

Friedreich Ataxia

Genetics • mitochondrial pathology • neuroanatomy • clinical correlation

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Learning outcomes

- Explain how an intronic FXN GAA repeat expansion reduces frataxin expression.
- Relate frataxin deficiency to mitochondrial iron–sulfur proteins and cellular injury.
- Localize the neurological findings to affected tracts and sensory neurons.
- Construct a molecularly informed diagnostic and surveillance approach.

Friedreich ataxia: Defining phenotype

- Autosomal recessive, progressive multisystem neurodegenerative disease.
- Progressive gait ataxia coexists with large-fiber sensory dysfunction and pyramidal signs.
- Cardiomyopathy, skeletal deformity and disturbed glucose homeostasis may accompany neurologic decline.
- A pathogenic FXN genotype establishes the molecular diagnosis.

Where Friedreich ataxia fits among inherited ataxias

Group	Inheritance	Mechanism / defining distinction
Friedreich ataxia	Autosomal recessive	Intronic GAA expansion reduces frataxin
Many spinocerebellar ataxias	Autosomal dominant	Often coding CAG/polyglutamine or other variants
Ataxia-telangiectasia	Autosomal recessive	ATM-related DNA-damage response defect

A disorder of more than one organ

Somatosensory system

Loss of proprioception; Absent reflexes

Motor pathways

Spasticity; Extensor plantar responses

Cardiac muscle

Cardiomyopathy; Rhythm disturbances

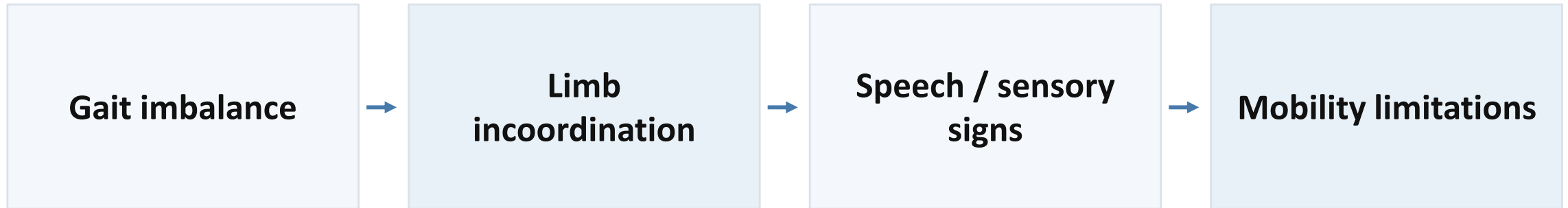
Metabolic / skeletal

Diabetes risk; Scoliosis; Pes cavus

Typical and atypical age at presentation

- Typical disease begins in childhood or adolescence; Early gait imbalance is common.
- Later-onset disease can occur, including presentations after early adulthood.
- Retained tendon reflexes do not exclude genetically confirmed disease.
- Age and rate of progression vary; A single stereotyped time course is misleading.

Clinical evolution: A characteristic sequence



- The sequence illustrates a common pattern rather than a mandatory timetable.
- Cardiac abnormalities may emerge before or independently of neurological disability.

Inheritance is autosomal recessive

- Disease ordinarily requires pathogenic variants affecting both FXN alleles.
- Both sexes may be affected; Carrier parents can be clinically unaffected.
- Recurrence risk in a carrier–carrier pregnancy follows Mendelian inheritance.
- Family history may be negative because affected siblings are uncommon in small families.

Carrier $\times$ carrier: Recurrence probabilities

Parents: Both carriers ($Ff \times Ff$)

	F	f
F	FF Unaffected	Ff Carrier
f	Ff Carrier	ff Affected

25% unaffected

50% carriers

25% affected

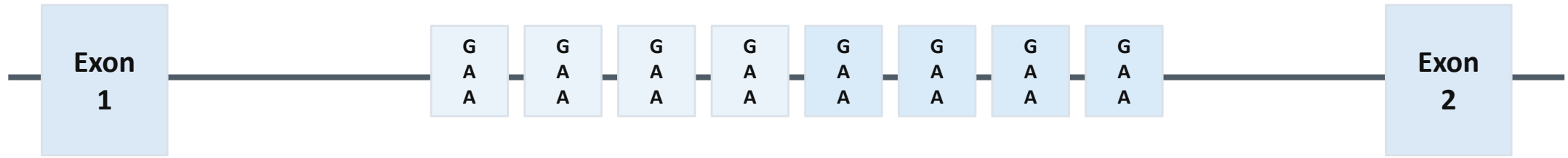
FXN: The molecular locus

- FXN is a nuclear gene encoding mitochondrial frataxin.
- The characteristic pathogenic repeat lies within intron 1, not the coding sequence.
- A noncoding expansion can reduce gene expression without altering the protein sequence.
- Gene-based testing must interrogate repeat expansions, not coding variants alone.

A GAA expansion in intron 1

Simplified FXN transcription unit

Intron 1



Expanded GAA repeat → reduced FXN transcription

Common molecular genotypes

Two expanded alleles

- Intronic GAA expansion on each copy of FXN
- The commonest disease-causing genotype
- Lowered transcription from both alleles

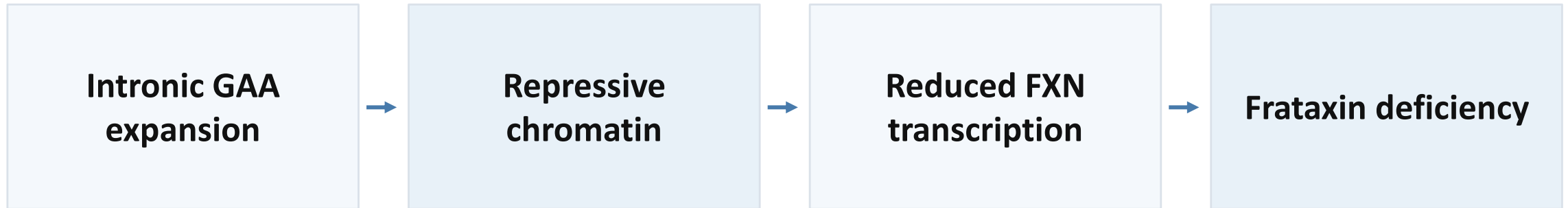
Expansion plus other variant

- GAA expansion on one allele
- Pathogenic FXN sequence variant or deletion on the other
- Still produces a biallelic loss-of-function state

Why a repeat expansion can be pathogenic

- Pathogenicity need not involve a translated repeat or abnormal amino-acid tract.
- Expanded intronic GAA sequence favors altered local chromatin and transcriptional repression.
- Reduced transcription means less functional frataxin is produced.
- This differs from polyglutamine toxicity in several dominant spinocerebellar ataxias.

Gene silencing: A mechanistic chain



- The clinical disease is chiefly a quantitative deficiency of a mitochondrial protein.
- Native schematic summarizes the gene-expression mechanism.

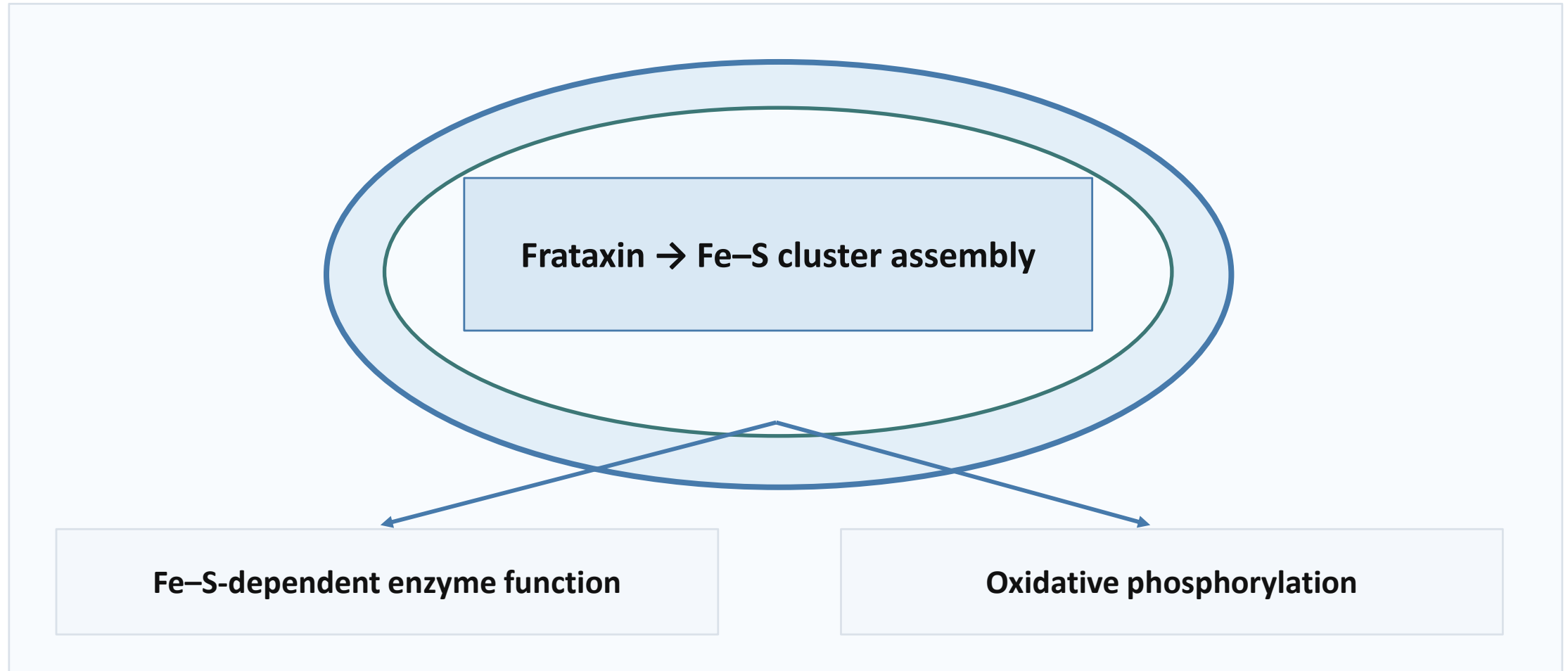
The distinction: Gene expression versus protein aggregation

- Friedreich ataxia: A noncoding expansion reduces production of frataxin.
- Several dominant SCAs: Expanded coding CAG tracts create polyglutamine-bearing proteins.
- Therefore the same clinical endpoint—ataxia—need not imply the same molecular lesion.
- Molecular grouping is essential when discussing causal therapies.

Frataxin: A mitochondrial protein

- Frataxin participates in biogenesis of iron–sulfur (Fe–S) clusters.
- Fe–S cofactors are needed for multiple mitochondrial enzymes.
- A fall in frataxin impairs mitochondrial bioenergetics.
- The consequences extend beyond neurons because the protein is widely required.

Iron–sulfur cluster biogenesis



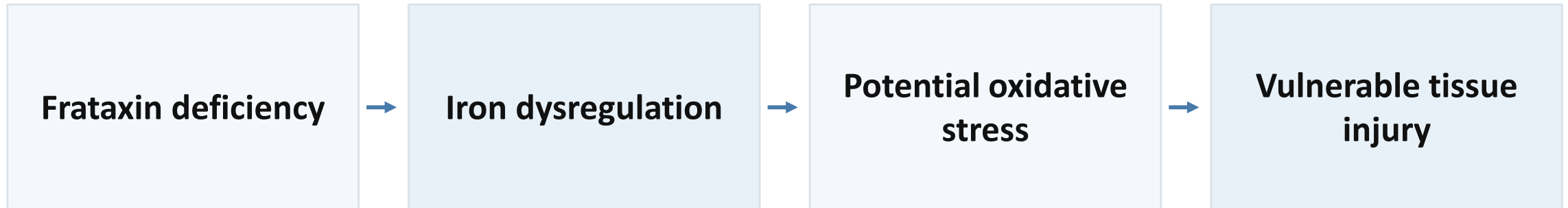
Original schematic — represents functional associations, not a biochemical structural model.

Deficient frataxin compromises energy production



- Robbins particularly links Fe-S proteins to respiratory-chain complexes I and II.
- The diagram describes a mechanistic pathway, not a measured patient ATP value.

Mitochondrial iron and redox injury



- Increased available mitochondrial iron may facilitate oxidative damage.
- The relative causal contribution of oxidative stress remains incompletely resolved.

What is established—and what is uncertain?

Well established

- Biallelic FXN disease-associated variants
- Frataxin deficiency
- Fe–S biogenesis and mitochondrial consequences

Not a complete explanation

- Why particular neuronal populations are vulnerable
- How iron/ROS pathways rank in human injury
- Why phenotype varies among affected people

From DNA repeat to clinical phenotype



- The causal hierarchy connects molecular and tissue-level observations.
- Selectivity of degeneration is not explained by frataxin deficiency alone.

Neuropathology: Principal sites of injury

Dorsal root ganglia

Large sensory-neuron hypoplasia / atrophy

Spinal cord

Dorsal column and spinocerebellar tract loss

Motor system

Corticospinal degeneration

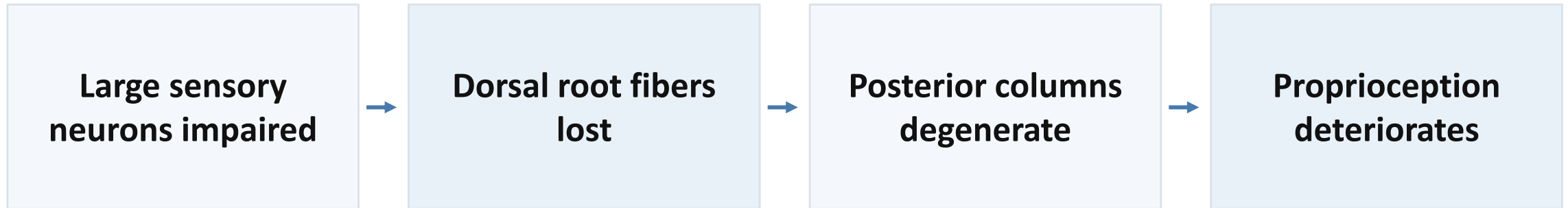
Cerebellar circuit

Dentate nucleus neuronal loss

Dorsal root ganglia are a major lesion

- Large primary sensory neurons are reduced in size and number.
- Developmental undergrowth and subsequent neuronal atrophy can coexist.
- The loss preferentially disrupts pathways conveying vibration and position.
- Degeneration of their central and peripheral processes links central tracts to neuropathy.

A dorsal-root-ganglion lesion has downstream effects



- This is an anatomically continuous sensory pathway.
- Loss of primary afferents can cause secondary degeneration in their central projections.

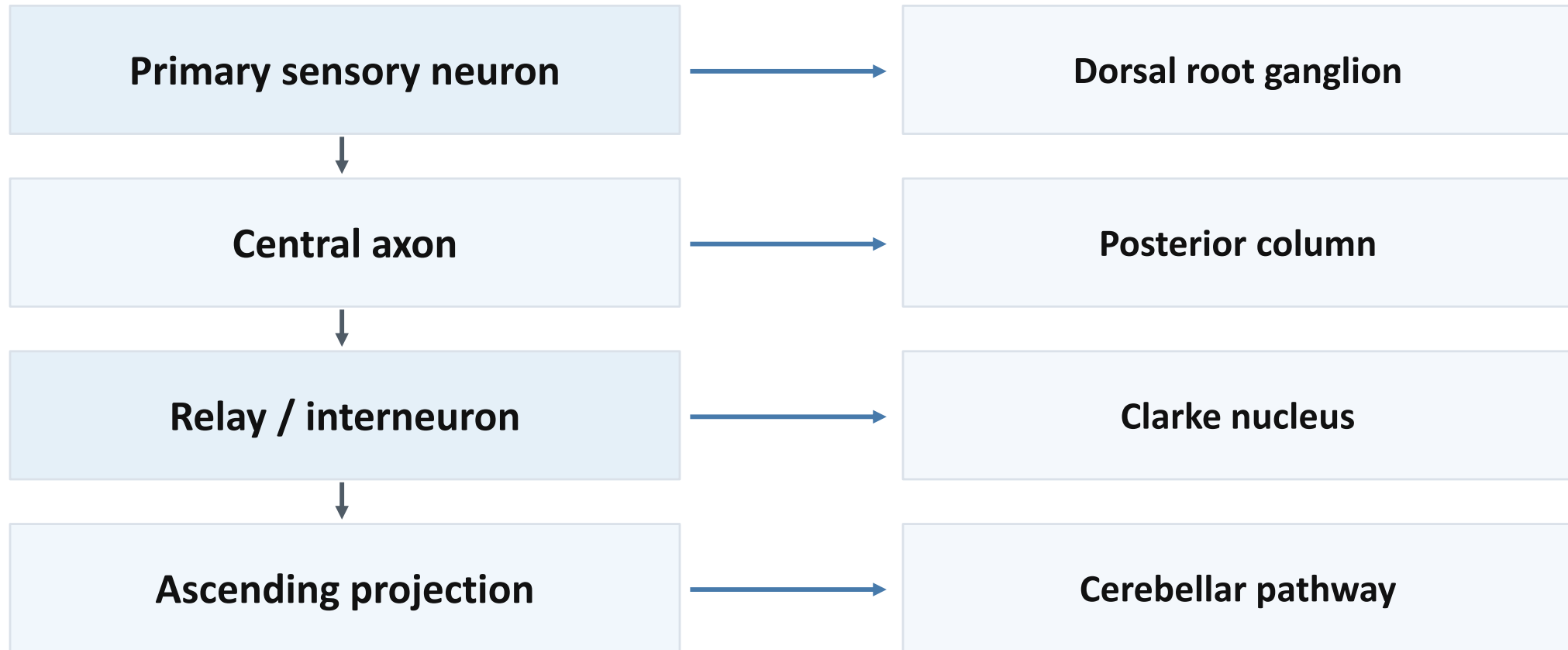
Posterior columns: Ascending sensory pathway

- The dorsal columns carry vibration and conscious joint-position information.
- Loss of long myelinated fibers helps explain impaired vibration sense.
- Reduced position sense produces sensory contributions to gait and limb ataxia.
- An abnormal posterior column does not require primary neuronal loss in its relay nuclei.

Clarke nucleus and spinocerebellar pathway

- Clarke-column neurons receive proprioceptive input from lower-body primary afferents.
- Loss of their afferent input accompanies neuronal and tract degeneration.
- The dorsal spinocerebellar pathway conveys unconscious proprioceptive information.
- Dysfunction contributes to impaired coordination during posture and gait.

Sensory pathway: Where the lesions accumulate



Simplified pathway map; Clarke nucleus receives sensory inputs rather than being a direct relay in the conscious dorsal-column system.

Corticospinal tract involvement

- Corticospinal degeneration introduces upper-motor-neuron signs into an ataxic phenotype.
- The extensor plantar response may coexist with diminished tendon reflexes.
- Loss of long descending tracts contributes to weakness and spasticity.
- Mixed motor and sensory signs are a localization clue rather than a contradiction.

Dentate nucleus: Cerebellar output is affected

- Large projection neurons within the dentate nucleus show selective neuronal loss.
- The cerebellar output circuit is disrupted even when superficial cortex is relatively preserved.
- This injury adds a central cerebellar component to limb and gait incoordination.
- Neuropathologic change may exceed what conventional imaging reveals early.

Sensory ataxia and cerebellar ataxia coexist

Sensory contribution

- Large-fiber deafferentation
- Impaired position / vibration
- Worsens when visual compensation is removed

Cerebellar contribution

- Spinocerebellar and dentate injury
- Impaired movement timing and coordination
- Limb dysmetria / dysarthria may appear

Peripheral nerve pathology

- Large myelinated sensory fibers are especially vulnerable.
- Sensory nerve action potentials may be markedly reduced or absent.
- A length-dependent neuropathy framework alone does not describe the entire disease.
- Motor abnormalities and central nervous system lesions accompany sensory neuropathy.

Correlating pathology with bedside signs

Sensory neuron / column

Reduced vibration and joint position sense

Reflex afferent limb

Depressed ankle and knee reflexes

Corticospinal tract

Babinski sign, spasticity

Dentate / cerebellar networks

Limb dysmetria and dysarthria

Pathology is anatomically selective

- Not every neuron is injured to the same degree despite systemic frataxin deficiency.
- Dorsal-root-ganglion and dentate changes have different anatomic and temporal features.
- Cerebellar cortex and cerebral hemispheres are not the only relevant structures.
- This selectivity helps explain the unusual neurologic sign combination.

First symptom: Progressive gait instability

- Insidious gait imbalance is the typical neurologic presentation.
- Combined proprioceptive and cerebellar dysfunction impairs walking.
- Onset during school-age years or adolescence is characteristic but not universal.
- Progression prompts reassessment for systemic and neurologic complications.

Gait ataxia: Interpret the mechanism

- An irregular, broad-based gait does not distinguish cerebellar from sensory causes alone.
- Loss of leg position input can aggravate unsteadiness when eyes are closed.
- Damage in cerebellar pathways impairs corrective movement coordination.
- Both processes can be present in a single person with Friedreich ataxia.

Hand clumsiness and upper-limb ataxia

- Upper-limb dyscoordination often follows gait manifestations.
- Imprecise limb placement reflects combined sensory and cerebellar pathway damage.
- Fine-motor impairment affects writing, feeding, dressing and other tasks.
- The pattern is progressive rather than episodic.

Dysarthria localizes coordination impairment

- Speech becomes slurred as fine control of articulation deteriorates.
- Dysarthria is distinct from language aphasia or primary cognitive deterioration.
- Additional bulbar dysfunction, including dysphagia, can develop.
- Speech/swallowing assessment becomes relevant as disease advances.

Position and vibration: High-yield examination

- Impaired toe joint-position sense signals large-fiber proprioceptive dysfunction.
- Reduced vibration sense is expected in a substantial proportion of cases.
- Visual cues can partly compensate for loss of proprioceptive input.
- Findings integrate peripheral afferent and posterior-column pathology.

Areflexia with extensor plantar responses

Peripheral sensory circuit

- Large primary afferents degenerate
- Stretch reflex input declines
- Tendon reflexes reduced / absent

Descending motor pathway

- Corticospinal tract degenerates
- Plantar response becomes extensor
- Spasticity may develop

Weakness and spasticity: Mixed motor signs

- Strength may decline with disease progression.
- Corticospinal involvement can increase tone and impair voluntary movement.
- Peripheral neuropathy contributes to weakness and muscle wasting.
- A comprehensive examination distinguishes pyramidal signs from peripheral weakness.

Sensory findings are not uniform

- Vibration and joint-position loss are the most characteristic modalities.
- Pain, temperature and light-touch deficits occur in some individuals.
- Clinical complaint severity need not mirror the degree of electrophysiologic sensory loss.
- Absence of a striking sensory complaint should not eliminate FRDA from consideration.

Orthopedic manifestations

Pes cavus

A high-arched foot often accompanies long-standing neuropathic disease

Kyphoscoliosis

Spinal deformity may progress during growth

Contractures

Weakness and spasticity restrict joint range

Functional effect

Walking, transfers, sitting balance and care needs may be affected

Cardiomyopathy is not incidental

- Cardiac muscle is a major extra-neural target of frataxin deficiency.
- Hypertrophic remodeling is a characteristic phenotype, but cardiac presentations vary.
- Structural disease may be present before prominent neurologic impairment.
- Cardiac involvement importantly affects risk and long-term outcome.

Cardiac complications: Clinical consequences



- The flow is conceptual: Different complications can coexist or arise independently.
- Routine and symptom-driven cardiac assessment is justified.

Diabetes and impaired glucose regulation

- Disrupted glucose homeostasis occurs in a subset of affected individuals.
- Cardiometabolic disease adds to the burden of a neurologic disorder.
- Glucose assessment is part of longitudinal surveillance.
- Specific diabetes treatment requires individualized endocrine management.

Neurologic and systemic feature matrix

Domain	Representative feature	Teaching implication
Sensory	Position/vibration loss	Check distal proprioception
Motor	Areflexia + Babinski	Localize two pathways
Cerebellar	Ataxia, dysarthria	Assess coordination
Systemic	Cardiac, metabolic, skeletal	Screen beyond the nervous system

Typical versus later-onset FRDA

Typical pattern

- Childhood / adolescent gait onset
- Progressive sensory and pyramidal involvement
- Cardiomyopathy is a key consideration

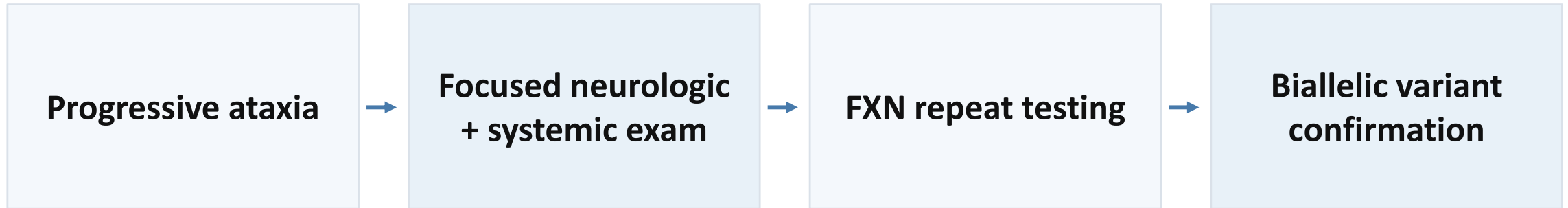
Atypical variants

- Later onset, including after age 25
- Some retain tendon reflexes
- Molecular confirmation overrides classic checklists

When to suspect Friedreich ataxia

- Child or young adult with progressive gait ataxia and reduced tendon reflexes.
- Impaired joint-position / vibration sense reinforces a large-fiber phenotype.
- Extensor plantar responses suggest simultaneous long-tract disease.
- Cardiomyopathy, pes cavus or scoliosis strengthens the syndromic impression.

Diagnostic reasoning from phenotype to genotype



- Testing must be chosen to detect the expanded GAA repeat.
- In atypical or unresolved cases, broaden the genetic differential.

Examination: Three localization questions

- Is incoordination sensory, cerebellar, or a combination?
- Are tendon reflexes reduced while plantar responses are extensor?
- Are cardiac, skeletal or metabolic signs present?
- Does the onset and inheritance pattern warrant targeted FXN analysis?

Molecular confirmation: Choose the right assay

- Targeted testing for intron-1 FXN GAA expansion is a core diagnostic step.
- Most molecularly confirmed cases have expanded repeats on both alleles.
- If only one expansion is detected, evaluate the other allele for sequence/CNV variants.
- Interpretation requires the laboratory method and variant classification.

A negative exome is not enough

- Routine exome sequencing does not reliably resolve the pathogenic intronic repeat.
- Repeat-aware assays are needed when the clinical suspicion is high.
- Gene panels differ in whether they test short variants, copy-number changes and repeats.
- A result must be interpreted in light of what the assay did—and did not—detect.

Electrophysiology: An adjunct, not the genotype

- Sensory nerve action potentials can be profoundly reduced or absent.
- Motor nerve conduction may be comparatively preserved, particularly early.
- Results support large-fiber sensory neuropathy but do not establish FXN causation.
- Use studies to answer anatomical questions or evaluate possible alternatives.

Neuroimaging: Interpret a normal early MRI carefully

- Conventional brain MRI can be unremarkable early in disease.
- Later abnormalities may include spinal cord and cerebellar volume loss.
- Imaging findings are supportive and may help assess alternate etiologies.
- Molecular diagnosis is more specific than visual pattern recognition on MRI.

Genotype–phenotype: Trends are not predictions

- Length of the shorter expanded GAA allele is associated with onset and severity at group level.
- Clinical variability remains substantial, even among people with related genotypes.
- Do not assign an individual prognosis from repeat number alone.
- Cardiac burden, functional trajectory and other modifiers need direct assessment.

Differential: Autosomal dominant SCA

Friedreich ataxia

- Autosomal recessive pattern
- FXN intronic GAA expansion
- Large-fiber sensory loss and cardiac disease

Many dominant SCAs

- Vertical family transmission may occur
- Heterogeneous genes; Some coding CAG repeats
- Clinical overlap; Variant-specific features

Differential: Ataxia-telangiectasia

Friedreich ataxia

- Frataxin deficiency
- Sensory neuropathy and cardiomyopathy
- No defining telangiectasia–immunodeficiency syndrome

Ataxia-telangiectasia

- ATM pathway defect
- Conjunctival / skin telangiectasias
- Immunodeficiency and cancer predisposition

Treatable mimics must not be missed

Alternative	Overlap with FRDA	Helpful distinction
Vitamin E deficiency / TTPA	Sensory ataxia, areflexia	Low vitamin E; treatable cause
Abetalipoproteinemia	Ataxia / sensory neuropathy	Fat malabsorption, lipid abnormalities
Other recessive ataxias	Early ataxia + neuropathy	Different molecular/clinical clues

Longitudinal care must be multidisciplinary

Neurology / rehabilitation

Function, mobility, speech and swallowing

Cardiology

Rhythm and myocardial function

Endocrinology

Glucose metabolism and diabetes

Orthopedics / allied health

Scoliosis, feet, contractures, support devices

Cardiac surveillance: Risk is actionable

- An electrocardiogram and echocardiogram are recommended at diagnosis.
- The 2022 consensus guidelines advise repeating both at least annually.
- Palpitations or possible arrhythmia warrant symptom-directed rhythm monitoring.
- Cardiology input is indicated for cardiac symptoms or abnormal investigations.

Glucose surveillance and diabetes care

- At least annual fasting glucose and HbA1c screening is recommended.
- Consider oral glucose tolerance testing selectively when screening is abnormal.
- Review symptoms of hyperglycemia during routine clinical encounters.
- Glucose-lowering therapy is individualized; No single regimen suits all FRDA patients.

Preserving function through supportive care

- Physical and occupational therapy address mobility, safety and daily activities.
- Orthopedic assessment addresses scoliosis, foot deformity and contractures.
- Speech and swallowing professionals evaluate dysarthria or dysphagia.
- Supportive interventions remain important even with disease-targeted medication.

Omaveloxolone: Disease-targeted treatment

- Omaveloxolone is an Nrf2-pathway activator approved in the United States for FRDA.
- The FDA indication covers adults and adolescents aged 16 years or older.
- Its therapeutic goal is to slow functional disease progression—not replace rehabilitation.
- Approval and safety labeling should be checked against the jurisdiction and current label.

Treatment limitations and monitoring

- Omaveloxolone is not a cure and does not reverse established neuronal loss.
- The FDA label specifies monitoring of liver enzymes, bilirubin, BNP and lipid parameters.
- Cardiac, diabetic, orthopedic and functional surveillance continues during treatment.
- The decision to use therapy requires patient-specific assessment of benefit and safety.

Clinical application 1: Identify the localization

Hypothetical teaching vignette

A 13-year-old develops progressive unsteadiness, impaired toe-position sense, absent knee reflexes and extensor plantar responses.

Which neural systems explain absent reflexes and Babinski signs occurring together?

Clinical application 1: Explanation

Sensory-afferent and corticospinal lesions coexist.

- Loss of large sensory fibers reduces tendon-reflex afferent input.
- Corticospinal degeneration produces an extensor plantar response.
- Dorsal-column and cerebellar circuit disease account for the ataxia.

Clinical application 2: Select a molecular test

Hypothetical teaching vignette

A patient has childhood-onset ataxia, dysarthria, sensory neuropathy and a normal nondiagnostic exome sequencing report.

Does the normal exome exclude Friedreich ataxia? What testing is needed?

Clinical application 2: Explanation

No. Test specifically for the intronic FXN GAA expansion.

- Routine exome sequencing does not adequately interrogate this repeat.
- Investigate a second pathogenic variant if a single expansion is found.
- The molecular diagnosis needs biallelic pathogenic FXN variants.

Integrated synthesis: Four linked levels

DNA

FXN intron-1 GAA expansion

Protein

Reduced mitochondrial frataxin

Tissue

Selective sensory, spinal and dentate injury

Patient

Ataxia plus neuropathy, pyramidal and cardiac signs

High-yield diagnostic conclusions

- Friedreich ataxia is an autosomal recessive frataxin-deficiency disorder.
- The core biochemical lesion impairs mitochondrial Fe–S cluster biology.
- Areflexia with extensor plantar responses is anatomically coherent.
- Genetic testing confirms disease; Care must assess heart and metabolism.

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