
Frontotemporal Lobar Degenerations

Anatomic patterns · Protein pathology · Clinicopathologic interpretation

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Learning objectives

- Distinguish frontotemporal lobar degeneration (FTLD) from the clinical label frontotemporal dementia (FTD).
- Compare FTLD-tau and FTLD-TDP using protein biology, genes and inclusion morphology.
- Recognize characteristic changes of Pick disease and the limitations of clinical subtype prediction.
- Integrate protein pathology with clinical presentation and anatomical vulnerability.

FTLD defines a heterogeneous pathologic group

Anatomic target

Focal degeneration predominantly affecting frontal and/or temporal lobes.

Clinical expression

Early changes in behavior, personality or language are common.

Protein classification

Abnormal tau or TDP-43 inclusions define the major pathologic patterns.

FTLD and FTD are related, not identical

FTLD: Pathology

- Describes the pattern of lobar neurodegeneration.
- Specifies the tissue lesion and proteinopathy.
- Definitive classification relies on neuropathology.

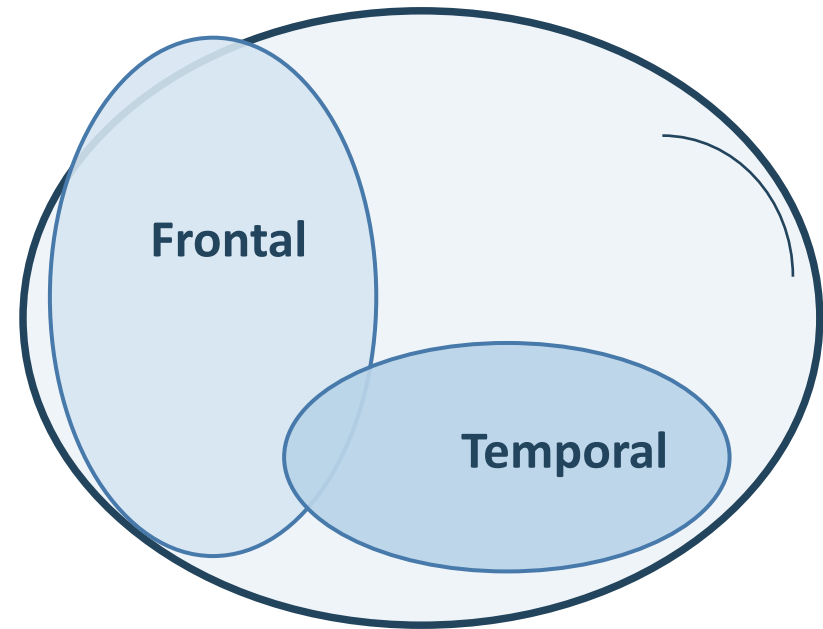
FTD: Clinical syndrome

- Used in clinical settings for frontotemporal dementias.
- Describes behavioral and language presentations.
- Does not uniquely predict the deposited protein.

Focal degeneration gives clinical specificity

Simplified lobar schematic—not anatomical imaging

- Frontal-predominant damage: Disturbances of personality and behavior.
- Temporal language-network involvement: Progressive aphasic manifestations.
- Regional involvement may be mixed and becomes broader with progression.



Behavioral change can be the initial signal

- Alterations in personality and behavior may precede prominent memory loss.
- Behavior-led presentations are clinically recognizable, but not pathologically uniform.
- Progression can add language deficits and more generalized cognitive decline.

Language deficits can dominate presentation

- Aphasia may precede major memory disturbance in frontotemporal dementia.
- Language-led and behavior-led forms overlap as the disease evolves.
- Clinical language presentation by itself does not establish tau versus TDP-43 pathology.

Two common initial clinical emphases

Behavior-dominant

- Early personality alteration.
- Early behavioral disturbance.
- Language impairment may emerge later.

Language-dominant

- Early progressive aphasia.
- Personality/behavior change may follow.
- Global deficits eventually develop.

Clinical syndromes show overlapping features

Not rigid categories

The textbook recognizes several variants organized by dominant symptoms.

Cross-domain evolution

Behavioral and aphasic symptoms are not mutually exclusive.

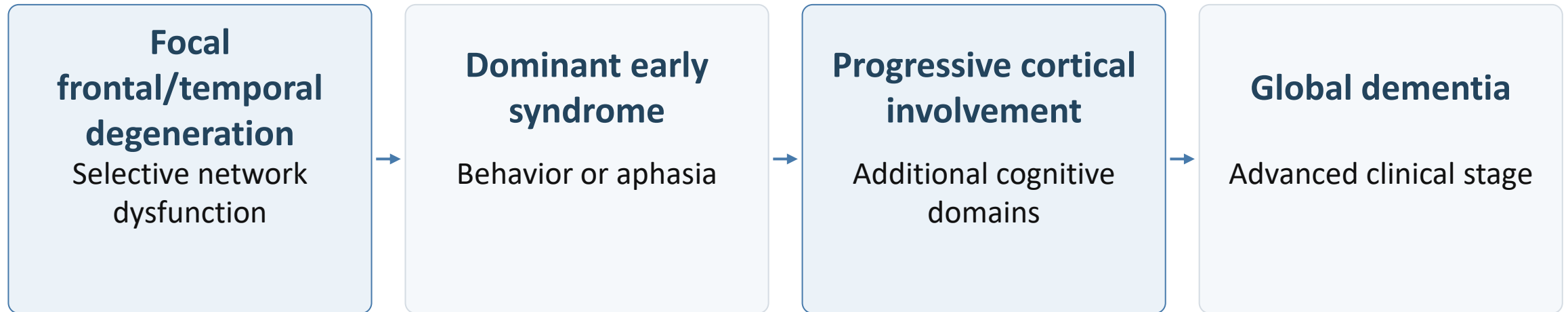
Protein heterogeneity

A clinical variant cannot be equated with one aggregate type.

FTLD versus Alzheimer disease: Presenting emphasis

Feature	FTLD (typical emphasis)	Alzheimer disease (typical emphasis)
Early prominent change	Personality, behavior, language	Forgetfulness and memory disturbance
Later disease	Global dementia may develop	Language, skilled actions and other domains deteriorate
Definitive pathology	Proteinopathy and distribution	Amyloid- β plaques with tau tangles

Focal impairment can progress to global dementia



An initially focal syndrome does not imply a persistently restricted disease.

Motor dysfunction does not exclude FTLN

Primary presentation

- Personality, behavior or language changes typically dominate.
- Early memory impairment need not be the chief problem.

Possible additional findings

- Some patients develop extrapyramidal motor symptoms.
- Certain subtypes show nigral degeneration at autopsy.

Early-onset dementia: An important context

Younger onset

FTLD is among the more common causes of early-onset dementia.

Textbook comparison

FTLD and AD occur with similar frequency below age 65.

Interpretation

This textbook statement is population/context dependent; It is not a universal risk estimate.

Why clinical examination cannot provide full classification

Can suggest

- A frontal or temporal functional syndrome.
- A pattern of dominant behavioral or aphasic deficits.
- Probable neurodegenerative disease.

Cannot establish on its own

- The molecular protein of the inclusions.
- The definitive neuropathologic subtype.
- Whether tau- or TDP-43-related histology is present.

FTLD classification centers on abnormal proteins

FTLD-tau

Cytoplasmic tau inclusions in affected neurons; May include Pick bodies.

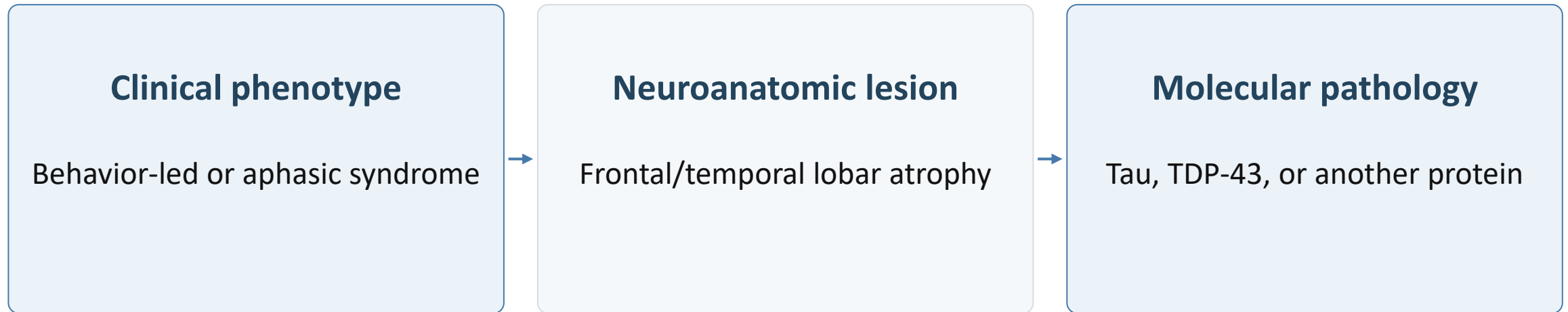
FTLD-TDP

Abnormal TDP-43-containing inclusions in neuronal compartments and processes.

Other inclusion proteins

FUS is also linked to FTLD in the chapter's neurodegeneration table; Not the main focus here.

Three levels of description must stay separate



A clinical syndrome is not equivalent to a protein-defined diagnosis.

Sporadic and heritable FTLD coexist

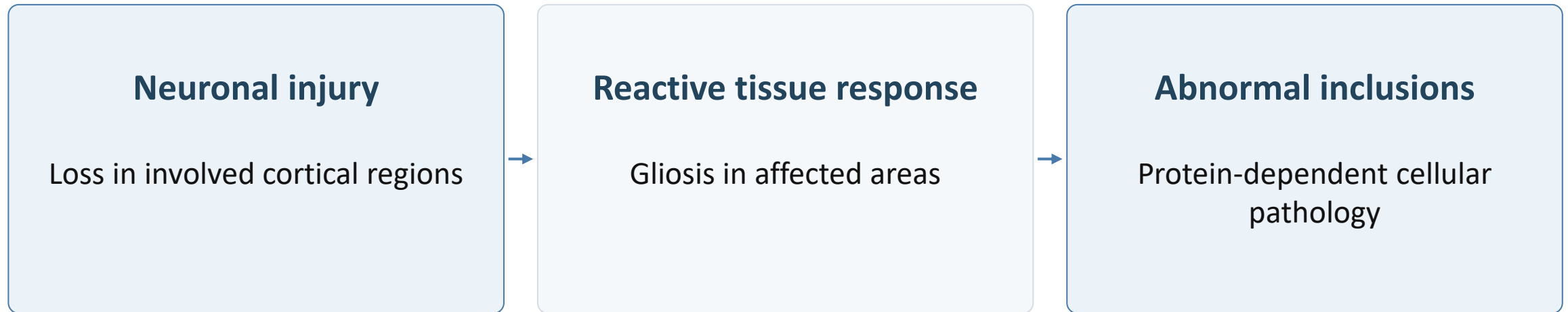
Sporadic disease

- Most FTLD cases are sporadic.
- Absence of family history does not exclude the diagnosis.

Inherited forms

- Genetic examples include MAPT, C9orf72, TARDBP and GRN.
- Familial forms illuminate how proteins become dysregulated.

Shared histopathologic response to degeneration

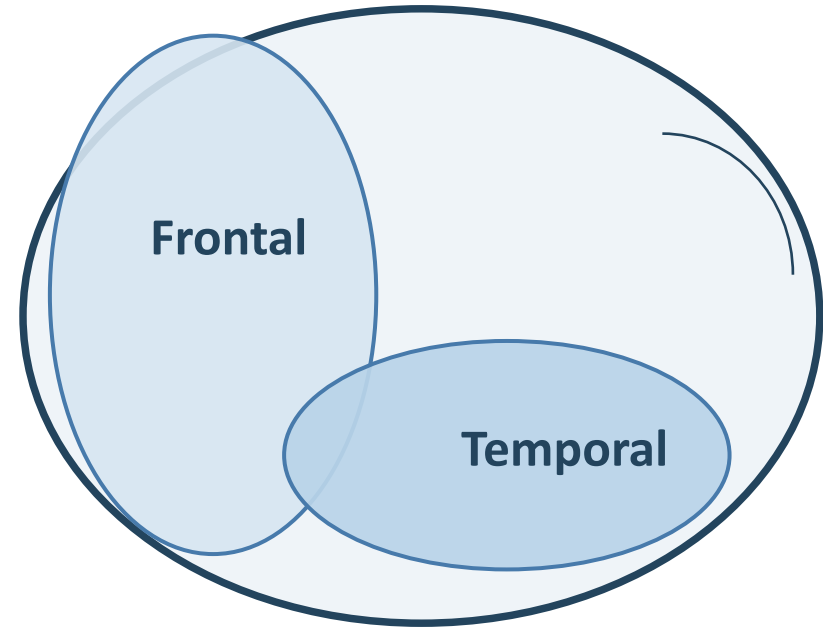


The atrophy seen grossly reflects loss of neuronal tissue, accompanied by gliosis.

Topography links pathology to phenotype

Simplified lobar schematic—not anatomical imaging

- Atrophy is variable in severity and distribution among FTLD forms.
- Clinically dominant deficits often correspond to the affected lobar territories.
- Distribution alone does not prove the molecular subtype.



FTLD-tau is a tau accumulation disorder

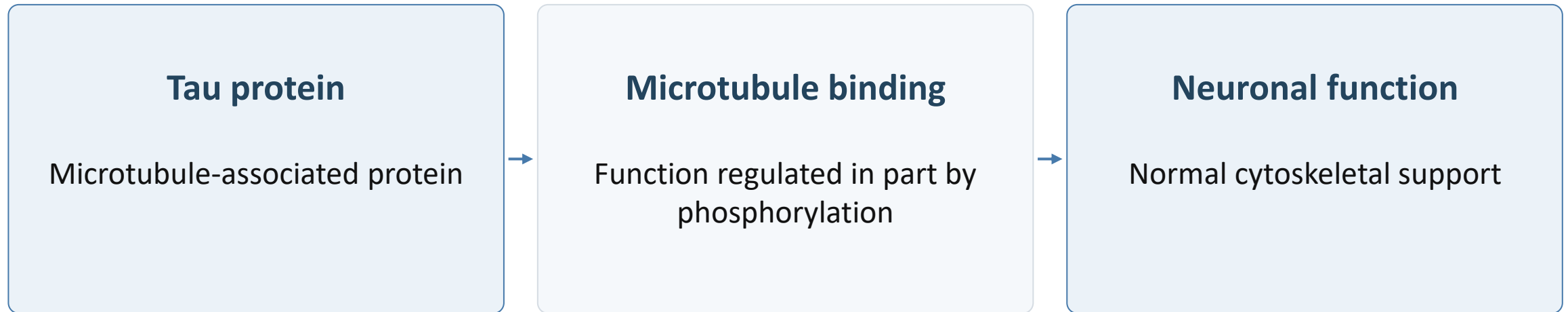
Core lesion

- Progressive neuronal loss and reactive gliosis in involved cortex.
- Cytoplasmic neuronal inclusions containing tau.

Variable inclusion pattern

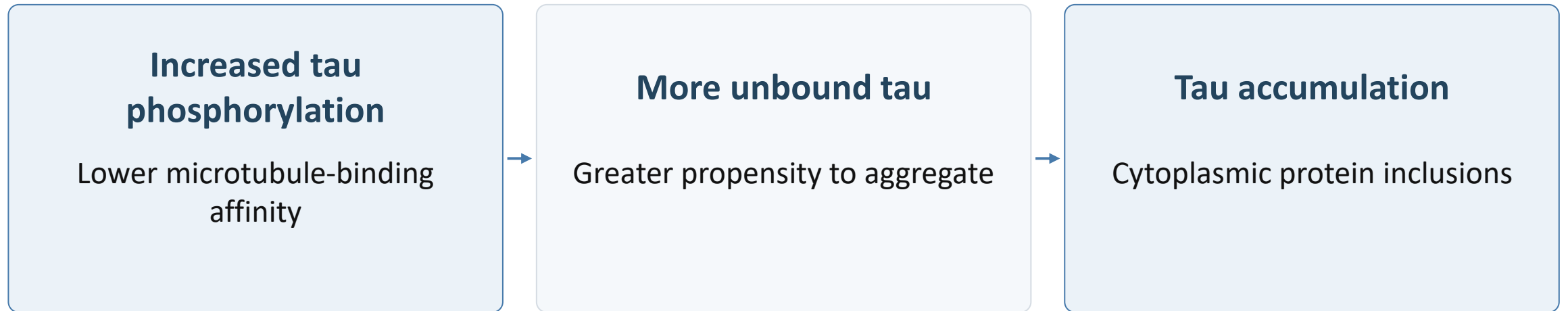
- Some inclusions resemble Alzheimer-type tangles.
- Others are rounded and smooth: Pick bodies.

Physiologic tau is associated with microtubules



Binding becomes less favorable as tau phosphorylation increases.

Phosphorylation changes tau behavior



A biochemical association, not a fully resolved explanation of neurotoxicity.

Tau isoform balance is biologically relevant

Alternative mRNA splicing

MAPT transcripts encode multiple tau isoforms.

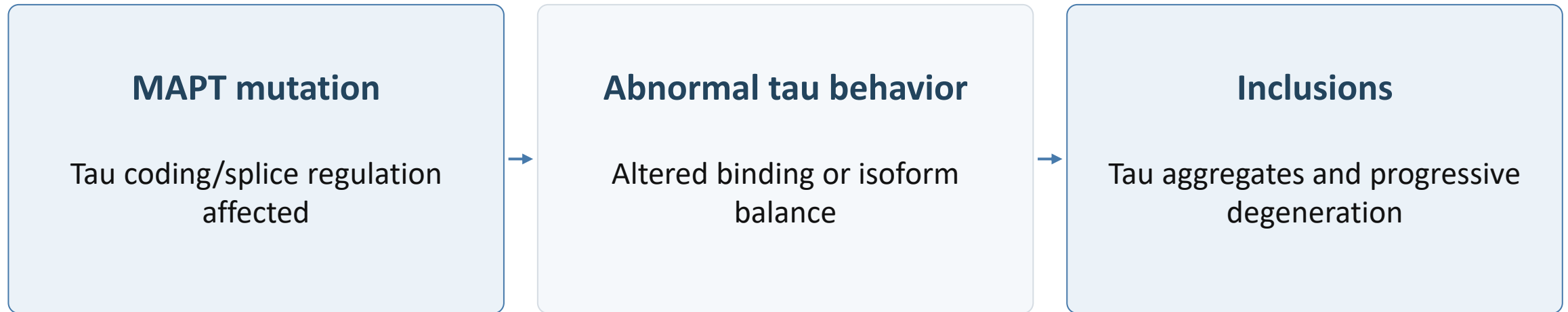
Physiologic balance

Relative abundance of isoforms contributes to normal neuronal function.

Disease association

An altered isoform ratio may encourage aggregation and dysfunction.

MAPT mutations provide a genetic route to FTLD-tau



Sporadic FTLD-tau also occurs without a detected inherited MAPT cause.

MAPT mutation mechanism I: Altered tau protein

Molecular event

- Missense mutations may alter tau phosphorylation behavior.
- This shifts tau away from microtubule binding.

Pathologic interpretation

- Aggregation becomes more favorable.
- Insoluble inclusions occur in vulnerable neurons.

MAPT mutation mechanism II: Altered RNA splicing

Molecular event

- Some variants affect splice-related RNA structure.
- Many relevant variants are intronic.

Pathologic interpretation

- Relative tau isoform expression changes.
- Abnormal isoform balance can provoke dysfunction and aggregation.

Tau toxicity may involve two mechanisms

Loss of physiologic function

Aggregated tau is less available for its normal microtubule-associated role.

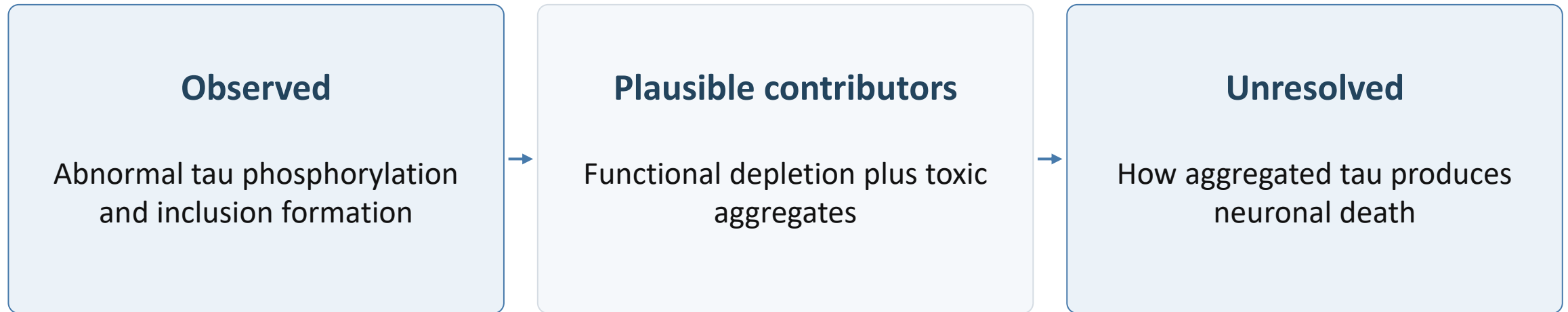
Toxic gain of function

Abnormally phosphorylated aggregated tau may itself impair neurons.

Open mechanistic issue

The relative contributions to neuronal death remain unresolved.

Do not equate tau aggregation with a proven pathway



Separate morphologic association from a demonstrated causal step.

FTLD-tau and Alzheimer disease are not synonymous

Feature	FTLD-tau	Alzheimer disease
Defining accumulated proteins	Tau predominant; no defining amyloid- β plaque pathology	Amyloid- β deposition plus tau tangles
Common clinical emphasis	Behavior and/or language first	Memory disturbance early
Shared finding	Tau-related neuronal inclusions	Tau-related neuronal inclusions

Microscopy in FTLD-tau: Three central findings

- Neuronal loss in the affected cortical regions.
- Reactive gliosis accompanying loss of cortical neurons.
- Tau-immunoreactive fibrillary cytoplasmic inclusions in residual neurons.
- Some subtypes also contain abnormal tau in glial cells.

Glial inclusions broaden the cellular substrate

Neurons

Cortical neuronal inclusions dominate the core description.

Glia

Some FTLD-tau forms contain additional glial tau inclusions.

Diagnostic point

Protein immunoreactivity must be interpreted with cell type and anatomical distribution.

Pick disease is a distinct FTLT-tau subtype

Gross feature

Severe frontal and temporal atrophy, often asymmetric.

Cellular feature

Swollen Pick cells and characteristic cytoplasmic Pick bodies.

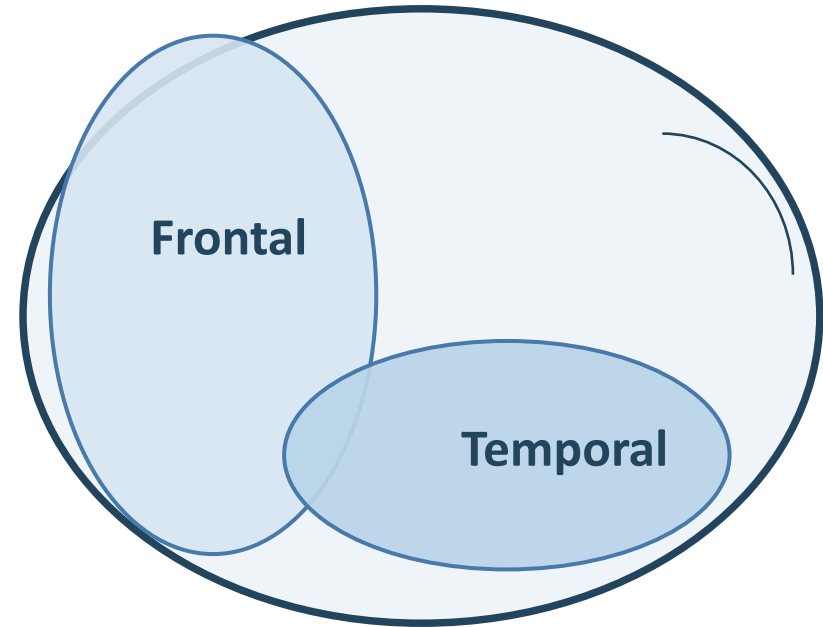
Protein feature

Pick bodies are tau-positive neuronal inclusions.

Pick disease may cause knife-edge gyral atrophy

Simplified lobar schematic—not anatomical imaging

- Atrophy may be especially severe in the frontal and temporal lobes.
- Gyri can become wafer thin, producing a “knife-edge” appearance.
- Frequently asymmetric atrophy helps characterize the gross pattern.



Pick disease shows a selective lobar distribution

Typically affected

- Frontal lobes.
- Temporal lobes.
- Asymmetry is frequent.

Relatively spared

- Posterior two-thirds of the superior temporal gyrus.
- Parietal and occipital lobes usually minimally involved.

Pick disease: Cortical loss favors superficial layers

- Neuronal loss is especially marked in the outer three cortical layers.
- Laminar selectivity is a microscopic counterpart of cortical thinning.
- Layer emphasis contributes to the pathologic pattern but is not sufficient alone.

Conceptual cortical laminae, superficial → deep

Layer I

Layer II

Layer III

Layer IV

Layer V

Layer VI

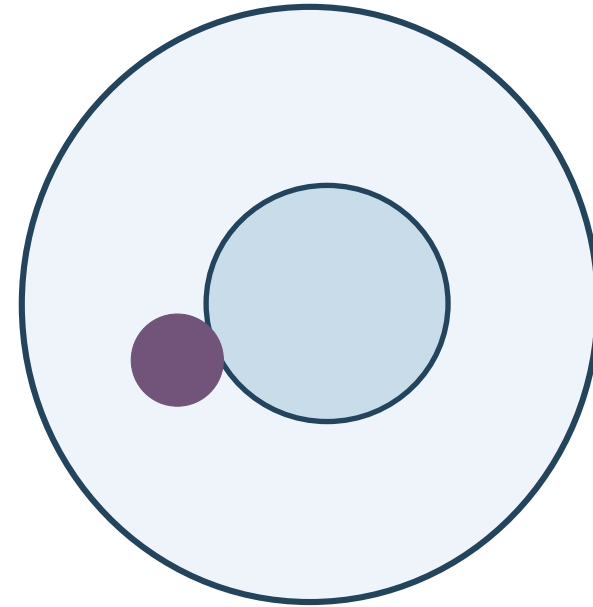
Predominant neuronal loss in outer three layers

Pick cells: Swollen residual neurons

- Some surviving cortical neurons have a chromatolysis-like swelling.
- These swollen neurons are Pick cells.
- Pick cells should be distinguished from the intracellular Pick body inclusions.

Pick bodies are rounded cytoplasmic inclusions

- Pick bodies are round to oval and filamentous.
- They occur within neuronal cytoplasm.
- They are not synonymous with neuronal swelling (Pick cells).



Simplified cellular schematic—not a tissue section

Pick bodies: Complementary staining evidence

Silver impregnation

- Pick bodies stain intensely with appropriate silver stains.
- The inclusion is round to oval and cytoplasmic.

Tau immunohistochemistry

- Pick bodies are immunoreactive for tau.
- Tau labeling confirms the principal deposited protein.

Not every FTLD-tau inclusion is a Pick body

Pattern	Typical description	Interpretation
Tangle-like	Fibrillary tau inclusion resembling AD-type tangles	Tau-positive, not necessarily Pick disease
Pick-body type	Rounded or oval neuronal cytoplasmic inclusion	Defines the characteristic Pick disease morphology
Glial tau inclusion	Tau-positive cytoplasmic lesion in glia	Found in some FTLD-tau subtypes

FTLD-TDP is a distinct proteinopathy

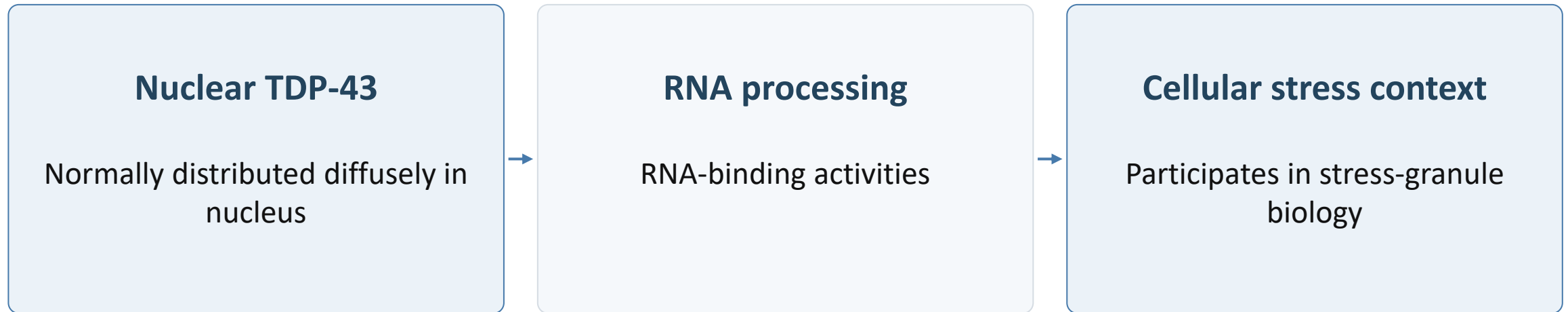
Protein

- TDP-43: Transactive response DNA-binding protein 43.
- An RNA-binding protein normally enriched in the nucleus.

Disease lesion

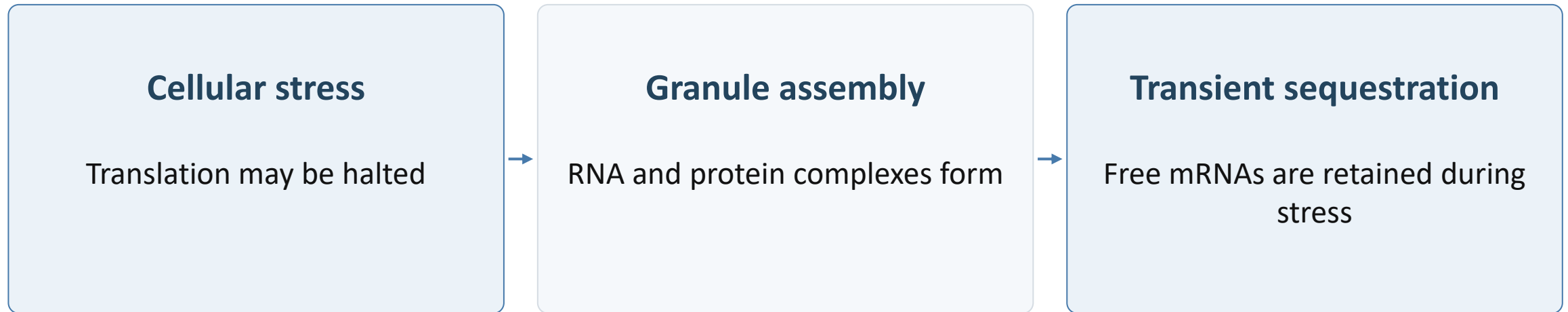
- TDP-43-containing inclusions replace the tau-dominant profile.
- Associated with neuronal loss, gliosis and lobar atrophy.

Physiologic TDP-43 supports RNA processing



Abnormal redistribution and inclusion formation characterize FTLD-TDP.

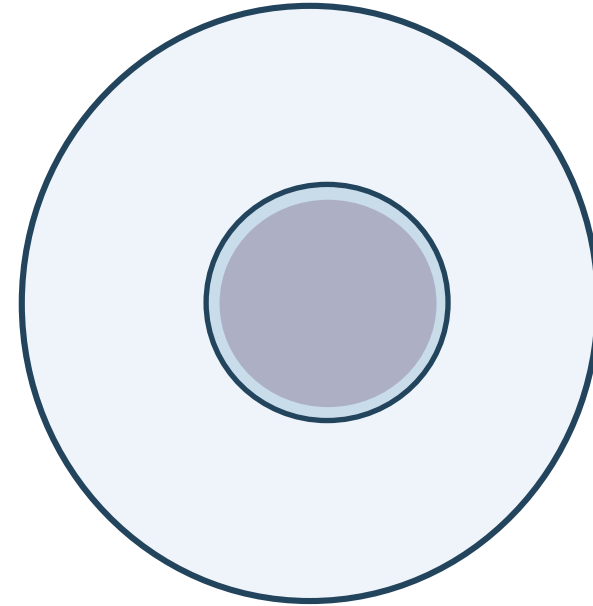
Stress granules are RNA–protein assemblies



TDP-43 contributes to stress-granule biology; The source does not define a simple granule-to-inclusion mechanism.

Normal TDP-43 distribution is predominantly nuclear

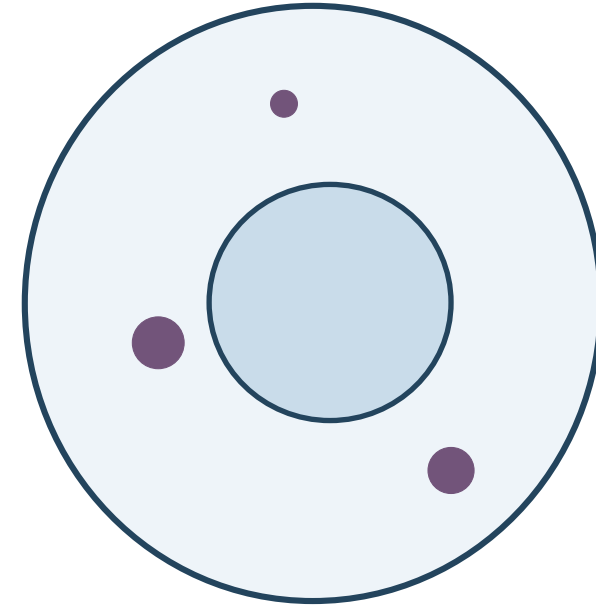
- Normal immunoreactivity is diffuse within the neuronal nucleus.
- Physiologic nuclear localization is the reference against which disease is recognized.
- A nuclear signal is different from an abnormal intranuclear inclusion.



Simplified cellular schematic—not a tissue section

Cytoplasmic TDP-43 inclusions are abnormal

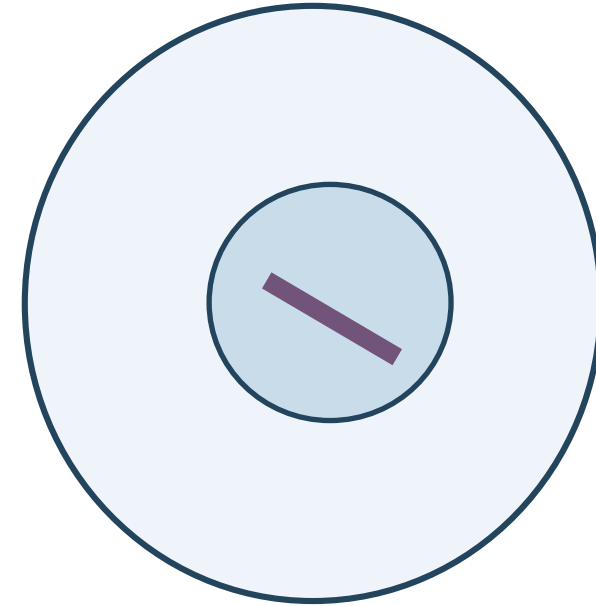
- TDP-43 appears as discrete neuronal cytoplasmic inclusions.
- Affected cells often lose normal diffuse nuclear TDP-43 immunoreactivity.
- Morphology reflects protein redistribution/aggregation, not simply overexpression.



Simplified cellular schematic—not a tissue section

TDP-43 may form intranuclear inclusions

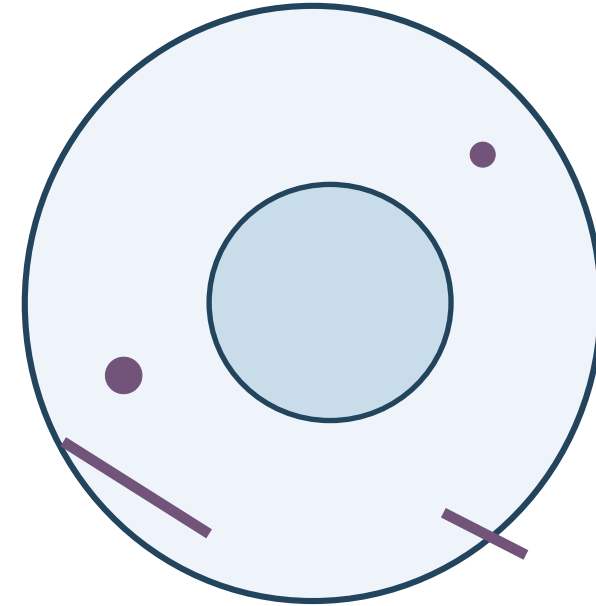
- Some neurons contain TDP-43-positive intranuclear inclusions.
- This is an inclusion, rather than the normal diffuse nuclear staining pattern.
- Needle-like intranuclear inclusions correlate strongly with GRN mutations.



Simplified cellular schematic—not a tissue section

TDP-43 inclusions also occur in neuronal processes

- Abnormal TDP-43 aggregates may form thread-like neuronal process inclusions.
- The pathologic deposits are not restricted to neuronal cell bodies.
- Immunohistochemistry clarifies protein composition and cellular location.



Simplified cellular schematic—not a tissue section

TDP-43 inclusions undergo disease-associated modification

Phosphorylation

Aggregated TDP-43 in FTLD-TDP is phosphorylated.

Ubiquitination

The same inclusions can be ubiquitinated.

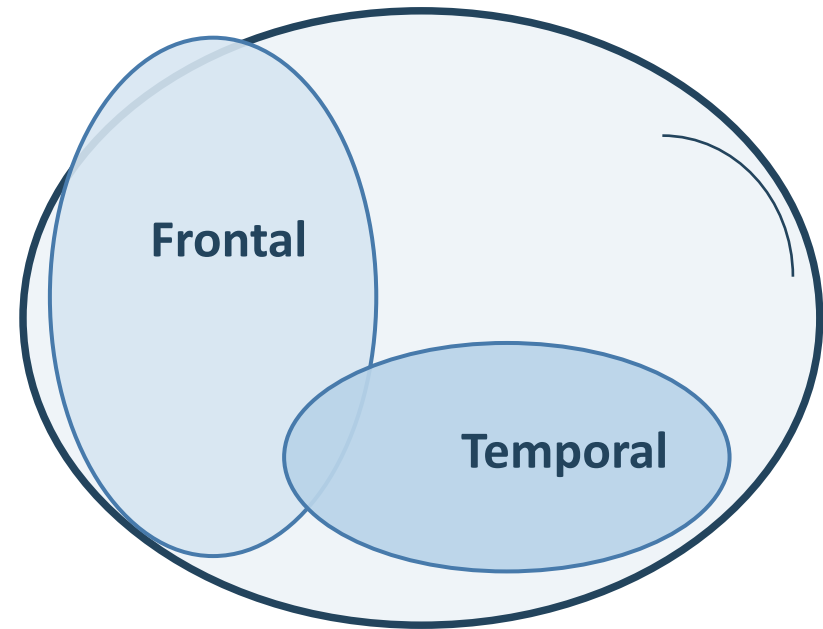
Pathology readout

Abnormal protein localization, morphology and modification support tissue interpretation.

FTLD-TDP: Regional distribution of inclusions

Simplified lobar schematic—not anatomical imaging

- Inclusions are frequent in frontal and temporal cortices.
- The striatum and hippocampal dentate gyrus may also be affected.
- Regional neuronal loss and gliosis coexist with the inclusions.



Gross morphology alone does not sort tau from TDP

Feature	FTLD-tau	FTLD-TDP
Gross change	Frontal/temporal atrophy of variable severity	Similar variable frontal/temporal atrophy
Tissue response	Neuronal loss and reactive gliosis	Neuronal loss and reactive gliosis
Key separator	Tau-positive inclusions	TDP-43-positive inclusions

Inherited FTLD-TDP highlights three genetic routes



Different inherited abnormalities converge on TDP-43 protein pathology.

C9orf72: Hexanucleotide repeat expansion

Variant class

Expanded hexanucleotide repeat in the 5' region of C9orf72.

Clinical spectrum

Associated with FTLD-TDP and amyotrophic lateral sclerosis.

Molecular uncertainty

The precise path to TDP-43 aggregation is not fully defined.

C9orf72 connects FTLD and ALS

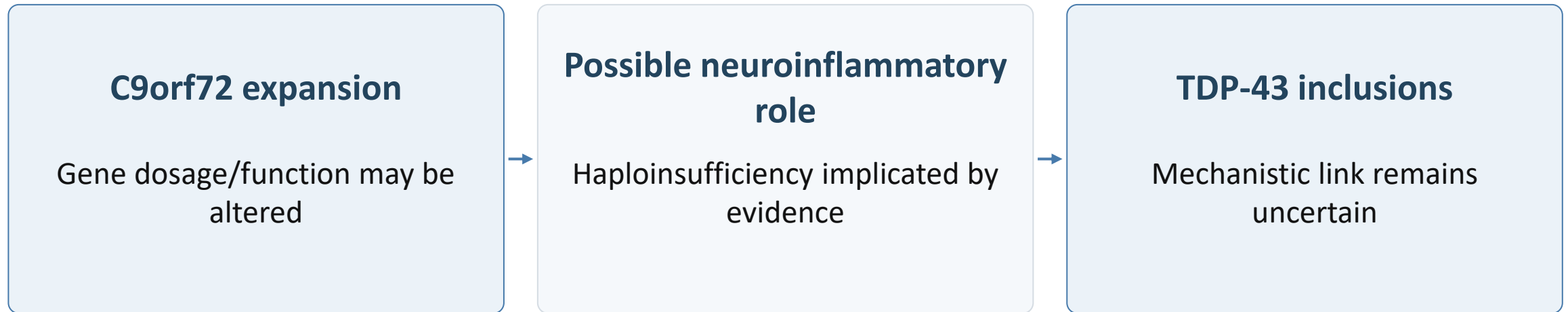
FTLD expression

- Behavioral or language-led cognitive syndrome.
- Frontal and temporal neurodegeneration.

ALS relationship

- The same expanded repeat can be found across the FTLD–ALS spectrum.
- Clinical syndrome alone does not establish an exclusive molecular diagnosis.

C9orf72 inflammation hypothesis remains incomplete



Do not present the inflammatory route as a proven complete causal chain.

TARDBP mutations directly involve the inclusion protein

Gene product

- TARDBP encodes TDP-43 itself.
- Pathogenic variants are relatively uncommon in familial FTLD-TDP.

Disease connection

- Variants can also appear in inherited ALS.
- Functional dysregulation and aggregate toxicity may both contribute.

TDP-43 dysfunction: Loss and gain of function

Loss of normal activity

Disrupted nuclear RNA-related functions may contribute to neuronal injury.

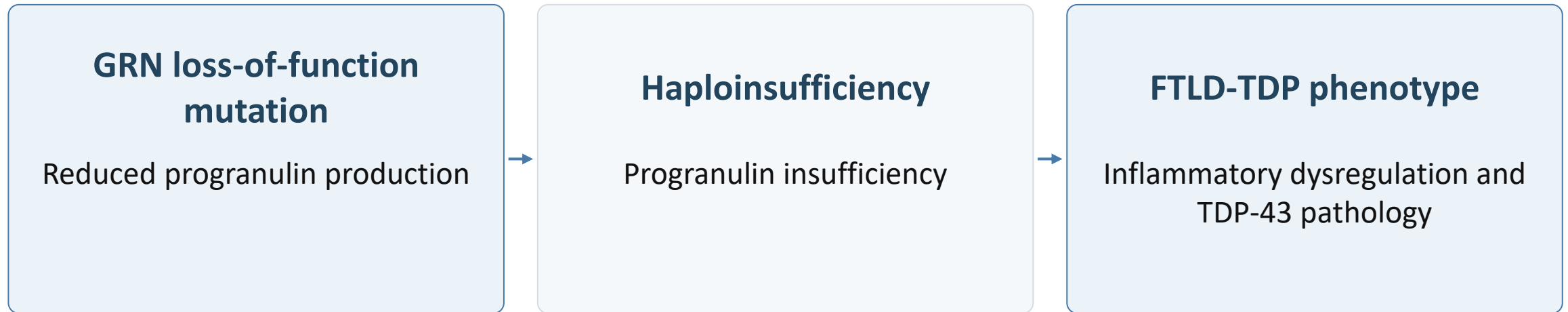
Toxic protein accumulation

Aberrant aggregate species may exert additional cellular toxicity.

Interpretive caution

The source describes both mechanisms as potentially contributory, not quantified causes.

GRN mutations cause progranulin deficiency



The route from inflammation to aggregation has unresolved steps.

Progranulin links FTLD-TDP with brain inflammation

Protein

Progranulin is a secreted protein.

Biological role

Implicated in regulating inflammation in the brain.

FTLD context

Reduced progranulin is associated with a proinflammatory state and TDP-43 pathology.

GRN-associated FTLD differs from C9orf72-associated FTLD

GRN

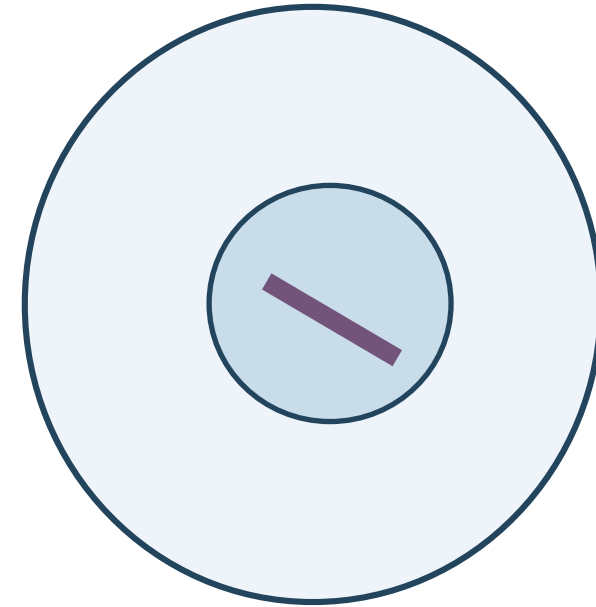
- Progranulin haploinsufficiency.
- Robbins does not link GRN mutations with ALS.

C9orf72 / TARDBP

- Genetic abnormalities may be associated with both FTLD and ALS.
- Shared molecular spectrum does not mean identical clinical presentation.

GRN mutations: Needle-like intranuclear inclusions

- Needle-like TDP-43-positive intranuclear inclusions show a strong association with GRN mutation.
- Morphologic association supports, but does not independently replace, molecular testing.
- Other FTLD-TDP inclusions may coexist.



Simplified cellular schematic—not a tissue section

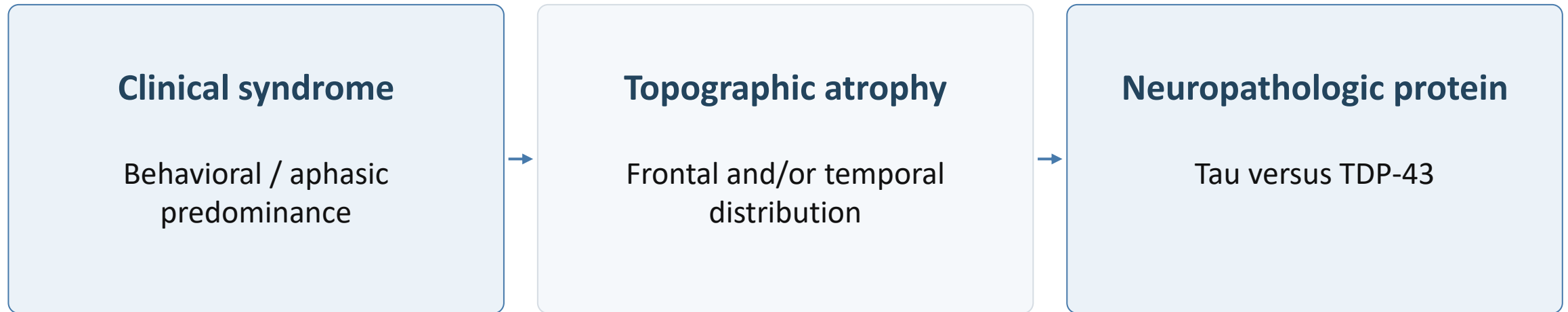
Genetic pathways: What is altered?

Gene	Protein / variant	Major teaching implication
MAPT	Tau; missense or splicing changes	FTLD-tau protein dysregulation
C9orf72	Expanded hexanucleotide repeat	FTLD-TDP–ALS disease spectrum
TARDBP	TDP-43 protein	FTLD-TDP; also familial ALS
GRN	Progranulin; loss of function	FTLD-TDP, inflammation link; not ALS in source

FTLD-tau versus FTLD-TDP: Tissue distinctions

Criterion	FTLD-tau	FTLD-TDP
Accumulating protein	Tau	TDP-43
Mutation examples	MAPT	C9orf72, TARDBP, GRN
Typical cellular site	Neuronal cytoplasmic; some glial	Neuronal cytoplasm, nuclei, processes
Specific association	Pick bodies in Pick disease	Needle-like nuclear inclusions with GRN
Common lesion	Cortical neuronal loss and gliosis	Cortical neuronal loss and gliosis

Clinicopathologic interpretation uses complementary axes



Protein subtype cannot be deduced securely from the first two axes.

Applied case: Behavior-led presentation

An adult develops progressive personality change and disturbed behavior. Memory loss is less conspicuous early. Over time, language and global cognition decline.

What anatomic pattern is suggested—and what cannot be inferred?

Hypothetical teaching vignette

Case analysis: Behavior-led presentation

Most compatible syndrome

Frontotemporal dementia clinical phenotype.

Suggested pathology

FTLD is a plausible anatomic pathologic correlate.

Important limit

Neither tau nor TDP-43 inclusions can be inferred reliably from presentation alone.

Applied case: A distinctive neuropathologic lesion

Autopsy demonstrates severe, asymmetric frontal and temporal atrophy, superficial cortical neuronal loss, ballooned neurons and rounded tau-positive neuronal cytoplasmic inclusions.

Which FTLD-tau subtype best fits this pattern?

Case analysis: Pick disease

Gross clue

Marked asymmetric frontal/temporal atrophy.

Cellular clues

Pick cells plus round tau-positive Pick bodies.

Diagnosis

Pick disease, a morphologically distinctive FTLD-tau form.

Applied case: TDP-43 pathology and genetics

A degenerating frontal cortex contains TDP-43-positive cytoplasmic inclusions, nuclear immunoreactivity loss and numerous needle-like neuronal intranuclear inclusions.

Which gene association should be considered?

Case analysis: Intracellular TDP-43 inclusions

Protein family

The pathologic aggregate is TDP-43, not tau.

Clue

Needle-like neuronal intranuclear inclusions correlate with GRN mutation.

Interpretive limit

A morphologic association should not be treated as standalone genetic proof.

Critical interpretation: Avoid three category errors

- Do not use “FTD” (clinical) and “FTLD” (pathologic) as fully interchangeable labels.
- Do not assign a tau/TDP subtype from behavioral versus aphasic presentation alone.
- Do not treat a pathogenesis hypothesis (for example inflammation → aggregation) as fully established.
- Do not interpret simplified teaching diagrams as diagnostic microscopy.

Integrated high-yield synthesis

Anatomy → syndrome

Frontal/temporal neuronal loss explains early behavioral and aphasic deficits.

Protein → subtype

Tau and TDP-43 inclusions define major pathologic patterns.

Genetics → mechanism

MAPT, C9orf72, TARDBP and GRN help explain distinct molecular routes.

References and source limitations

Primary textbook

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 28: The Central Nervous System; Frontotemporal Lobar Degenerations, pp. 1164–1166.

Source qualification

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