

Spinocerebellar Ataxias

Inherited neurodegeneration • mutation classes • molecular pathology

Pathology lecture

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Learning outcomes

- Define the autosomal dominant spinocerebellar ataxias within the broader spinocerebellar degenerations.
- Distinguish coding-repeat, noncoding-repeat, and conventional-mutation disease classes.
- Explain established and proposed molecular consequences of polyglutamine expansion.
- Relate selected SCA names and molecular categories to meaningful differential diagnoses.

Spinocerebellar degenerations: Affected systems

Cerebellum	Spinal cord	Peripheral nerves
Neuronal loss and dysfunction impair the machinery of coordinated movement.	Degeneration can extend beyond cerebellar structures.	Peripheral nerve involvement contributes to the multi-system category.

The shared lesion distribution at the family level—not an identical distribution in every subtype.

One category, many diseases

- The spinocerebellar degenerations differ in genetics, age at onset, and presenting manifestations.
- The shared neuroanatomic theme does not imply a single causative gene or pathway.
- Genetic analysis has improved classification more than it has resolved disease pathogenesis.
- A mechanistic classification is therefore more informative than the generic label “ataxia.”

Where SCAs sit in the disease hierarchy



- Friedreich ataxia and ataxia-telangiectasia belong to the broader degeneration discussion but are autosomal recessive.
- This inheritance distinction is a core boundary of the topic as presented.

What the term SCA means here

- Spinocerebellar ataxia (SCA) denotes a group of autosomal dominant inherited degenerations.
- “Ataxia” denotes the clinical coordination problem; “spinocerebellar” signals a wider neuroanatomic context.
- Genetic, clinical, and pathologic findings all contribute to subtype assignment.
- A family diagnosis is not equivalent to identifying the responsible molecular lesion.

Inheritance is a classification boundary

Group	Inheritance in Robbins	Teaching distinction
Spinocerebellar ataxias	Autosomal dominant	Several molecular subclasses
Friedreich ataxia	Autosomal recessive	Separate disease; FXN repeat expansion
Ataxia-telangiectasia	Autosomal recessive	Separate disease; ATM pathway

All three can involve spinocerebellar degeneration; They are not synonymous diagnoses.

The classification problem

- More than 40 distinct SCA subtypes in classifications integrating several evidence streams.
- The disease family is too diverse for one universal histologic or genetic signature.
- Subtype names remain useful only when paired with a molecular or clinicopathologic explanation.
- Different mutation classes require different mechanistic reasoning.

Three ways to classify the same phenotype

Genetic	Clinical	Pathologic
What type of pathogenic variant is present?	Which manifestations accompany the ataxia?	Which neuronal populations and cellular abnormalities are implicated?

These classifications overlap but are not interchangeable.

Three mutation classes organize the SCAs

Coding CAG repeats	Noncoding expansions	Conventional variants
Repeat translation produces expanded polyglutamine proteins.	The disease-linked repeat lies outside the translated coding tract.	Sequence and copy-number changes can alter signaling proteins.

Parallel genetic classes—not a single stepwise pathway.

Why a mutation-based approach helps

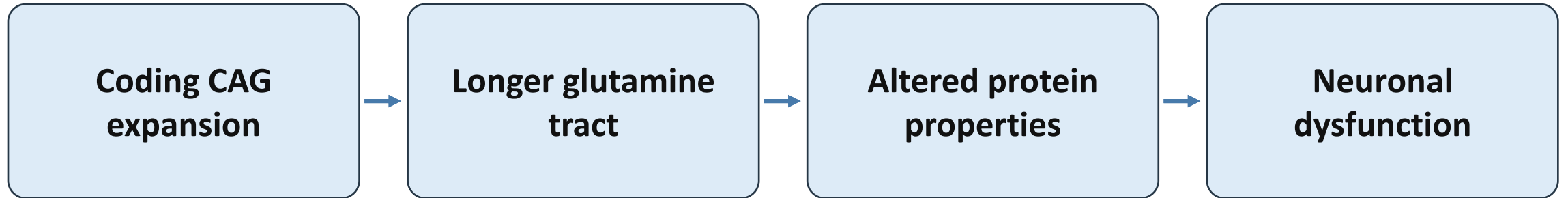
- An inherited ataxia phenotype is a downstream consequence—not a molecular diagnosis.
- Expanded coding repeats act through altered proteins; Noncoding expansions may act differently.
- Conventional mutations span several sequence and copy-number variant classes.
- Start with the variant mechanism before inferring pathogenesis.

Trinucleotide repeats: A genetic substrate

Repeat motif	Expanded allele	Disease context
A short three-base DNA sequence is arranged in tandem copies.	The number of consecutive copies is increased.	Coding position versus noncoding position changes possible consequences.

The same “repeat expansion” label can conceal fundamentally different molecular mechanisms.

The coding CAG repeat pathway



- CAG specifies glutamine; An expanded CAG tract produces polyglutamine.
- This is a class-level schematic: The particular affected protein differs by subtype.

A codon is not a protein inclusion

- CAG is a DNA/RNA coding triplet, whereas polyglutamine is an amino-acid segment of a protein.
- Translation links the expanded coding repeat to the longer glutamine-containing protein tract.
- Subsequent protein misfolding and accumulation are separate downstream events.
- Distinguish the genetic event from the microscopic finding.

Genomic location predicts the first mechanistic question

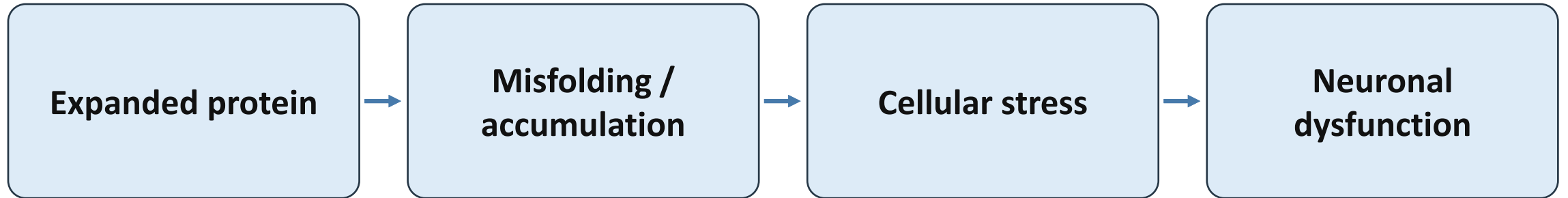
Location	Direct consequence	What to investigate
Coding CAG repeat	Expanded polyglutamine protein	Protein folding and toxicity
Noncoding repeat	Repeat outside translated coding sequence	RNA or other regulatory consequences
Conventional mutation	Sequence or copy-number alteration	Function of the affected protein

This table is a mechanistic framework, not a definitive mechanism for every subtype.

Polyglutamine: A protein-level lesion

- The chapter identifies eight SCA-related forms with CAG-driven polyglutamine expansion.
- The expanded tract modifies the product of the disease-associated gene.
- Affected proteins differ, but accumulation in nuclear inclusions is described across this group.
- Shared inclusion morphology does not prove identical neuronal vulnerability.

Polyglutamine: Proposed injury sequence



- Plausible toxic pathways; The precise causal contributions remain unresolved.
- An arrow in this diagram indicates a proposed relationship, not a demonstrated universal sequence.

Toxic gain of function

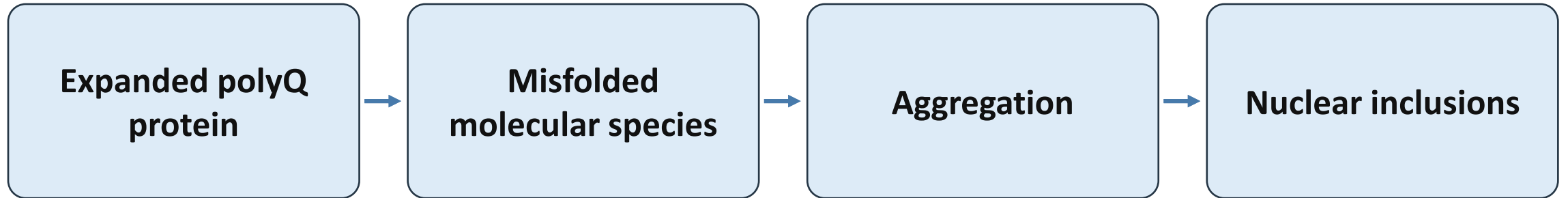
- Expanded polyglutamine proteins can gain activities harmful to cells.
- Proposed actions include interfering with the normal protein or acquiring a novel toxic activity.
- This differs conceptually from simple absence of a gene product.
- The chapter does not identify a single universal downstream toxic process.

Two models of altered protein function

Interference	Novel activity	Net consequence
Mutant protein impairs the normal protein or its interactions.	The expanded protein acquires a pathogenic property.	Neuronal dysfunction arises despite protein production.

Both within the toxic gain-of-function framework.

How abnormal proteins appear in nuclei



- Large intranuclear aggregates are a morphologic hallmark of many polyglutamine diseases.
- The inclusion is an observed correlate, not automatic proof of direct toxicity.

Intranuclear inclusions: What they establish

- An inclusion indicates accumulation of abnormal protein material within a neuronal nucleus.
- Nuclear inclusions in the CAG-polyglutamine SCA group.
- This is a cellular pathology clue to disturbed protein homeostasis.
- The presence of aggregates alone cannot resolve the precise neuronal injury mechanism.

Aggregation: Two competing interpretations

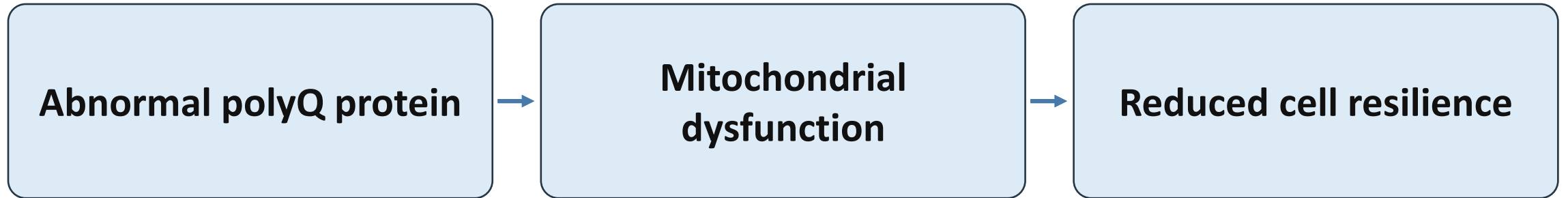
Potential harm	Potential protection
Protein assemblies may disrupt transcription or cellular processes.	Sequestration into larger aggregates may limit freely toxic species.

Robbins explicitly cautions that a direct toxic role of visible inclusions is not universal.

Transcriptional dysregulation is a candidate pathway

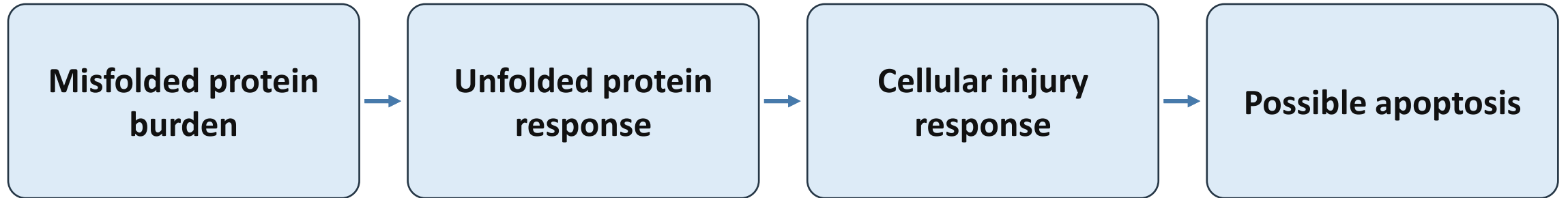
- Aggregated or misfolded polyglutamine proteins may affect transcription of other genes.
- This is one proposed toxic consequence, not a proven explanation for every SCA.
- Distinguish a general disease-class mechanism from an established subtype-specific mechanism.

Candidate mitochondrial injury pathway



- Mitochondrial dysfunction as a possible effect of protein aggregation.
- The schematic does not assert that all polyglutamine SCAs share this single mechanism.

Proteostasis stress and apoptosis



- The unfolded-protein response and programmed cell death are proposed downstream processes.
- Not every histologic inclusion represents a cell currently undergoing apoptosis.

Proteolytic fragments: Another hypothesis

- Robbins also considers downstream toxicity mediated by fragments of expanded polyglutamine proteins.
- This concept differs from assigning toxicity solely to a large visible aggregate.
- Fragment-mediated injury remains mechanistic context rather than a definitive subtype criterion.

Observed feature versus pathogenic hypothesis

Observation	Interpretation	Evidence boundary
CAG expansion	Translated polyglutamine tract	Coding context required
Nuclear inclusion	Abnormal protein accumulation	Not necessarily the toxic agent
Cell stress	Possible downstream mechanism	Not universal for all SCAs
Neuronal dysfunction	Clinical/pathologic consequence	Subtype distribution varies

What neuropathology can and cannot tell us

- The broad degeneration category includes neuronal loss and dysfunction in several nervous-system regions.
- Polyglutamine SCAs can show neuronal intranuclear inclusion pathology.
- A shared microscopic feature does not identify which CAG-expanded gene is responsible.
- Subtype-level interpretation requires the clinical and genetic context.

The eight polyglutamine-associated entities named

Named forms	Textbook distinction
SCA1, SCA2	Included in coding-CAG class
SCA3, SCA6	SCA3 is also Machado–Joseph disease
SCA7, SCA8	SCA7 has visual impairment as a distinguishing clue
SCA17, DRPLA	Listed with the polyglutamine diseases

This reproduces the source’s grouping; Its description of SCA8 is not independently reclassified here.

SCA1: Gene–repeat association

- SCA1 with the ATXN1 gene.
- The reported expansion is a coding CAG repeat, placing it in the polyglutamine model.
- The molecular name identifies the subtype more precisely than the generic phenotype.
- Locus identification is more specific than shared ataxia or aggregate morphology.

SCA2: Another distinct ataxin locus

- The source identifies ATXN2 as the gene associated with SCA2.
- SCA2 belongs to the coding-CAG/polyglutamine category of the SCA family.
- Identical repeat motifs at different genes do not create identical genetic diseases.
- An SCA label must remain linked to the specific locus under investigation.

SCA3: Machado–Joseph disease

- SCA3 is explicitly identified as Machado–Joseph disease.
- This entity to the ATXN3 gene and a coding CAG expansion.
- The alternate eponym and genetic designation refer to the same subtype.
- The eponym by itself does not explain why its expanded protein is neurotoxic.

SCA6: A channel-related protein

- Robbins groups SCA6 with the coding-CAG polyglutamine disorders.
- The textbook associates its protein with a voltage-dependent calcium-channel subunit.
- This links a named SCA protein to membrane excitability machinery at the molecular level.
- The supplied chapter does not specify an entire SCA6 injury cascade.

SCA7: A clinically useful association

- SCA7 belongs to the textbook's CAG/polyglutamine-associated group.
- The text singles out visual impairment as a relatively unusual accompanying feature.
- The associated gene is ATXN7.
- Visual involvement supports targeted consideration of SCA7; It is not a stand-alone molecular test.

Less detailed members of the listed group

SCA8	SCA17	DRPLA
Listed polyglutamine group.	Listed group; Phenotype details are not established in this discussion.	Dentatorubral–pallidoluysian atrophy is listed with these diseases.

The Robbins section does not supply enough detail to create phenotype-specific claims for these entities.

Genetically mapped coding-repeat examples

Subtype	Gene/protein association	Mechanistic class
SCA1	ATXN1 / ataxin-1	CAG / polyglutamine
SCA2	ATXN2 / ataxin-2	CAG / polyglutamine
SCA3	ATXN3 / ataxin-3	CAG / polyglutamine
SCA6	Voltage-dependent Ca ²⁺ -channel α 1A subunit	CAG / polyglutamine
SCA7	ATXN7 / ataxin-7	CAG / polyglutamine

Gene/protein names are transcribed only where supported by the source table; Numerical repeat cutoffs are intentionally omitted.

Why one repeat motif yields different diseases

- The disease-linked locus determines which protein acquires the expanded glutamine tract.
- Polyglutamine proteins differ in their normal biological roles.
- Heterogeneity across genetic and clinical features despite shared molecular themes.
- A shared mutation class is not a sufficient diagnostic description.

Applied interpretation: Ataxia plus visual impairment

Clinical vignette — hypothetical

A hypothetical multigenerational family has progressive ataxia; Several affected members also report worsening vision.

Which named SCA is specifically highlighted by this combination in the source?

SCA7 should be considered because visual impairment is a distinguishing association. A molecular diagnosis remains necessary.

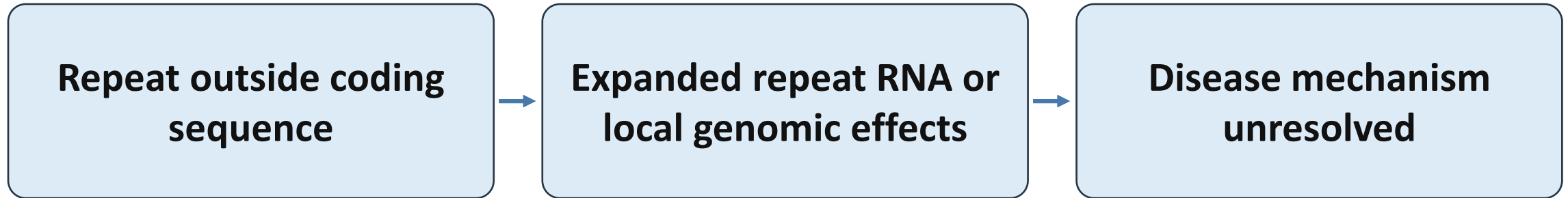
Huntington disease is a mechanism comparator

- Both Huntington disease and several SCAs belong to the repeat-expansion/polyglutamine disease group.
- Huntington disease classically targets the striatum, whereas the SCA family has spinocerebellar involvement.
- The common inclusion/proteostasis model should not erase the major clinical-anatomic differences.

Shared mechanism does not mean shared anatomy

Feature	Huntington disease	PolyQ SCA group
Inheritance	Autosomal dominant	Autosomal dominant SCA family
Relevant repeat	Coding CAG	Coding CAG for this subset
Principal disease emphasis	Striatal degeneration	Spinocerebellar degeneration
Protein pathology	Intranuclear inclusions	Intranuclear inclusions described

Noncoding expansions begin differently



- Unlike coding-CAG disease, a noncoding expansion does not directly create an elongated polyglutamine tract by standard translation.
- Robbins specifically states that the mechanism of SCA noncoding-repeat disease remains unknown.

Six noncoding-repeat SCAs in the chapter

- SCA10, SCA12, and SCA27B are identified as noncoding-repeat forms.
- SCA31, SCA36, and SCA37 complete the six named examples.
- In most, the underlying disease-linked locus has been defined.
- The common pathogenic sequence from noncoding expansion to neuronal injury is not established.

Source-defined noncoding-repeat classification

Noncoding-repeat subtype	What the Robbins excerpt establishes
SCA10	Class membership
SCA12	Class membership
SCA27B	Class membership
SCA31	Class membership
SCA36	Class membership
SCA37	Class membership

The excerpt supplies a list, not six validated subtype-specific molecular cascades.

Coding and noncoding are not synonyms

Coding CAG	Noncoding repeat	Unresolved pathway
Directly changes amino-acid repeat length of the protein.	Does not necessarily change an encoded polyglutamine tract.	Mechanism requires evidence beyond identifying the expanded repeat.

A noncoding SCA should not inherit the entire polyglutamine schematic by analogy alone.

The myotonic dystrophy comparison has limits

- A mechanistic resemblance between noncoding-repeat SCAs and myotonic dystrophy.
- The analogy identifies an expansion in noncoding sequence, not a proven identical toxic pathway.
- The textbook explicitly calls the mechanism of these noncoding SCAs unknown.
- Avoid depicting RNA toxicity as conclusively demonstrated for every subtype.

Molecular identification $\neq$ pathogenetic explanation

- Locating an expanded repeat can establish a strong molecular association.
- Understanding how that repeat injures neurons is a distinct research question.
- The Robbins account acknowledges that locus discovery has outpaced mechanistic understanding.
- Classification should preserve this difference between association and explanation.

Applied interpretation: A noncoding expansion

Clinical vignette — hypothetical

A hypothetical laboratory report identifies a pathogenic repeat expansion outside the coding sequence of an SCA-associated locus.

Is an expanded polyglutamine protein necessarily produced?

No. The direct coding-CAG-to-polyglutamine inference does not follow from a noncoding expansion. Mechanism must be evaluated separately.

Conventional SCA mutations: Several variant types

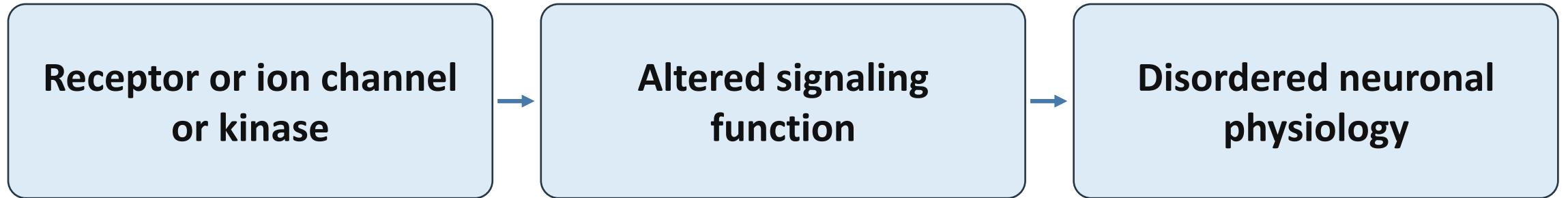
Copy-number changes	Deletions / insertions	Point mutations
Alter dosage of a chromosomal segment or gene.	Remove or add DNA sequence.	Change one nucleotide at a specific site.

All are represented among the non-repeat forms.

“Conventional” is not a single molecular pathway

- The category includes diverse sequence and structural variants.
- Affected genes are likewise diverse rather than members of one protein family.
- Proteins functioning in cellular signal transduction.
- Interpretation therefore depends on the gene product and specific variant.

Signal-transduction proteins: The common theme



- Robbins gives protein categories, not a universal receptor-to-degeneration chain.
- This is a conceptual framework for variants affecting signaling proteins.

Conventional variant class versus protein class

Variant form	Potential protein target	Source-supported conclusion
Point mutation	Receptor / channel / kinase	Amino-acid or regulation may change
Deletion / insertion	Many possible proteins	Function depends on site and size
Copy-number variation	Many possible proteins	Gene dosage can be altered

Rows illustrate how the two axes differ; They are not confirmed subtype–gene pairings.

Receptors: A mechanistic category, not a named SCA gene

- Receptors participate in transmitting extracellular or synaptic information to cells.
- Receptor proteins among SCA-relevant signal-transduction targets.
- It does not claim that all receptor changes cause the same cellular response.
- Do not assign a specific receptor mutation without a supported genotype.

Ion channels: Another affected protein class

- Ion channels regulate ionic flux and contribute to neuronal excitability.
- The SCA chapter identifies channel proteins as one signal-transduction class.
- Channel dysfunction is a plausible functional bridge to impaired neuronal signaling.
- A specific electrophysiologic defect is not established for every conventional SCA.

Kinases: Regulation through phosphorylation

- Kinases modify signaling proteins through phosphorylation reactions.
- Kinases in the broad set of SCA-associated proteins.
- A kinase lesion can influence cellular communication or regulation.
- The named excerpt does not provide a kinase-specific SCA pathway.

Three mechanistic classes at a glance

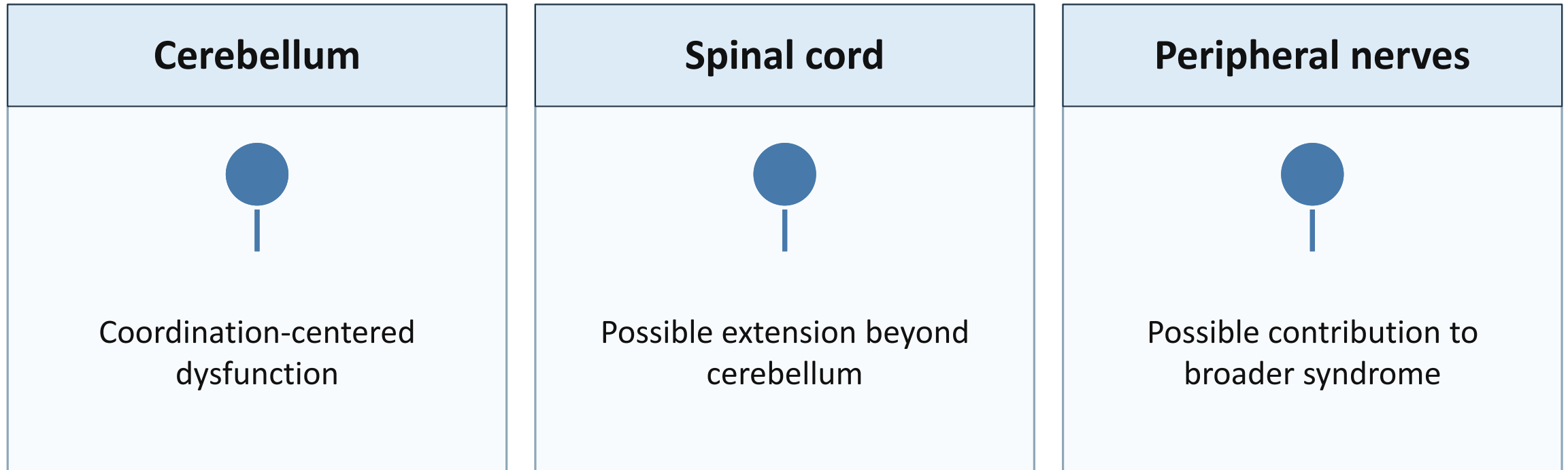
Class	Variant substrate	Level of explanation
Coding CAG repeats	Protein with expanded polyglutamine	Misfolding/inclusions; toxicity debated
Noncoding repeats	Repeat expansion outside coding tract	Pathogenic mechanism unknown
Conventional variants	Copy-number or sequence changes	Diverse signaling-protein effects

The boundaries matter more than memorizing a single molecular cartoon.

From mutation to clinicopathologic phenotype

- Different inherited lesions converge on dysfunction in cerebellar and related circuits.
- Neuronal loss and dysfunction explain why a molecularly diverse family shares a neurologic label.
- Distribution of injury and extra-cerebellar involvement help determine clinical patterns.
- The source does not support a uniform anatomic map for all individual SCA types.

Anatomic distribution: Shared category, variable involvement



The diagram depicts the family-level distribution—not the expected lesion burden in a given genotype.

Ataxia as a presenting label has limited specificity

- Several distinct degenerative entities can produce a cerebellar ataxia phenotype.
- Clinical phenotype must be paired with inherited versus sporadic context.
- Mode of inheritance is informative but does not identify a precise SCA subtype.
- A molecular diagnosis cannot be deduced from the word “ataxia” alone.

Dominant SCAs versus Friedreich ataxia

Characteristic	SCA family	Friedreich ataxia
Inheritance	Autosomal dominant	Autosomal recessive
Disease classification	Multiple mutation classes	FXN GAA repeat expansion
Additional findings in text	Subtype-variable	Neuropathy, cardiomyopathy, other systemic effects
Teaching value	Heterogeneous family	Distinct recessive diagnosis

Do not conflate the noncoding GAA expansion in FXN with a named autosomal dominant SCA subtype.

Dominant SCAs versus ataxia-telangiectasia

Characteristic	SCA family	Ataxia-telangiectasia
Inheritance	Autosomal dominant	Autosomal recessive
Molecular focus	Multiple variant classes	ATM-dependent DNA damage response
Accompanying clues	Subtype-dependent	Recurrent infections and lymphoid neoplasms
Disease grouping	Dominant SCAs	Separate recessive degeneration

Inherited SCAs versus multiple system atrophy

Characteristic	Inherited SCA family	Multiple system atrophy
Disease setting	Autosomal dominant	Sporadic disorder
Protein theme	Several classes; polyQ subset	α -synuclein inclusions in oligodendrocytes
Anatomic emphasis	Spinocerebellar circuits variable	Cerebellar, extrapyramidal, autonomic systems
Diagnostic caution	Genetic heterogeneity	Different proteinopathy and distribution

A clinical phenotype cannot resolve repeat location

- Ataxia does not distinguish a coding repeat from a noncoding repeat.
- Even among polyglutamine SCAs, different genes can yield overlapping disease-family features.
- Genetic testing or documented familial molecular findings are necessary to define a specific molecular class.
- The clinical workup must respect this underdetermination.

Applied interpretation: Autosomal dominant ataxia

Clinical vignette — hypothetical

A hypothetical pedigree shows progressive ataxia in several successive generations, affecting both sexes.

What family-level classification is most consistent with the source, and what remains unknown?

An autosomal dominant SCA is compatible. The pathogenic gene, mutation class, and subtype cannot be inferred from the pedigree alone.

Applied interpretation: Nuclear inclusions

Clinical vignette — hypothetical

A hypothetical neuropathology description reports neuronal nuclear aggregates in a patient with progressive inherited ataxia.

Do these aggregates prove which SCA subtype is present or that inclusions themselves are toxic?

Neither. Polyglutamine disease is a possible mechanistic category; Locus and causation require independent evidence.

Applied interpretation: Variant versus mechanism

Clinical vignette — hypothetical

A hypothetical sequencing result identifies a pathogenic point mutation affecting a neuronal signaling protein.

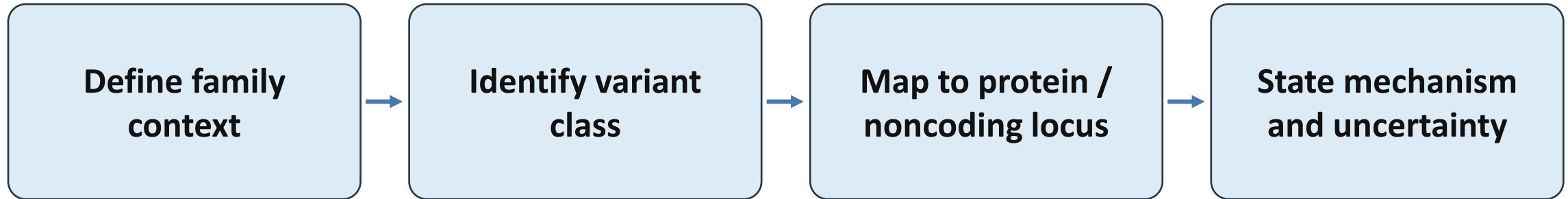
Which SCA mechanistic class applies, and what should not be inferred?

This fits the conventional-mutation class. It does not establish a coding-CAG expansion or polyglutamine nuclear-inclusion mechanism.

Three errors to avoid in SCA teaching

- Do not treat all autosomal dominant SCAs as one molecular disease.
- Do not infer polyglutamine protein expansion from a noncoding-repeat allele.
- Do not claim visible inclusions are necessarily the direct toxic species.
- Do not include recessive Friedreich ataxia or ataxia-telangiectasia as dominant SCA subtypes.

A defensible molecular interpretation sequence



- Report clearly what Robbins establishes and where it explicitly leaves causality unresolved.
- Keep clinical phenotype, observed morphology, and proposed mechanism in separate evidentiary categories.

Summary: The stable conceptual framework

- Autosomal dominant SCAs are genetically and clinicopathologically heterogeneous.
- Coding CAG expansions link a subset to polyglutamine-associated neuronal protein accumulation.
- Noncoding expansions and conventional mutations create different mechanistic questions.
- Shared ataxia does not replace molecular classification or eliminate uncertainty.

Selected source readings

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026): Spinocerebellar Ataxias.
- Robbins, Cotran & Kumar. Diseases Caused by Trinucleotide-Repeat Expansions; repeat-disease table.
- Supporting textbook sections: Friedreich Ataxia; Ataxia-Telangiectasia; Huntington Disease; Multiple System Atrophy.