

Diseases Caused by Trinucleotide-Repeat Expansions

Genetic instability • molecular pathology • clinicopathologic correlations

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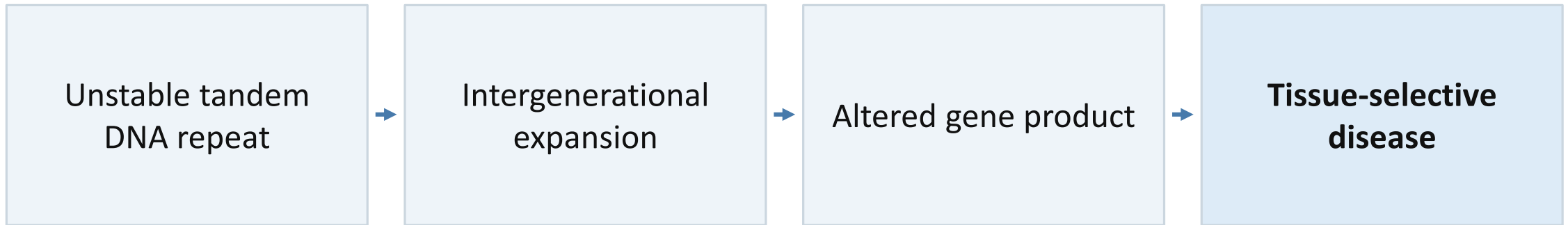
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Learning objectives

- Define repeat expansion as a dynamic mutation and explain anticipation.
- Predict pathogenic mechanisms from repeat location: UTR, intron, or coding exon.
- Contrast FMR1 full-mutation disease with FMR1 premutation-associated disorders.
- Connect the molecular defects in Huntington disease, Friedreich ataxia, and myotonic dystrophy to their clinical phenotypes.

Expanded repeats alter gene function by multiple routes



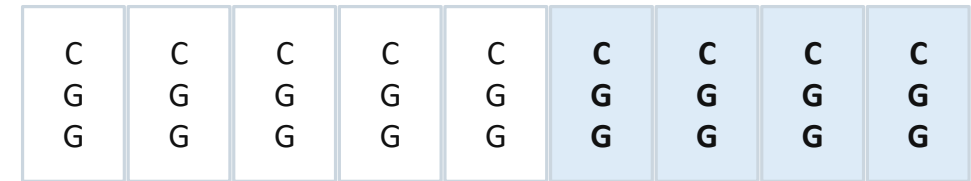
The mutation mechanism is shared; The molecular consequences are not identical.

A tandem repeat becomes pathogenic when it expands

Unexpanded locus



Expanded locus



Illustrative unit count; Not a diagnostic threshold

Stable range

Repeat tract remains below the disease-associated expansion threshold.

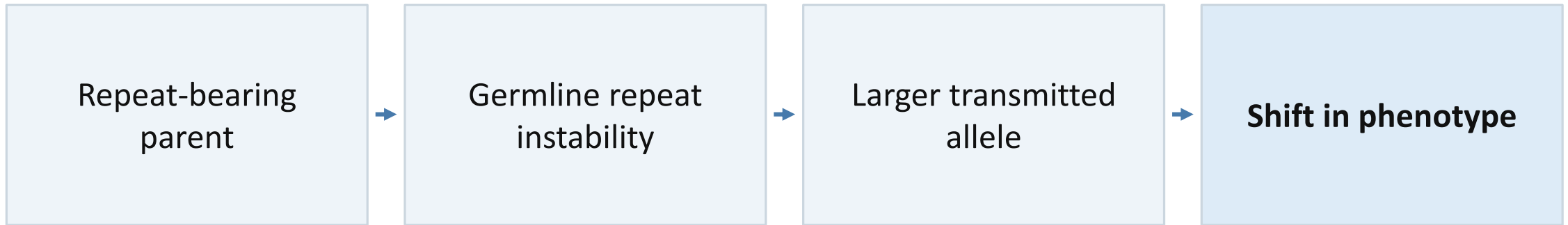
Pathogenic expansion

The enlarged repeat alters gene expression, RNA processing, or protein function.

Trinucleotide repeats are a form of dynamic mutation

- The repeat tract may change length during transmission between generations.
- Allele size and stability can influence phenotype and age at manifestation.
- This instability helps explain patterns not captured by simple Mendelian segregation.
- Expansion beyond a locus-specific threshold can impair gene expression or protein function.

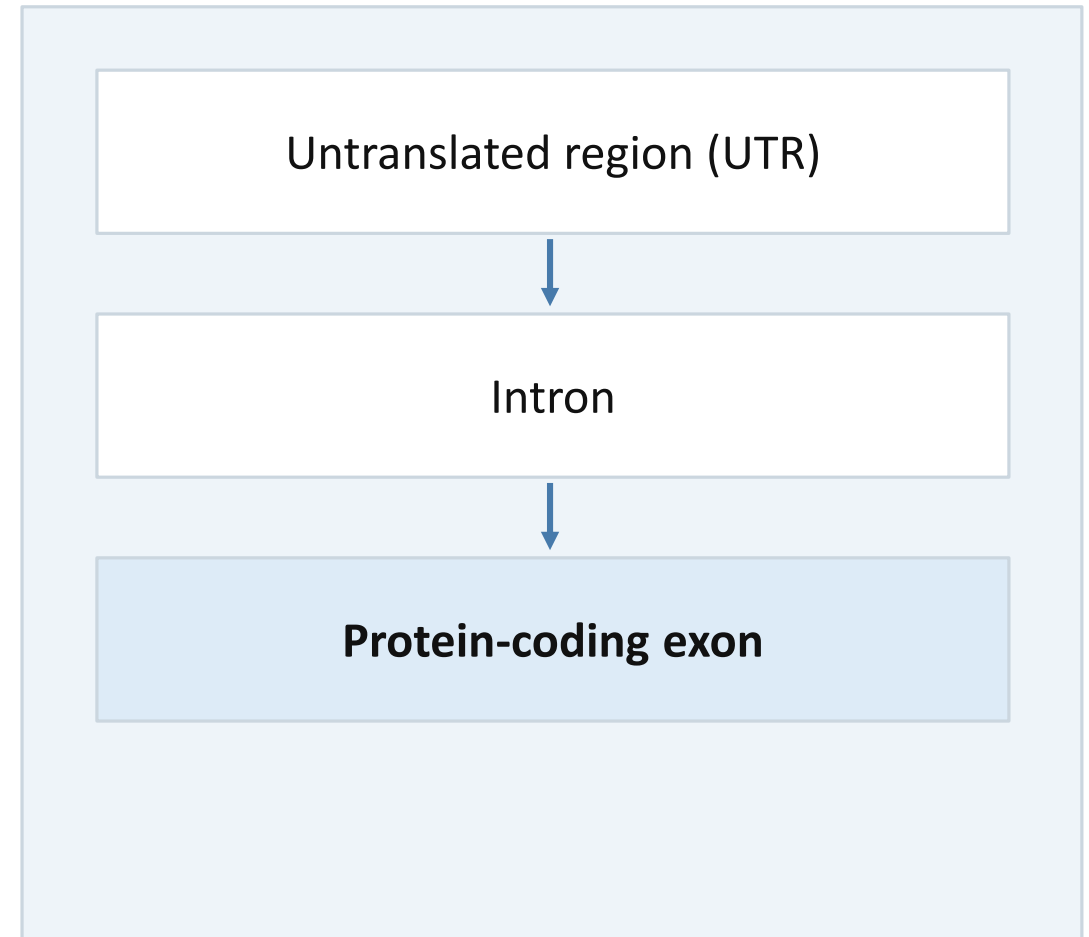
Anticipation links repeat growth to earlier or more severe disease



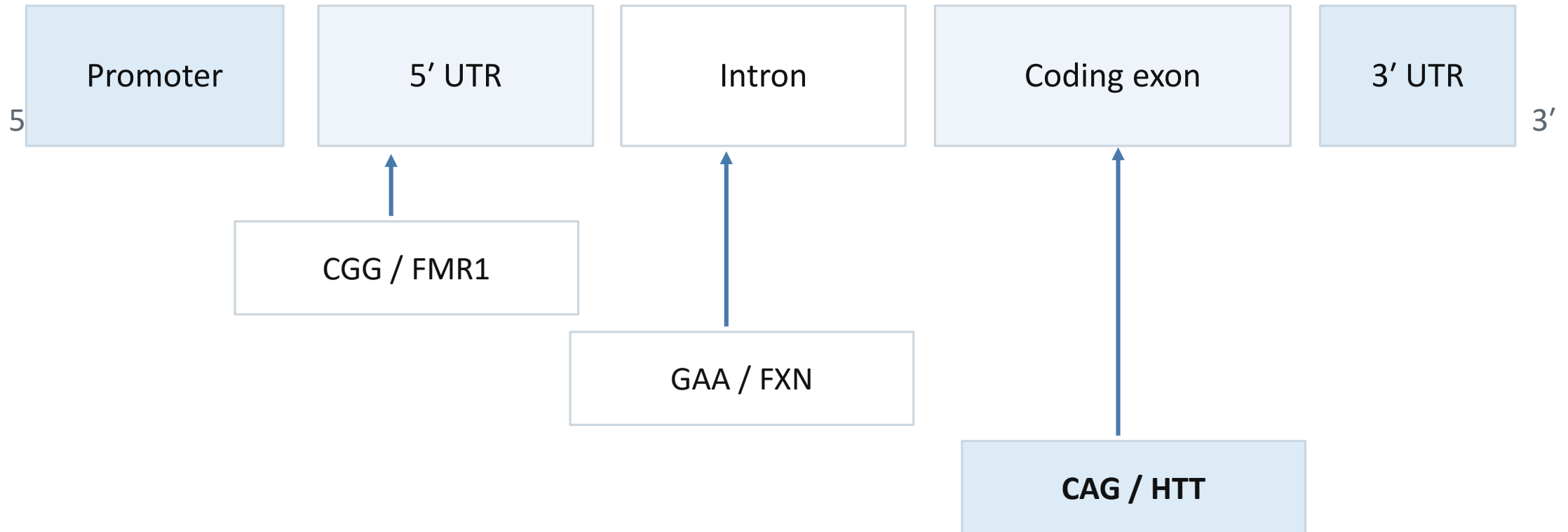
- Anticipation describes more severe or earlier manifestations in successive generations.
- Its presence and parental transmission pattern are disease-specific.

Repeat location is a major pathogenic determinant

- An expansion in a regulatory region can suppress transcription.
- A noncoding transcript can acquire toxic RNA-binding properties.
- A coding CAG expansion produces an elongated polyglutamine tract.



Coding and noncoding repeat sites are distinct



Illustrative gene layout • sites represent different genes, not one continuous locus

Three core mechanisms of repeat-expansion disease

Mutated region	Primary molecular change	Representative disease
5' untranslated region	FMR1 methylation / silencing	Fragile X syndrome
Intron	Reduced FXN expression	Friedreich ataxia
Protein-coding exon	Expanded polyglutamine protein	Huntington disease
Noncoding transcript	RNA-mediated gain of function	Myotonic dystrophy type 1

Gain and loss of function are not interchangeable

- Loss of function: The cell lacks sufficient functional gene product.
- Protein gain of function: Mutant protein acquires harmful properties.
- RNA gain of function: Expanded-repeat RNA perturbs RNA-binding proteins.
- The same locus can produce different disorders at different repeat lengths.

Transcriptional silencing: A route to loss of function



- Gene silencing decreases formation of the normal protein.
- FMR1 full mutation and intronic FXN expansion illustrate distinct silencing contexts.

Toxic RNA: Transcription without harmless function



- Repeat-containing RNA can bind and sequester regulatory proteins.
- Disordered RNA processing may occur despite continued transcription.

Polyglutamine toxicity: A coding expansion



- CAG encodes glutamine; Expansion lengthens a protein's glutamine tract.
- Mutant protein misfolding and altered cellular interactions contribute to injury.

Disease-repeat-gene map

Disorder	Gene	Repeat / location
Fragile X syndrome	FMR1	CGG; 5' UTR
Huntington disease	HTT	CAG; Coding exon
Friedreich ataxia	FXN	GAA; Intron
Myotonic dystrophy type 1	DMPK	CTG; Noncoding transcript
Kennedy disease	AR	CAG; Coding region

Fragile X syndrome: The FMR1 locus

- Fragile X syndrome is an X-linked disorder associated with CGG expansion.
- The repeat lies in the 5' untranslated region of FMR1 on Xq27.3.
- The major full-mutation mechanism is epigenetic silencing and loss of FMRP.
- A premutation may instead remain transcribed and produce distinct disease.

FMR1 alleles form a molecular spectrum

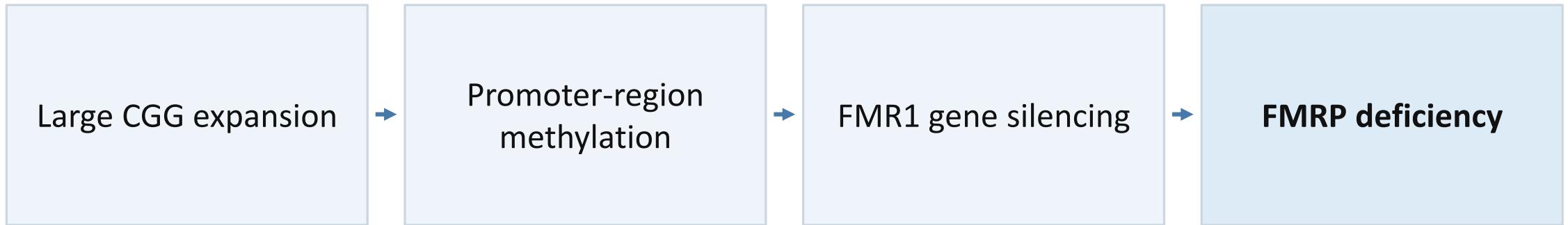


The gene dosage and toxic-RNA consequences differ markedly across classes

FMR1 repeat lengths: Interpret the source cautiously

- Typical alleles with relatively short CGG tracts (average about 29).
- Premutations are described as approximately 55–200 CGG repeats.
- Full mutations are very large expansions, generally exceeding about 200 repeats.
- The source uses slightly differing full-mutation bounds across text and table; Do not substitute those approximations for laboratory interpretation.

Full FMR1 expansion promotes transcriptional shutdown

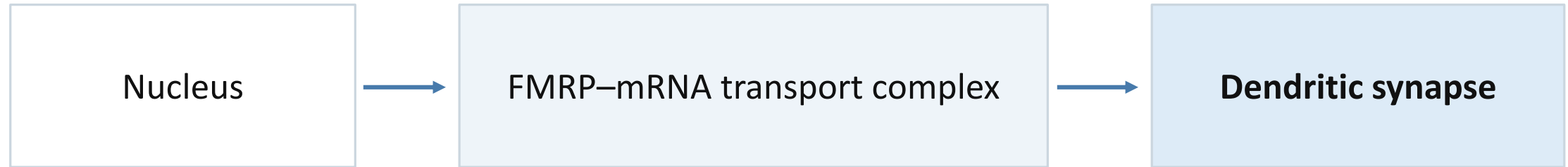


- Dense methylation reaches the 5' region and promoter of FMR1.
- Transcriptional suppression markedly reduces FMRP production.

FMRP regulates neuronal messenger RNA

- FMRP is expressed widely, with high abundance in brain and testis.
- It binds selected mRNAs and associates with neuronal transport complexes.
- FMRP helps regulate where and when proteins are synthesized at synapses.
- Loss of these controls disrupts the cellular basis of neuronal adaptation.

FMRP connects mRNA transport to synaptic translation



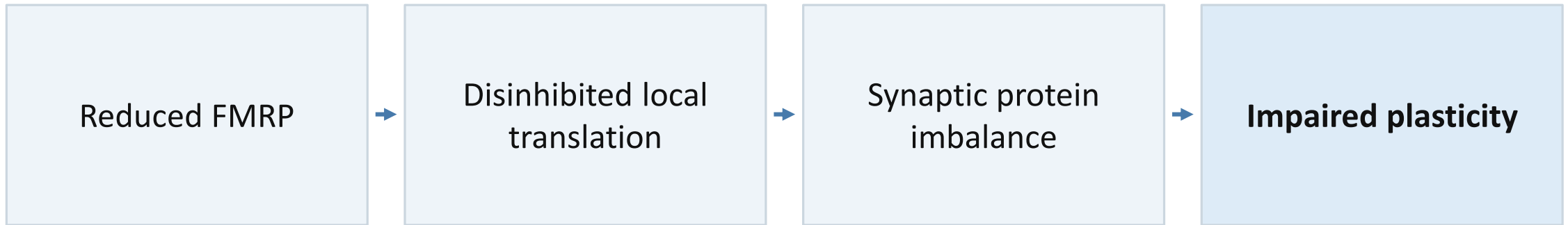
With FMRP

Localized translation is regulated in response to neuronal signals.

With FMRP deficiency

Dysregulated translation contributes to impaired synaptic plasticity.

Loss of FMRP disrupts synaptic plasticity



- FMRP deficiency with increased translation of bound synaptic mRNAs.
- Imbalanced synaptic protein production compromises plasticity relevant to learning and memory.

Fragile X syndrome: Neurodevelopmental consequences

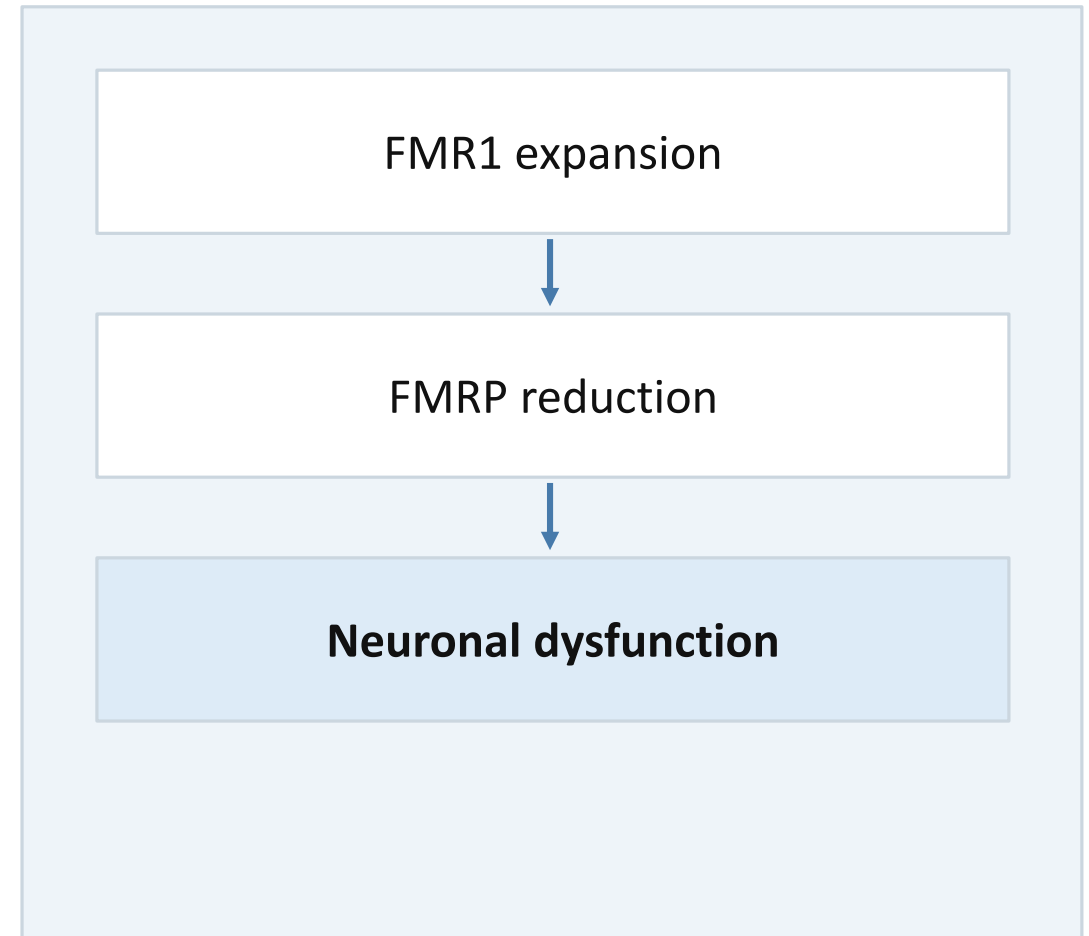
- Intellectual disability is a major phenotype, particularly in affected males.
- Autism spectrum manifestations, hyperactivity and anxiety are recognized.
- Epilepsy and behavioral dysregulation can accompany developmental impairment.
- Expression varies among affected individuals and between sexes.

Fragile X syndrome: Characteristic physical findings

- Long face, prominent mandible and large/everted ears may be present.
- Macroorchidism is a distinctive finding in postpubertal affected males.
- Hyperextensible joints, high-arched palate and mitral valve prolapse may occur.
- Absence of a stereotypic appearance does not exclude the diagnosis.

Why the phenotype is not purely a “facial syndrome”

- The molecular defect chiefly affects RNA regulation within cells.
- Synaptic protein homeostasis explains the strong neurodevelopmental emphasis.
- Physical signs are variable and may be subtle.
- Molecular testing is decisive when clinical suspicion is appropriate.

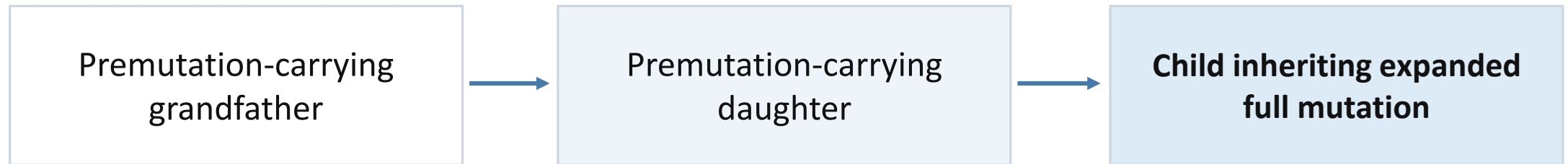


Sex-specific effects reflect X-linked biology

- Males have a single X chromosome and are often more severely affected.
- Females with a full mutation may have variable manifestations.
- Patterns of X-chromosome inactivation contribute to clinical heterogeneity.
- Inheritance depends on both the expanded allele and the transmitting parent.

Maternal transmission can expand an FMR1 premutation

Illustrative transmission of an FMR1 premutation



Paternal transmission usually involves modest repeat change

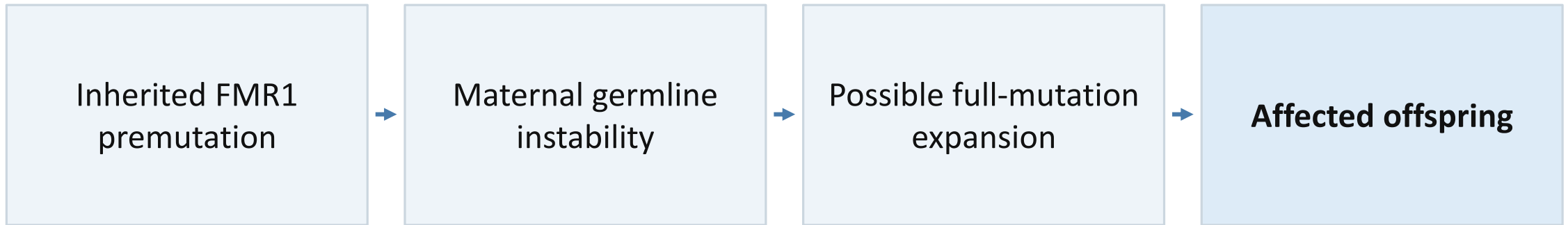
Substantial expansion may occur during maternal transmission

This is a risk illustration, not a deterministic offspring prediction

The historical “normal transmitting male” pattern

- Some premutation-carrying males may not show the classical fragile X phenotype.
- These males transmit their X chromosome to all daughters, not to sons.
- Daughters carrying premutations may pass expanded alleles to their children.
- This pedigree pattern historically helped reveal repeat instability.

Anticipation in fragile X is linked to oogenesis

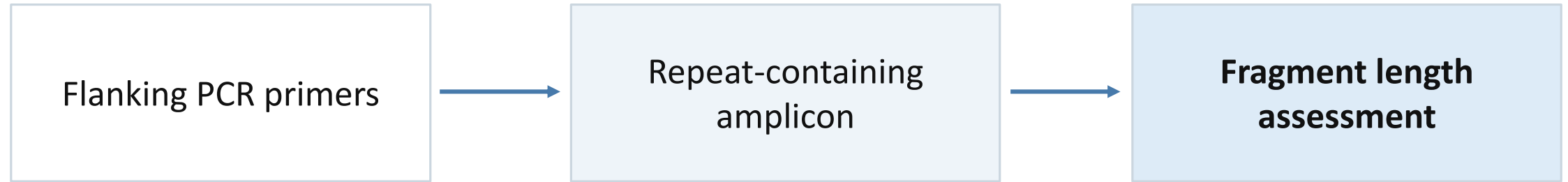


- Greater full-mutation expansion during maternal transmission.
- Clinical penetrance in descendants is not predicted from Mendelian allele inheritance alone.

A full FMR1 mutation is not equivalent to a premutation

- Full mutation: Promoter methylation and FMRP deficiency dominate.
- Premutation: FMR1 RNA production continues and toxic-RNA effects may occur.
- The classic syndrome and adult-onset premutation disorders have distinct mechanisms.
- Allele size alone does not replace molecular and clinical characterization.

Molecular testing can assess repeat tract length



Important limitation

Very large expansions may not amplify efficiently by conventional PCR; The source describes Southern blotting as an alternative.

The diagnostic assay has an amplification limitation

- Flanking PCR amplifies the sequence containing the repeat tract.
- Product length can distinguish shorter alleles and many premutations.
- Very large expanded alleles may be difficult to amplify conventionally.
- Southern blot analysis when a large expansion cannot be characterized by conventional PCR.

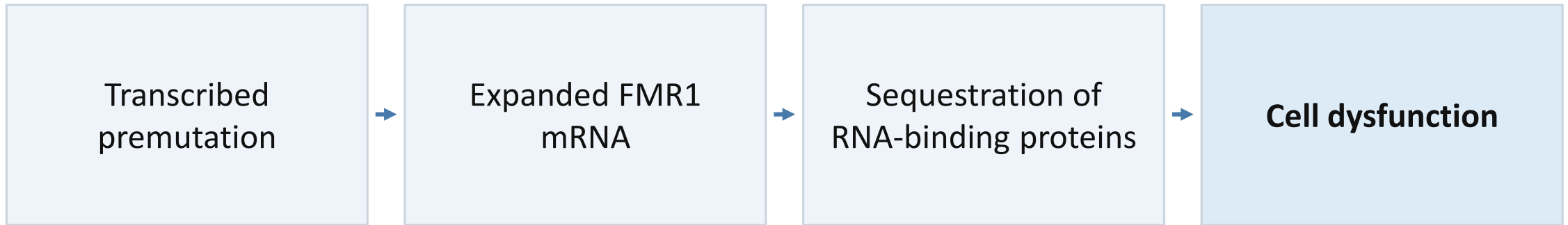
Diagnosing fragile X requires mechanism-aware interpretation

- A detected expansion must be interpreted in its allele-size category.
- Clinical signs do not reliably distinguish all premutation carriers from noncarriers.
- Assay limitations matter when apparent absence of an amplicon may reflect an enlarged repeat.
- Genetic counseling must consider the transmitting parent and reproductive context.

FMR1 premutations are biologically active

- Premutations are not simply clinically silent intermediates.
- The expanded locus remains transcribed rather than undergoing full-mutation silencing.
- Expanded FMR1 RNA can acquire toxic properties.
- The associated phenotypes differ from classic fragile X syndrome.

Premutation-associated disease is an RNA-mediated process



- Expanded CGG-containing RNA recruits proteins away from their normal functions.
- RNA/protein aggregates and nuclear inclusions are described in affected tissues.

Fragile X–associated tremor/ataxia syndrome

- An adult-onset progressive neurologic syndrome in some FMR1 premutation carriers.
- Characteristic findings include intention tremor and cerebellar ataxia.
- Progression to parkinsonian features can occur.
- Nuclear inclusions involving expanded FMR1 RNA and bound proteins.

Fragile X–associated primary ovarian insufficiency

- Premutation-carrying females can develop ovarian dysfunction before age 40.
- Features include menstrual irregularity and diminished fertility.
- Elevated FSH and reduced anti-Müllerian hormone.
- Intracellular expanded-RNA aggregates may contribute to follicular damage; The exact mechanism is less established.

Premutation and full mutation produce different outcomes

Property	FMR1 premutation	FMR1 full mutation
Gene expression	Transcription persists	Epigenetic silencing predominant
Molecular mechanism	Toxic CGG-containing RNA	Reduced / absent FMRP
Representative phenotype	Tremor/ataxia; Ovarian insufficiency	Neurodevelopmental fragile X syndrome
Typical timing	Often adult onset	Early developmental manifestations

Clinical application: Developmental phenotype

CLINICAL PATTERN

A boy has intellectual disability, prominent ears and macroorchidism after puberty.

PATHOLOGIC INTERPRETATION

A large FMR1 CGG expansion with epigenetic silencing explains the syndrome through reduced FMRP.

Clinical application: Adult premutation phenotype

CLINICAL PATTERN

An older man develops intention tremor and progressive gait ataxia; Family history suggests an FMR1 expansion.

PATHOLOGIC INTERPRETATION

Consider fragile X–associated tremor/ataxia syndrome: A transcribed premutation with RNA-mediated toxicity.

Huntington disease exemplifies a coding repeat expansion

- Autosomal dominant neurodegeneration with movement and cognitive manifestations.
- An expanded CAG tract occurs in the first exon of HTT.
- CAG encodes glutamine, making huntingtin an expanded polyglutamine protein.
- The primary pathogenic concept is toxic gain of protein function.

HTT CAG expansion changes a protein, not simply transcript abundance



DNA → protein composition → selective neuronal injury

Repeat length influences age at Huntington onset

- An inverse association between repeat number and age at onset.
- Longer expanded tracts are associated with earlier manifestations.
- Paternal transmission is especially relevant to further repeat expansion.
- The disease-specific pattern contrasts with maternal expansion in fragile X.

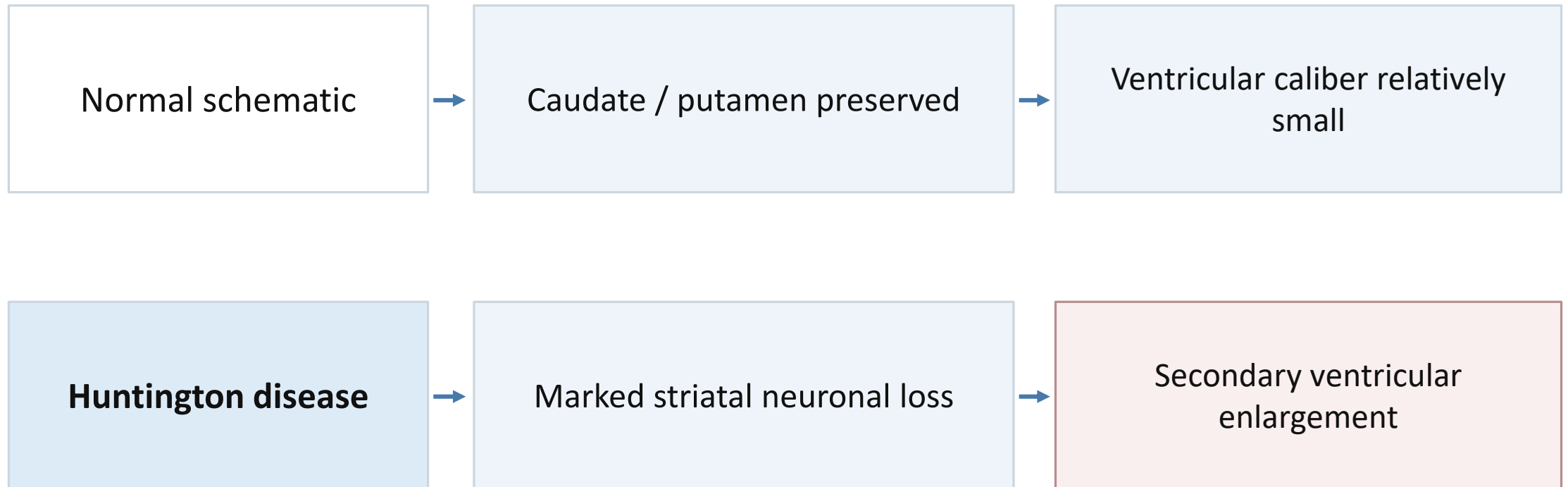
Huntington molecular injury is multifactorial

- Mutant huntingtin can dysregulate transcriptional regulators.
- Impaired mitochondrial-related responses may increase vulnerability to oxidative stress.
- Reduced brain-derived neurotrophic factor and altered proteostasis may contribute.
- No single inclusion-based mechanism explains all cellular injury.

Neuronal inclusions are not necessarily the toxic species

- Mutant huntingtin aggregates occur in striatal and cortical neurons.
- Inclusions are a pathologic hallmark, not proof of the immediate injury mechanism.
- Experimental observations compatible with sequestration of toxic species.
- A visible aggregate can therefore be associated with a protective response.

Huntington morphology: Striatum atrophy



Schematic relationships only; Not gross or histologic evidence

The striatum links structure to chorea

- Loss of caudate and putaminal neurons is the dominant gross pathologic feature.
- Striatal circuits normally participate in damping motor output.
- Disrupted inhibitory circuitry contributes to involuntary hyperkinetic movements.
- Caudate atrophy may coexist with ventricular enlargement.

Huntington disease: The clinical trajectory

- Chorea and other involuntary movements are characteristic.
- Cognitive and affective dysfunction may evolve to severe dementia.
- Later bradykinesia or rigidity may follow initial hyperkinetic manifestations.
- A progressive, ultimately fatal disease course.

Huntington anticipation is often paternal



- In the text, repeat expansion is associated with spermatogenesis.
- An expanded allele inherited from an affected father may produce earlier onset.

Clinical application: Autosomal dominant chorea

CLINICAL PATTERN

An adult with a family history of progressive chorea develops involuntary movements and cognitive change.

PATHOLOGIC INTERPRETATION

HTT coding CAG expansion produces mutant huntingtin; Caudate/putaminal neuron loss links the genotype to the motor phenotype.

Friedreich ataxia is a noncoding repeat disease

- Autosomal recessive disorder with progressive ataxia and systemic involvement.
- The GAA expansion lies in the first intron of FXN.
- An altered chromatin environment decreases frataxin expression.
- Loss of frataxin affects mitochondrial metabolism rather than polyglutamine production.

FXN expansion disrupts mitochondrial function



- Chromatin changes accompany suppression of FXN transcription.
- Reduced iron–sulfur cluster function and excess mitochondrial iron can increase oxidative stress.

Frataxin deficiency affects iron–sulfur cluster function

- Frataxin contributes to mitochondrial iron–sulfur cluster enzyme assembly.
- Reduced frataxin decreases oxidative phosphorylation capacity.
- Increased free mitochondrial iron may add oxidative stress.
- High-energy-demand neural and cardiac tissues are clinically prominent.

Friedreich ataxia: Characteristic neurologic findings

- Gait ataxia typically precedes hand clumsiness and dysarthria.
- Weakness, sensory neuropathy and impaired joint-position sense are common.
- Deep tendon reflexes may be depressed or absent.
- An extensor plantar response can coexist with absent peripheral reflexes.

Friedreich ataxia: The cardiac connection

- Cardiomyopathy is a major extra-neurologic manifestation.
- Arrhythmias and heart failure contribute substantially to morbidity.
- Diabetes can accompany the disorder.
- The multisystem phenotype reflects widespread effects of mitochondrial dysfunction.

Huntington versus Friedreich ataxia

Feature	Huntington disease	Friedreich ataxia
Inheritance	Autosomal dominant	Autosomal recessive
Repeat / gene	CAG / HTT	GAA / FXN
Molecular lesion	Polyglutamine gain of function	Reduced frataxin expression
Characteristic phenotype	Chorea and cognitive decline	Ataxia, neuropathy, cardiomyopathy

Clinical application: Recessive ataxia

CLINICAL PATTERN

A child develops progressive gait ataxia, impaired position sense, absent reflexes and cardiomyopathy.

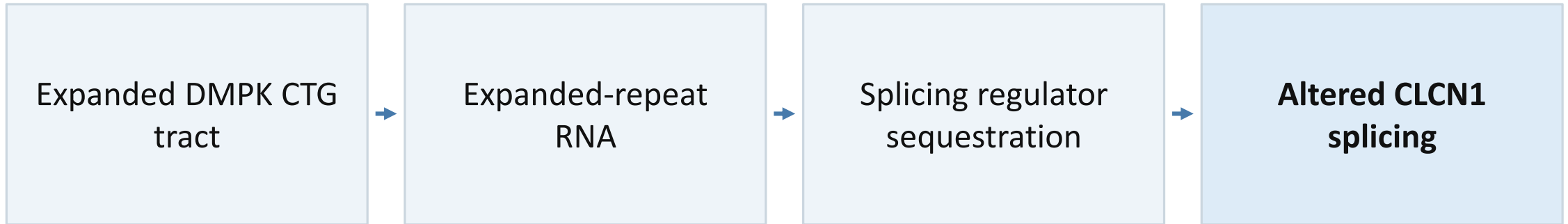
PATHOLOGIC INTERPRETATION

Intronic GAA expansion in FXN can reduce frataxin expression, causing a neurocardiac mitochondrial phenotype.

Myotonic dystrophy type 1 expands a noncoding CTG tract

- Myotonic dystrophy is an autosomal dominant, multisystem disease.
- Myotonic dystrophy type 1 (DM1) involves CTG expansion in DMPK.
- Expanded-repeat RNA mediates a toxic gain of function.
- Manifestations include myotonia, weakness, cataracts, endocrine and cardiac abnormalities.

Myotonic dystrophy: RNA toxicity disrupts splicing



Muscle phenotype

Decreased functional chloride-channel expression contributes to persistent muscle excitability (myotonia).

CLCN1 mis-splicing helps explain myotonia

- Expanded-repeat RNA sequesters muscle splicing regulators.
- Alternative splicing of CLCN1 reduces normal muscle chloride-channel function.
- Decreased chloride conductance alters membrane excitability.
- The result is delayed relaxation after voluntary muscle contraction.

RNA splicing defects extend beyond chloride channels

- Altered insulin-receptor isoform splicing may contribute to insulin resistance.
- Myotonic dystrophy affects multiple organs, not just skeletal muscle.
- Disease severity is not explained solely by repeat length.
- Severe congenital disease is associated in the text with larger expansions.

Trinucleotide and tetranucleotide expansions are distinct

- DM1 involves a CTG trinucleotide repeat in DMPK.
- DM2 involves a CCTG tetranucleotide repeat in CNBP.
- Both illustrate pathogenic expanded-repeat RNA effects.
- Do not incorrectly classify all repeat-expansion syndromes as trinucleotide diseases.

Spinocerebellar ataxias include polyglutamine forms

- Several autosomal dominant spinocerebellar ataxias involve coding CAG expansions.
- Examples include SCA1, SCA2, SCA3, SCA6 and SCA7.
- Dentatorubral-pallidoluysian atrophy is another polyglutamine example.
- Some other ataxia syndromes instead involve noncoding repeat expansions.

Repeat-expansion mechanisms: Integrated comparison

Disease / gene	Primary defect	Principal clinical theme
Fragile X / FMR1 full	FMRP loss of function	Neurodevelopmental impairment
FMR1 premutation	Expanded RNA toxicity	Tremor/ataxia; Ovarian dysfunction
Huntington / HTT	Mutant polyglutamine protein	Chorea and cognitive decline
Friedreich / FXN	Frataxin deficiency	Ataxia with cardiomyopathy
Myotonic dystrophy / DMPK	Aberrant RNA splicing	Myotonia and multisystem disease

Recognize the mechanism from clinical context

- Childhood intellectual disability with suggestive X-linked family history → assess FMR1 full mutation.
- Late-life intention tremor and ataxia with FMR1 family history → consider premutation-associated syndrome.
- Progressive chorea plus autosomal dominant inheritance → consider HTT CAG expansion.
- Childhood ataxia with cardiomyopathy → consider FXN GAA expansion.

Predict molecular pathology from expansion location

- FMR1 5' UTR expansion → promoter methylation and reduced FMRP when full mutation.
- FXN intronic GAA expansion → altered chromatin and reduced frataxin.
- HTT exonic CAG expansion → polyglutamine protein gain of function.
- DMPK repeat-containing RNA → sequestration of splicing regulators.

Integrated case: Muscle symptoms and cataracts

CLINICAL PATTERN

An adult has delayed hand-grip relaxation, muscle weakness and early cataracts.

PATHOLOGIC INTERPRETATION

A DMPK CTG expansion can produce toxic RNA and splicing defects; Impaired CLCN1 expression is linked to myotonia.

Common interpretation pitfalls

- Do not confuse the presence of repeat expansion with one universal cellular mechanism.
- Do not assume all expanded alleles have the same penetrance or intergenerational behavior.
- Do not equate FMR1 premutation disorders with FMR1 full-mutation syndrome.
- Do not interpret a negative conventional PCR result without considering very large expansions.

Key clinicopathologic synthesis

- Repeat tract location determines whether DNA, RNA or protein becomes the dominant pathological substrate.
- Germline instability explains anticipation and parent-of-origin effects.
- FMR1 full mutations impair protein availability; Premutations can cause RNA toxicity.
- HTT, FXN and DMPK show how distinct molecular lesions yield different target-organ phenotypes.

Primary source and extended textbook sections

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 5 — Genes and Human Diseases: repeat expansions, fragile X and molecular analysis.
- Chapter 28 — The Central Nervous System: Huntington disease, spinocerebellar ataxias and Friedreich ataxia.
- Chapter 27 — Peripheral Nerves and Skeletal Muscles: myotonic dystrophy.