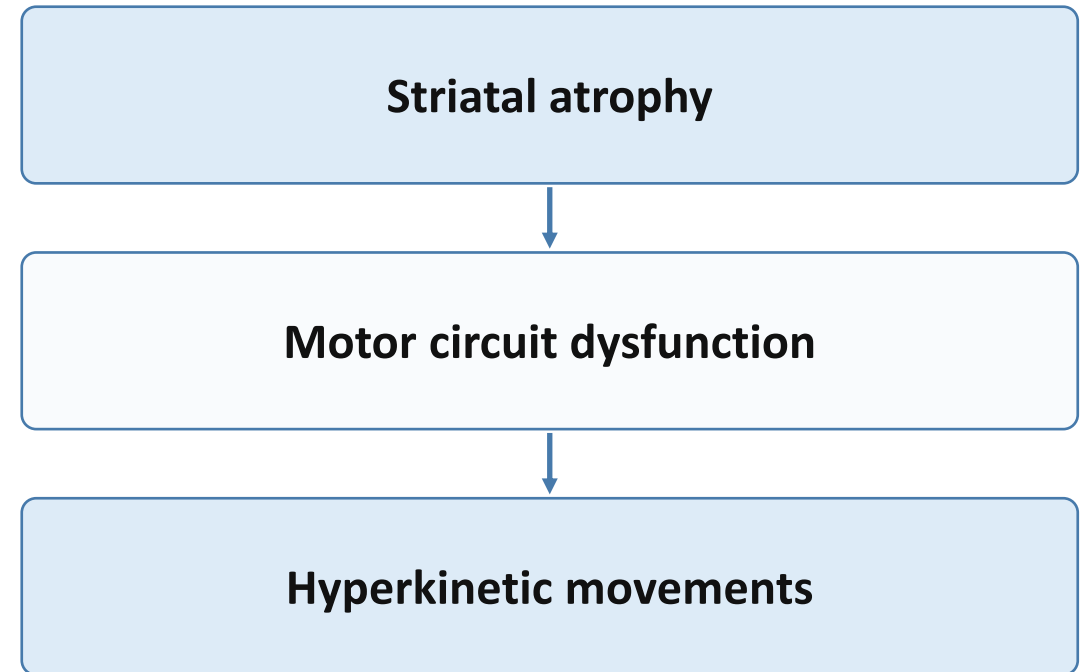
Huntington disease: Inherited polyglutamine



An expanded CAG repeat in HTT encodes mutant huntingtin. • Mutant protein is associated with intranuclear inclusions. • This is a clear genotype–proteinopathy association.

Huntington disease: Striatal degeneration

- The disease strongly affects the striatum.
- Loss of striatal neurons contributes to hyperkinetic motor abnormalities.
- Macroscopic striatal atrophy and ventricular enlargement are described.



Spinocerebellar ataxias are heterogeneous

CAG / polyglutamine

Noncoding repeats

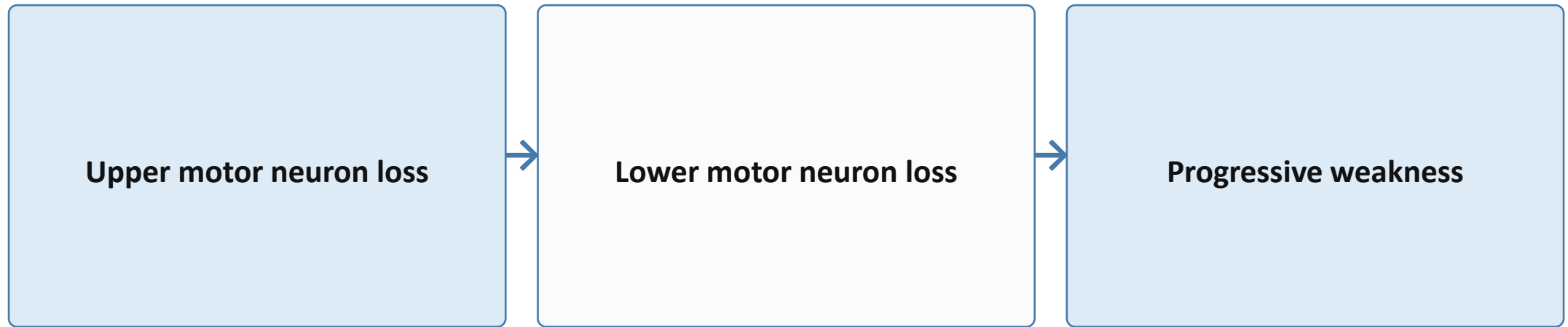
Conventional variants

Different SCAs share progressive impairment of coordination. • Several subtypes reflect expanded polyglutamine tracts. • Other subtypes involve noncoding repeat expansions or conventional mutations.

Three genetic routes in spinocerebellar ataxia

Genetic class	Interpretation
Coding CAG expansion	Polyglutamine protein
Noncoding repeat expansion	Mechanism variable / incompletely understood
Other sequence / dosage variants	Diverse protein functions

ALS: Upper and lower motor neuron disease



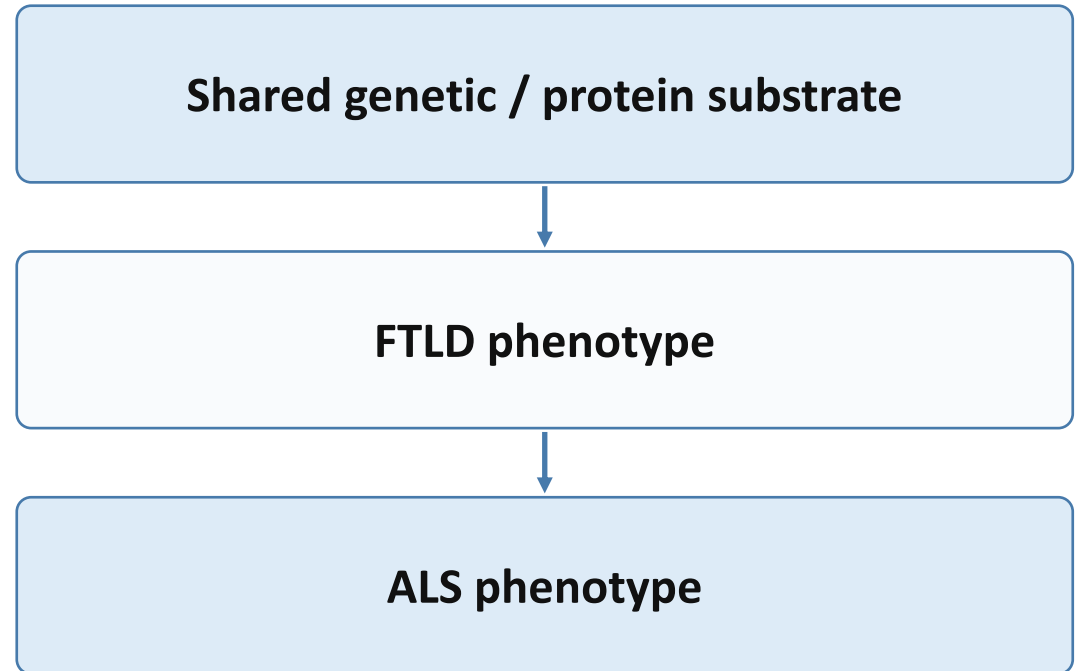
ALS affects cortical upper motor neurons and spinal/brainstem lower motor neurons. • Degeneration causes denervation and progressive muscle weakness. • Both motor neuron compartments help define the disorder.

ALS: Several aggregate proteins

Protein	Associated example
SOD1	SOD1-associated ALS
TDP-43	Many sporadic / selected inherited ALS forms
FUS	FUS-associated ALS

ALS and FTLD form an overlapping spectrum

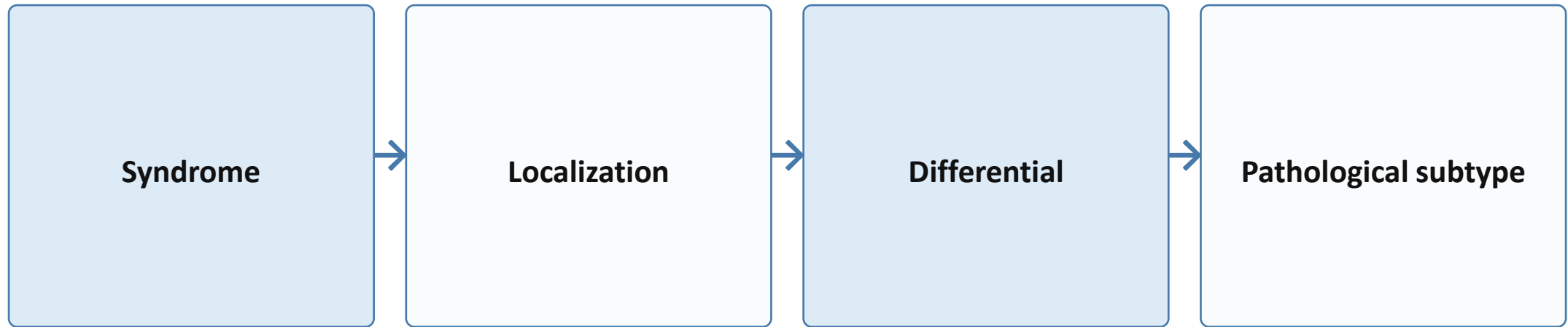
- FTLD and ALS share some genetic and protein abnormalities.
- C9orf72 repeat expansion is an important shared genetic association.
- Motor and cognitive / behavioral phenotypes can overlap.



Inherited causes provide molecular anchors

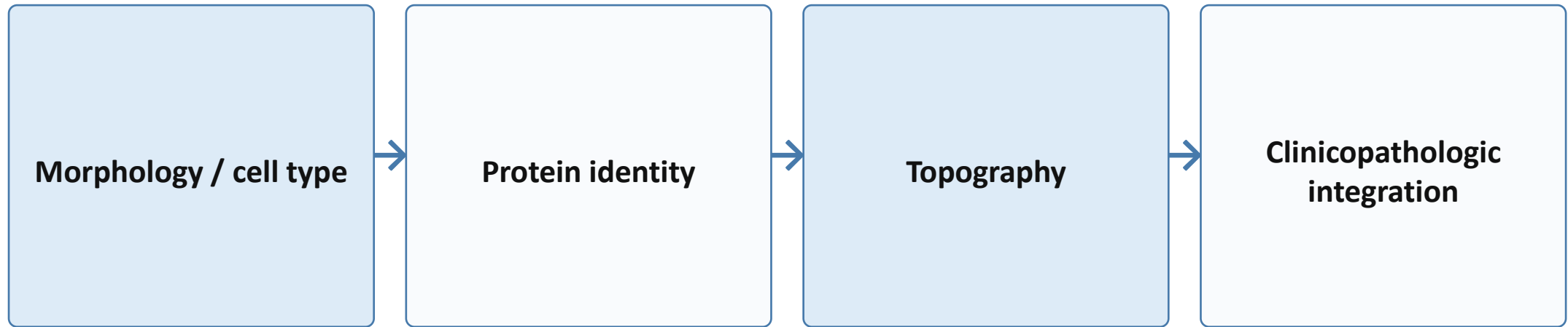
Genetic change	Illustrative disorder
HTT CAG expansion	Huntington disease
PRNP variant	Familial prion disease
C9orf72 repeat expansion	ALS / FTLD
SNCA variants	Inherited PD forms

A practical clinical-first interpretive sequence



Recognize the dominant neurological syndrome. • Localize the most affected functional system. • Construct a differential that includes different molecular pathologies.

A practical pathology-first interpretive sequence



Identify the inclusion morphology and affected cell type. • Determine the major aggregated protein where pathology permits. • Evaluate anatomical distribution and clinical information.

Potential diagnostic confusion: Overlapping pathways

Observation	Diagnostic implication
Same protein; different phenotypes	Topography matters
Same phenotype; different proteins	Protein studies matter
Mixed disease processes	Integrative evaluation required

Apply the framework: Four short vignettes

- Rapidly progressive dementia with spongiform change.
- Insidious dementia with plaques and tangles.
- Parkinsonism with oligodendroglial α -synuclein inclusions.
- Progressive weakness with upper and lower motor neuron loss.

Vignette solutions: Match the defining feature

Defining observation	Best-fitting group
Spongiform change / PrP	Prion disease
A β plaques + tau tangles	Alzheimer disease
Glial α -synuclein	MSA
Upper + lower motor neuron loss	ALS

Integrative matrix: Phenotype to pathology

Presentation	Illustrative pathology
Dementia	AD: A β /tau; FTLD: tau/TDP-43/FUS
Parkinsonism	PD: Lewy bodies; PSP: tau; MSA: glial α -synuclein
Hyperkinesia	HD: expanded huntingtin
Weakness	ALS: motor neuron degeneration

Foundational principles to retain

- Neurodegeneration is selective, progressive neuronal loss.
- Proteostasis failure and protein accumulation recur across most of these disorders.
- Oligomer toxicity, loss of normal protein function, and possibly intercellular transfer are distinct concepts.
- Clinical localization and molecular pathology are complementary but imperfect classification axes.

Primary reference and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
- Chapter 28: Neurodegenerative Diseases, p. 1159; Tables 28.3–28.4.
- Adjacent disease sections through motor neuron disorders inform brief comparisons.
- Schematic diagrams are original editable representations, not diagnostic specimens.