

Fragile X Syndrome

Molecular pathogenesis, clinical phenotype, inheritance and diagnosis

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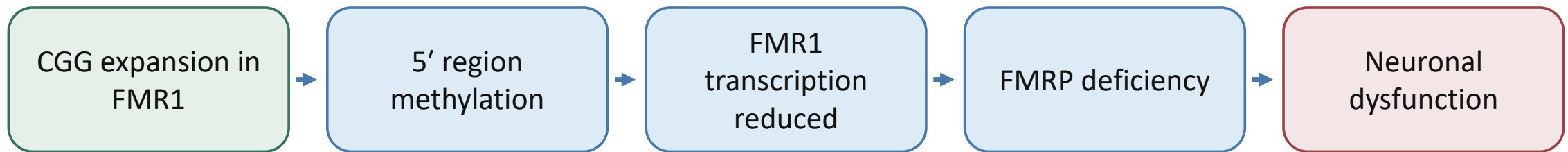
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Learning objectives

- Explain how a CGG-repeat expansion disrupts FMR1 expression.
- Connect FMRP deficiency to altered synaptic translation and plasticity.
- Recognize the characteristic clinical spectrum and its variability.
- Interpret the unusual transmission pattern and rationale for molecular testing.

Fragile X syndrome: A causal overview



The disease is a loss-of-function consequence of an unstable noncoding repeat.

Clinical and genetic significance

- FXS as the leading genetic cause of intellectual disability in males.
- It is a single-gene disorder with nonclassic transmission patterns.
- Molecular repeat analysis has superseded the historical chromosome-fragility assay.

Cognitive

Intellectual disability

Behavioral

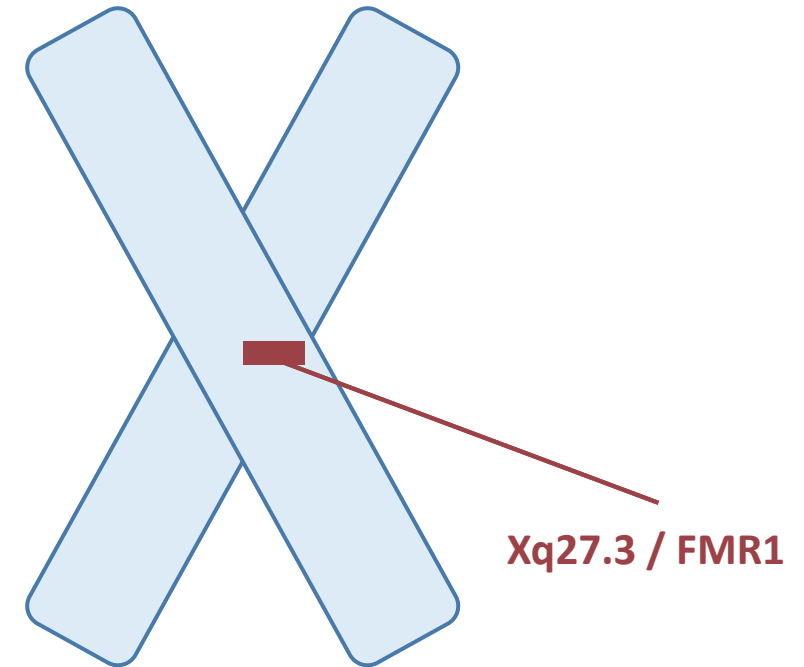
Autism; Anxiety; Hyperactivity

Somatic

Face; Macroorchidism; Joints

Why “fragile X”?

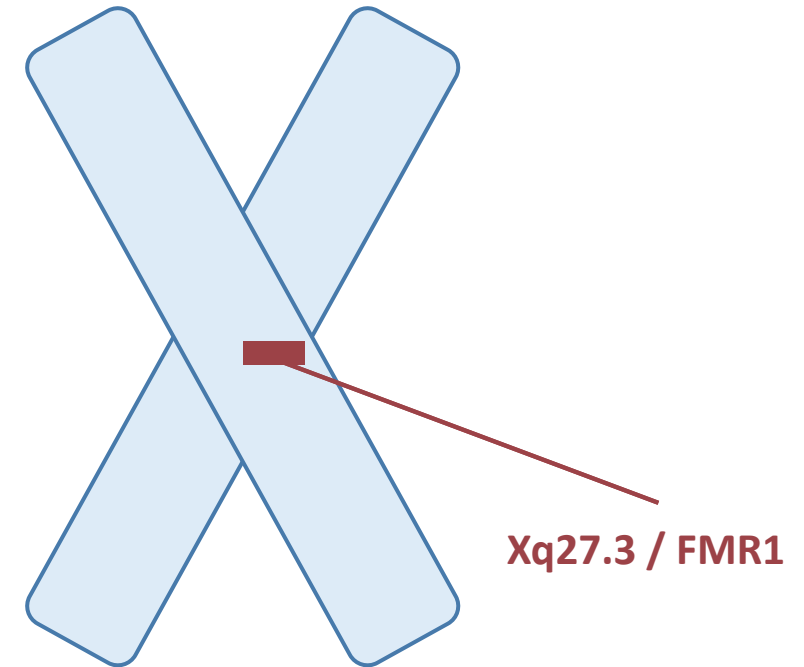
- The name describes a former cytogenetic finding on the X chromosome.
- Folate-deficient cell culture can reveal a gap or constriction by Giemsa staining.
- The apparent break maps near the FMR1 locus; DNA assays now establish the molecular lesion.



Simplified chromosome schematic

FMR1 maps to Xq27.3

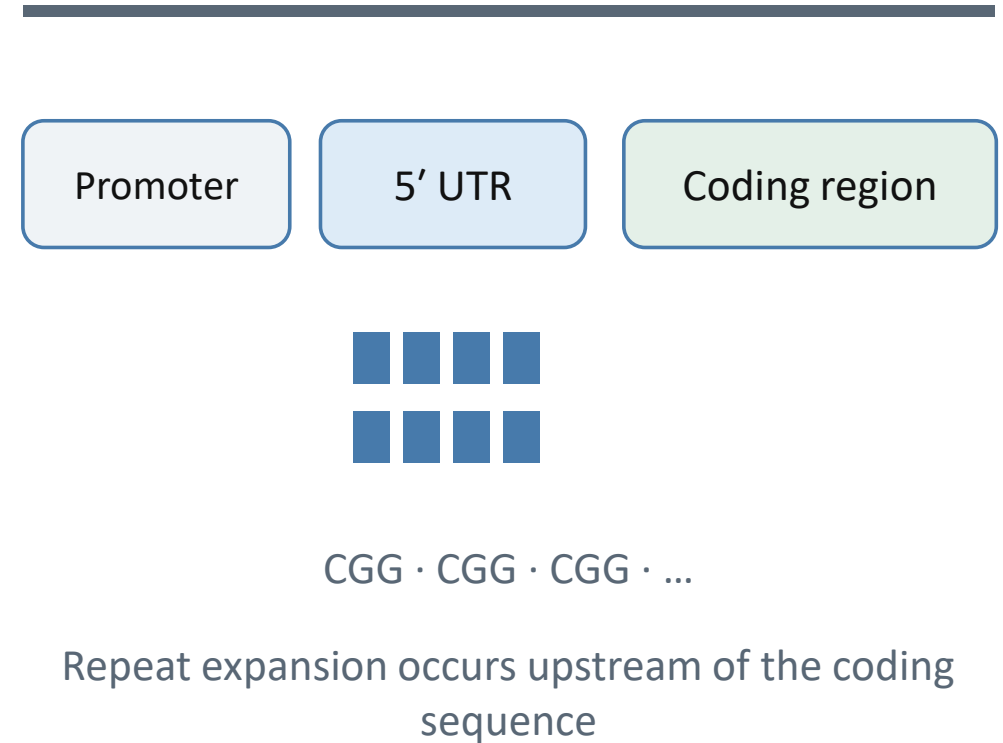
- FMR1 lies on the long arm of the X chromosome at Xq27.3.
- This localization linked the historical fragile site to a single disease gene.
- The abnormal repeat sequence is located within the FMR1 5' untranslated region.



Simplified chromosome schematic

The causal sequence is CGG

- The unstable repeat consists of tandem CGG trinucleotides.
- Expansions arise in the 5' untranslated region, not the protein-coding segment.
- The pathogenic effect depends on expansion size and its effect on gene regulation.



Repeat length is biologically unstable

- The number of CGG units can change during transmission.
- Expansion beyond a critical range alters the biological behavior of the locus.
- This repeat instability explains inheritance patterns that do not fit a simple static allele model.

Usual allele



Premutation



Full mutation



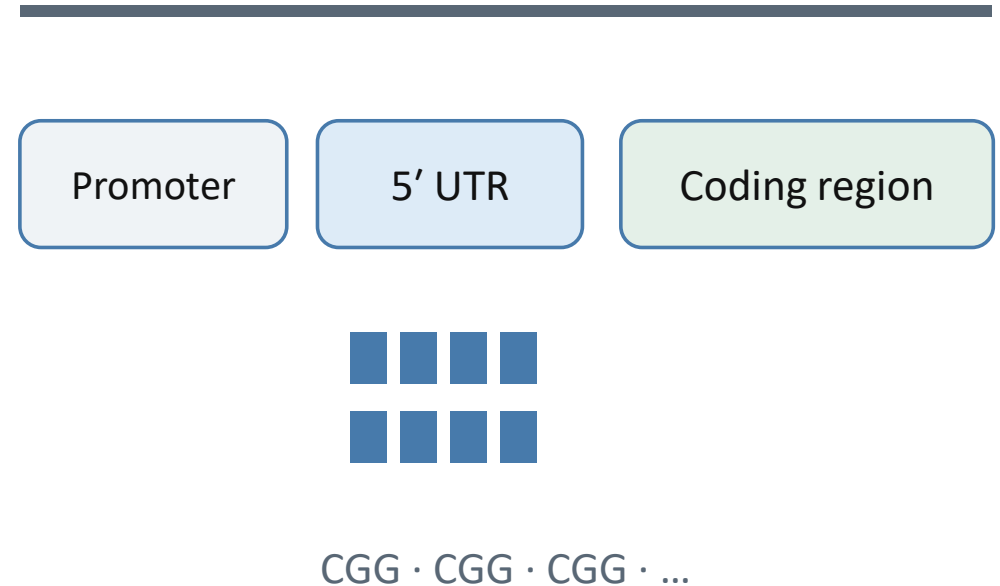
Normal, premutation and full mutation

Repeat category	CGG length	Usual implication
Normal	Approximately 6–55	FMR1 remains functionally expressed
Premutation	Approximately 55–200	May be transmitted and further expand
Full mutation	Approximately 200–4000	Often associated with gene silencing and FXS

Textbook intervals are approximate; The extracted source overlaps at the category boundaries.

The FMR1 repeat lies in the 5' UTR

- A 5' untranslated region is transcribed but is not translated into protein.
- An expanded CGG tract can therefore act through transcriptional control.
- The disease need not arise from an altered FMRP amino-acid sequence.



Repeat is in untranslated, noncoding sequence

Noncoding repeats and coding repeats differ

Fragile X: Noncoding CGG

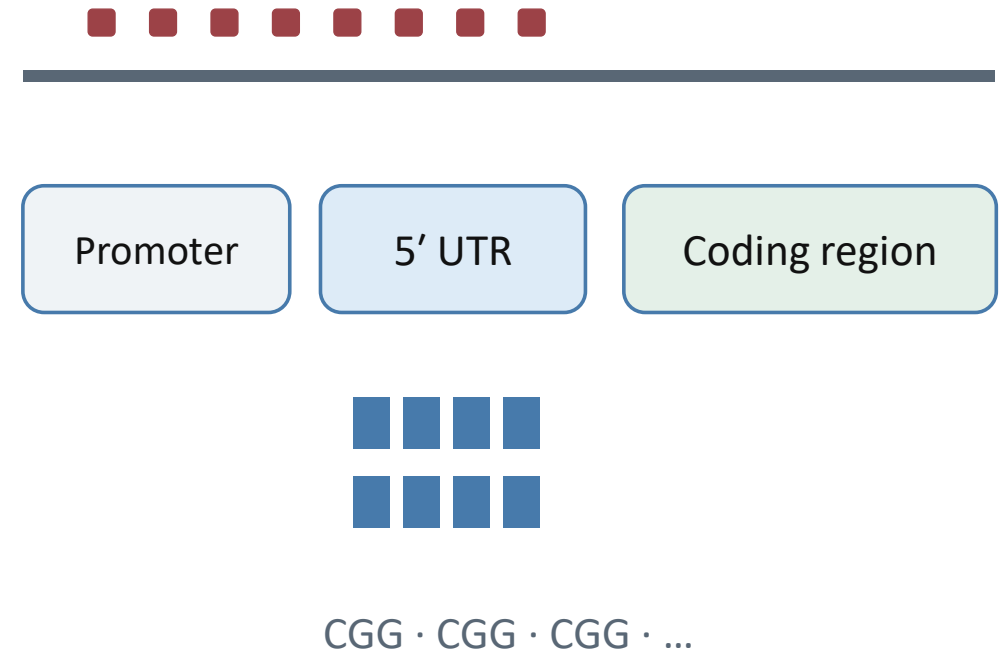
- Expanded repeat lies in the 5' UTR.
- Promoter methylation reduces FMR1 transcription.
- FMRP becomes deficient.

Huntington disease: Coding CAG

- Expanded repeat lies in a protein-coding region.
- An expanded polyglutamine protein is produced.
- Protein toxicity is mechanistically distinct.

Large expansions trigger abnormal methylation

- Abnormal methylation when CGG expansions exceed roughly 230 repeats.
- Methylation involves the 5' region and extends into the promoter.
- The promoter modification suppresses FMR1 transcription.



DNA methylation at 5' region / promoter

Promoter methylation silences FMR1

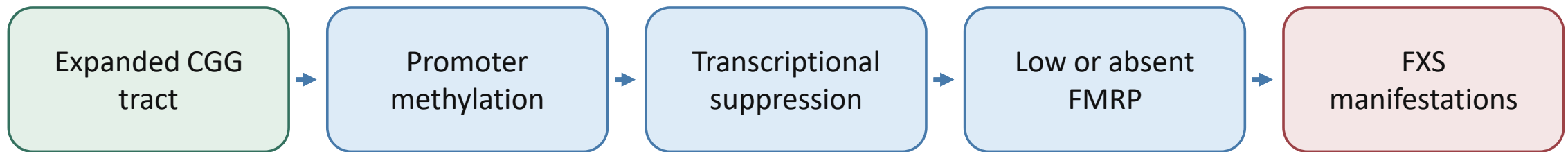
Expressed locus

- Promoter remains transcriptionally permissive.
- FMR1 mRNA is produced.
- FMRP is available.

Silenced full-mutation locus

- Extensive DNA methylation involves the promoter.
- FMR1 transcription decreases markedly.
- FMRP production is reduced or absent.

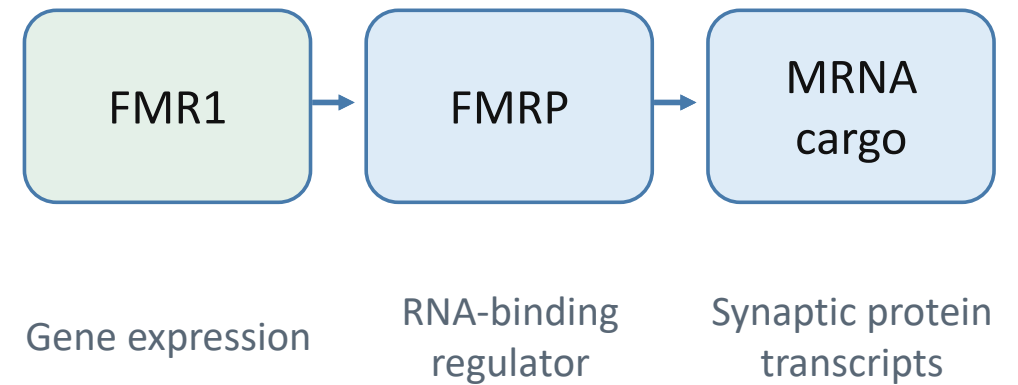
The full-mutation phenotype reflects loss of function



The repeat does not need to encode a novel toxic protein to produce FXS.

FMRP is the central affected protein

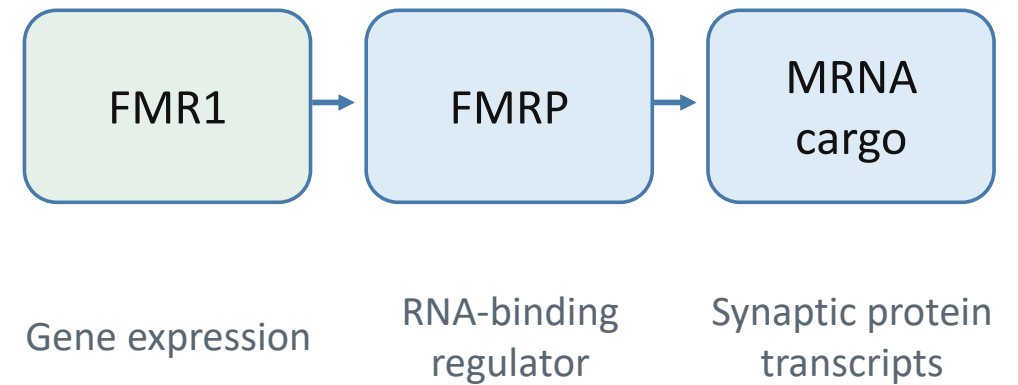
- FMRP is the protein product of FMR1.
- It is a cytoplasmic RNA-binding protein expressed in multiple tissues.
- The brain and testes have particularly abundant FMRP and are prominently affected in FXS.



MRNA localization and translational control

FMRP binds selected neuronal mRNAs

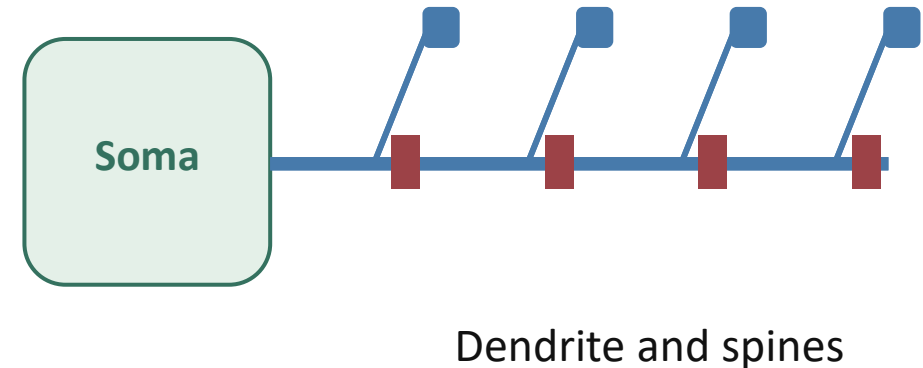
- FMRP associates with messenger RNAs linked to polyribosomes.
- Its cargo includes transcripts for proteins used at pre- and postsynaptic sites.
- The FMRP–mRNA complex helps position transcripts where neuronal activity requires them.



MRNA localization and translational control

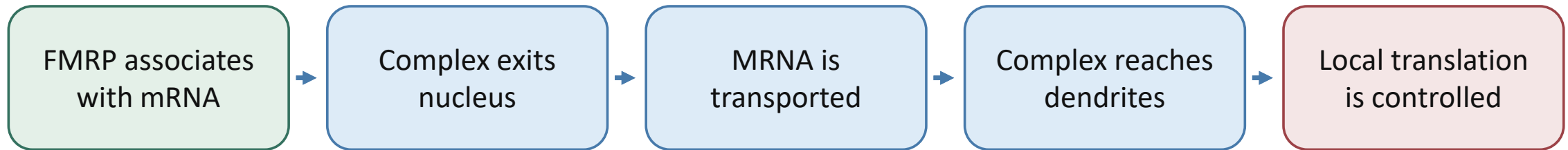
Neurons synthesize proteins locally

- Neuronal protein synthesis occurs in the soma and at dendritic spines.
- Local translation permits protein production near synapses.
- Control of the timing and amount of this translation is fundamental to synaptic regulation.



FMRP-mediated RNA control

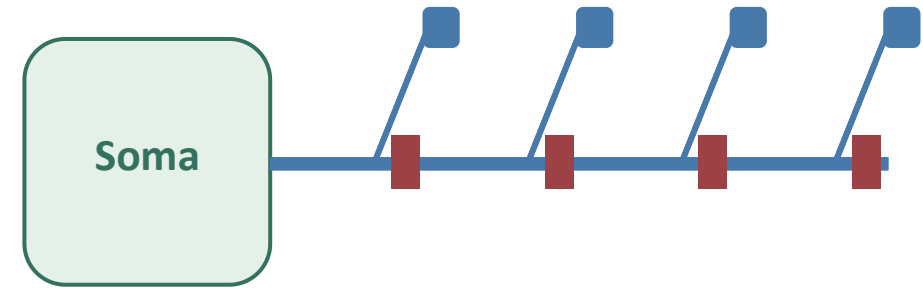
FMRP transports RNA to dendrites



FMRP as both an mRNA trafficking and translation-regulatory factor.

FMRP regulates translation at synapses

- At synaptic junctions, FMRP restrains translation of selected bound mRNAs.
- Its activity is described in relation to group I metabotropic glutamate receptor signaling.
- Loss of this restraint changes the balance of proteins produced at synapses.



FMRP-mediated RNA control

The local translation balance is disturbed

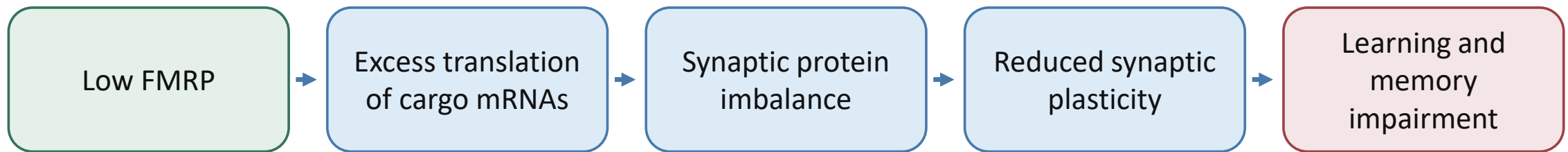
With FMRP

- RNA cargo reaches dendrites.
- Translation remains under FMRP-mediated restraint.
- Synaptic protein production is regulated.

Without FMRP

- Translation of regulated transcripts increases.
- Synaptic protein abundance becomes imbalanced.
- Normal synaptic adaptation is impaired.

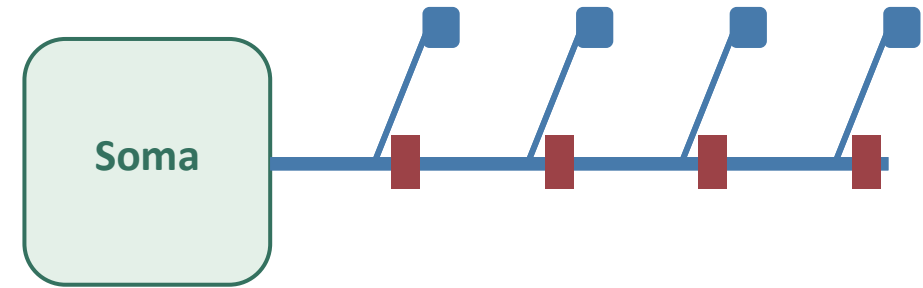
Synaptic plasticity provides the clinical bridge



Plasticity is the ability of synapses to change in response to signals.

Why intellectual disability develops

- FXS disrupts neuronal regulation rather than simply removing a structural brain component.
- FMRP deficiency alters the translation-dependent responses of synapses.
- Impaired synaptic plasticity provides a mechanism linking the mutation to cognitive dysfunction.



Dendrite and spines

FMRP-mediated RNA control

The clinical phenotype is multisystem

Domain	Textbook manifestations
Cognition	Intellectual disability; Learning and memory impairment
Behavior	Autism spectrum features, anxiety, hyperactivity, aggression
Neurology	Epilepsy in a subset of affected individuals
Somatic	Facial, gonadal and connective tissue-like features

Intellectual disability is a core feature

- Affected males often have substantial intellectual disability.
- Clinical severity is variable across individuals and between sexes.
- Neurodevelopmental findings should be integrated with molecular confirmation.

Cognitive

Intellectual disability

Behavioral

Autism; Anxiety; Hyperactivity

Somatic

Face; Macroorchidism; Joints

Characteristic craniofacial findings

- A long face and prominent mandible are commonly described.
- Large, everted ears contribute to the recognizable phenotype.
- A high-arched palate is another reported somatic feature.
- These findings are supportive, not individually diagnostic.

Craniofacial

Long face · prominent jaw

Ears

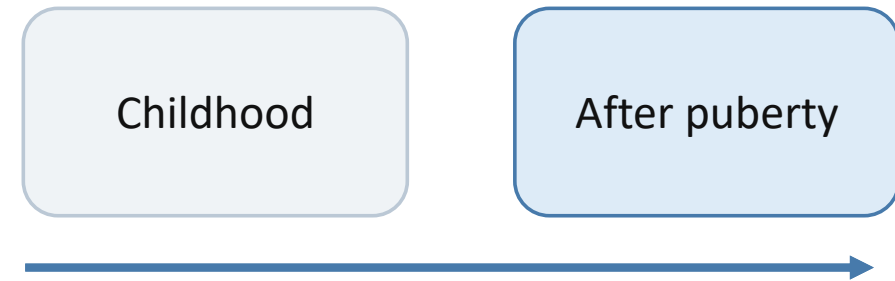
Large and everted

Palate

High arched

Macroorchidism is age-dependent

- Testicular enlargement is a particularly distinctive physical feature.
- Macroorchidism in at least 90% of affected postpubertal males.
- Its absence in young boys does not exclude the disease.



Absence of macroorchidism does not rule out FXS

Connective tissue-like manifestations

- Hyperextensible joints may be present.
- A high-arched palate and mitral valve prolapse are reported.
- These findings resemble a connective-tissue phenotype but occur in the FXS clinical spectrum.

Joints

Hyperextensible

Cardiac

Mitral valve prolapse

Palate

High-arched

Physical signs can be subtle

- The characteristic facial and somatic features do not appear uniformly.
- Some affected individuals have only mild or inconspicuous dysmorphology.
- Molecular testing cannot be replaced by recognition of a “classic face.”

Cognitive

Intellectual disability

Behavioral

Autism; Anxiety; Hyperactivity

Somatic

Face; Macroorchidism; Joints

Behavioral manifestations broaden the phenotype

- Aggression, anxiety and hyperactivity are described in affected individuals.
- Autism spectrum disorder is an important associated phenotype.
- Behavioral presentation may dominate the referral history.

Cognitive

Intellectual disability

Behavioral

Autism; Anxiety; Hyperactivity

Somatic

Face; Macroorchidism; Joints

Autism and fragile X are not synonymous

Fragile X syndrome

- Defined by a pathogenic FMR1 repeat expansion.
- May include autistic features.
- Also has specific inheritance and somatic findings.

Autism spectrum disorder

- A clinical neurodevelopmental diagnosis.
- Occurs with many different genetic backgrounds.
- Only a subset have FMR1 mutations.

Epilepsy is a recognized association

- Epileptic seizures occur in a subset of patients with FXS.
- Epilepsy in approximately 30% of affected cases.
- The seizure phenotype is an associated feature, not a molecular diagnostic criterion.

Cognitive

Intellectual disability

Behavioral

Autism; Anxiety; Hyperactivity

Somatic

Face; Macroorchidism; Joints

Recognize the breadth of expression

Feature	Clinical interpretation
Intellectual disability	Central neurodevelopmental manifestation
Facial configuration	Helpful pattern; May be subtle
Macroorchidism	More conspicuous after puberty
Autism/anxiety/hyperactivity	Frequent but variable behavioral associations
Epilepsy	Associated finding in a subset

X linkage explains male predominance

- FMR1 is located on the X chromosome.
- Males usually have a single X chromosome and thus lack a second allele on another X.
- Females can show a spectrum of impairment rather than uniform expression.

Male

$X \cdot Y$

Female

$X \cdot X$

**The number of X chromosomes shapes
genetic expression**

Female phenotype varies with X inactivation

- Some females carrying a full mutation have intellectual disability and related findings.
- That the active-versus-inactive X pattern influences clinical expression.
- Skewed activation of the mutation-bearing X is a proposed explanation, not a deterministic rule.

Male

$X \cdot Y$

Female

$X \cdot X$

Different X-inactivation patterns can modify expression

Transmission from fathers follows X inheritance

Father: X (premutation) + Y

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graph TD; A[Father: X (premutation) + Y] --> B[Daughter inherits paternal X]; A --> C[Son inherits paternal Y]; B --> D[May carry paternal FMR1 premutation]; C --> E[Does not inherit paternal FMR1 allele]
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Daughter inherits paternal X

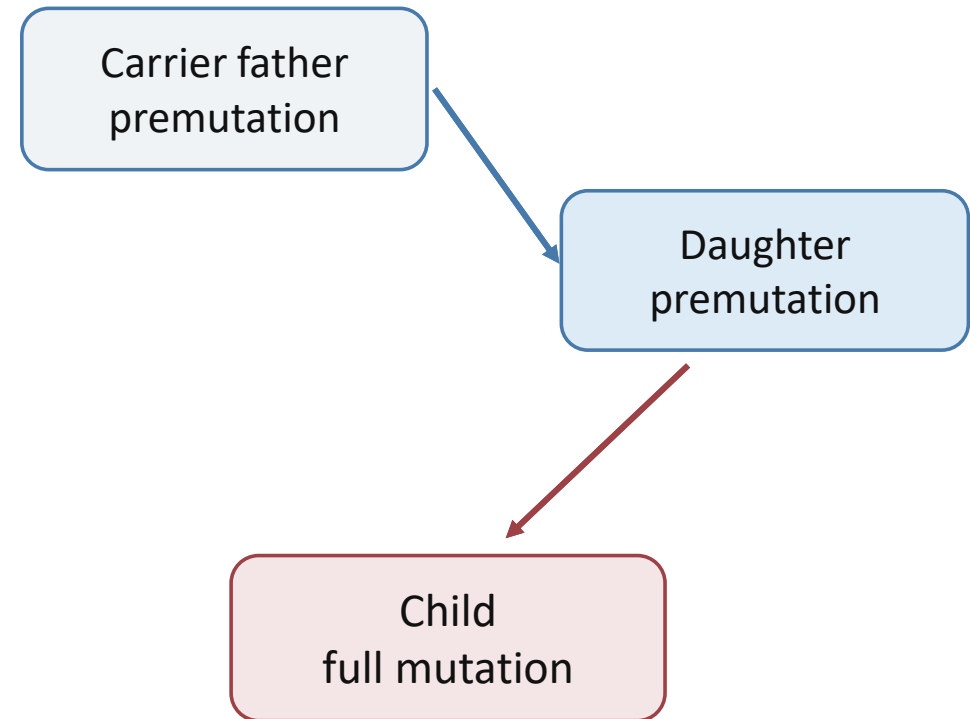
May carry paternal FMR1 premutation

Son inherits paternal Y

Does not inherit paternal FMR1 allele

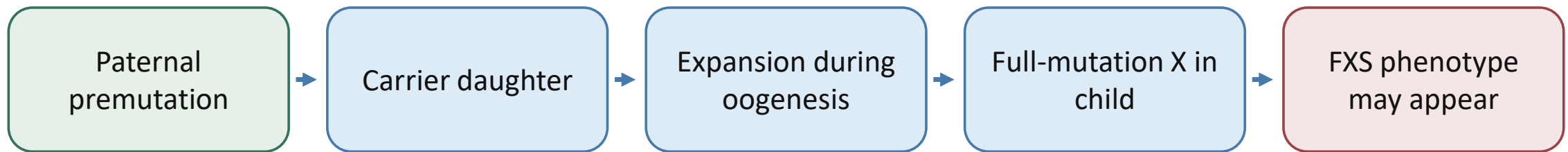
The “normal transmitting male” phenomenon

- Some men carrying an FMR1 premutation lack the classic childhood FXS phenotype.
- They can transmit their repeat-bearing X chromosome to daughters.
- A daughter’s maternal transmission can expand that repeat in the next generation.



Expansion during maternal transmission

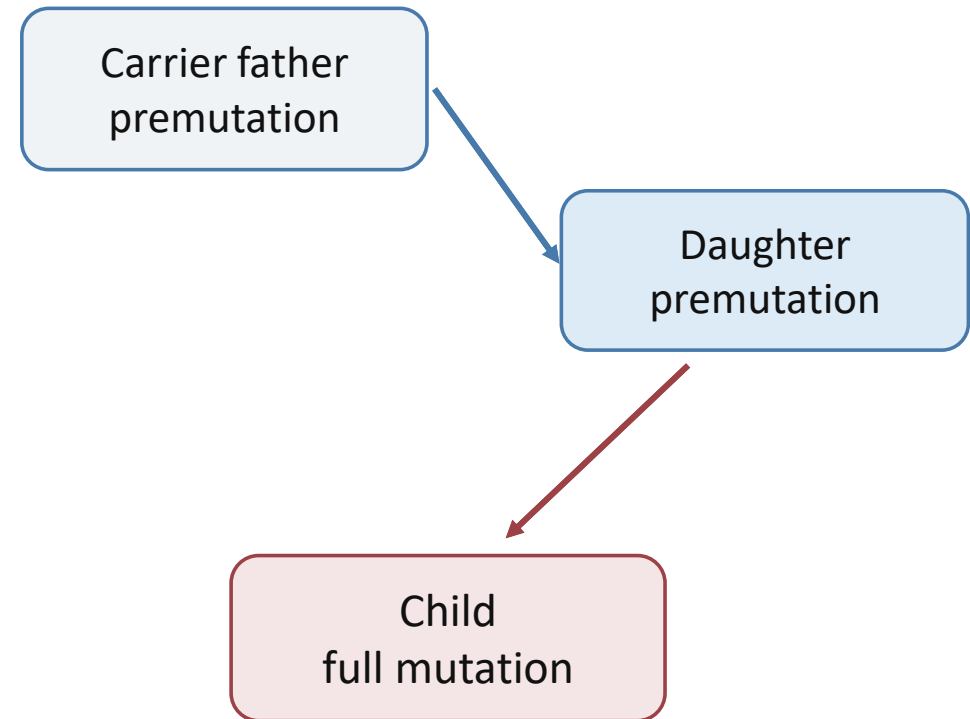
A carrier daughter can have affected offspring



An apparently unaffected family branch can precede a generation with affected children.

Large repeat expansion is linked to oogenesis

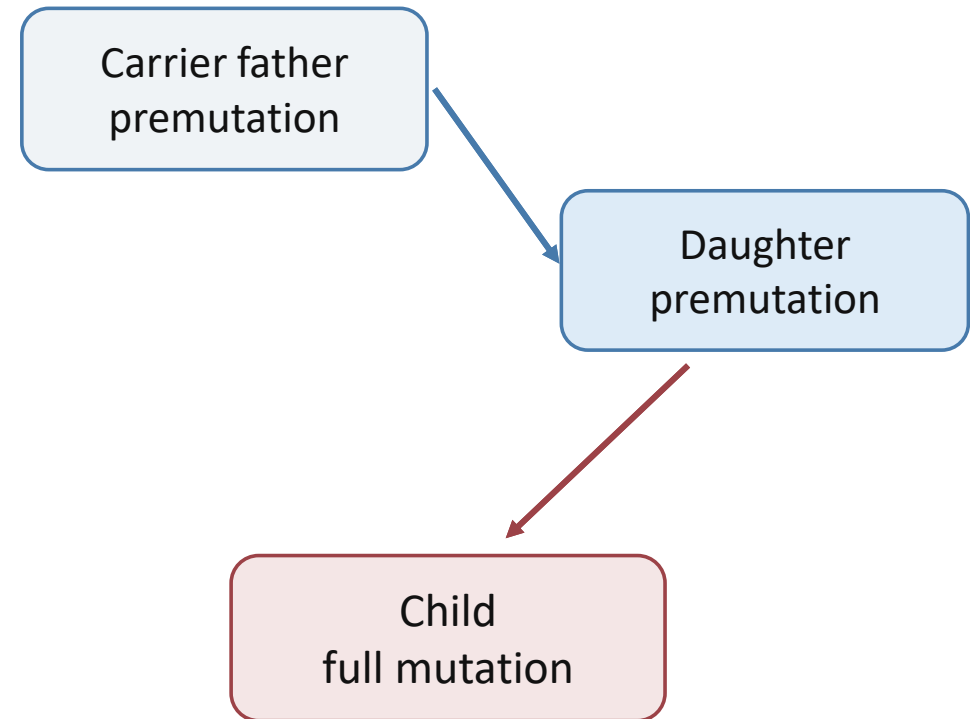
- That dramatic premutation-to-full-mutation expansion occurs during maternal transmission.
- Paternal transmission usually introduces only smaller repeat-length changes.
- This sex-of-transmitting-parent difference explains the unusual pedigree pattern.



Expansion during maternal transmission

Anticipation follows unstable repeat transmission

- Clinical effects can become more conspicuous in successive generations.
- A premutation can expand to a full mutation when passed through a female.
- This molecular mechanism explains the textbook's anticipation phenomenon.



Expansion during maternal transmission

Why ordinary X-linked models are insufficient

Typical X-linked model

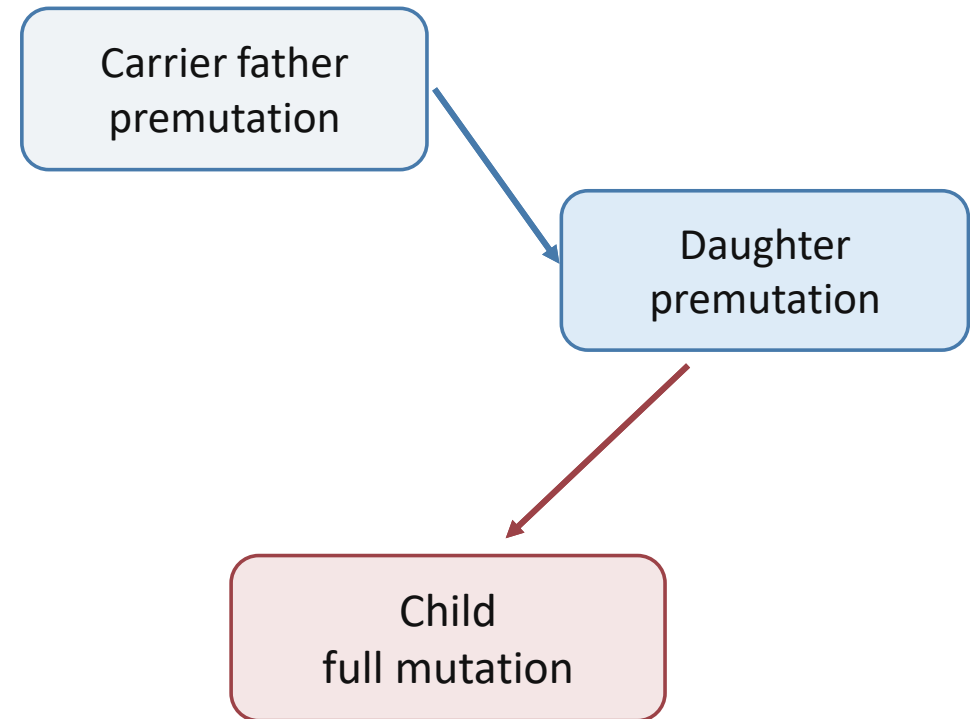
- Allele state is treated as stable across meiosis.
- Risk is modeled largely by the transmitted X.
- Phenotype reflects inheritance of that allele.

Fragile X transmission

- Repeat number itself may change.
- Maternal repeat expansion changes allele class.
- Phenotype may differ markedly across generations.

Pedigree position changes observed risk

- Different observed risks among relatives at different pedigree positions.
- This reflects the possibility of a premutation expanding during intervening maternal transmissions.
- A pedigree percentage from a particular family model is not a universal individual risk estimate.



Expansion during maternal transmission

Inheritance reasoning: Father to daughter

An unaffected man carries an FMR1 premutation. Which children inherit his repeat-bearing X chromosome?

Mechanistic interpretation

All of his daughters inherit his X; None of his sons inherit his paternal X.

Inheritance reasoning: Daughter to grandson

A daughter inherits a premutation from her father. Why might her son be affected even though the grandfather was not?

Mechanistic interpretation

During the daughter's oogenesis, the premutation may expand to a full mutation.

Repeat number, methylation and expression

Level	Key event	Consequence
DNA sequence	CGG repeat amplification	Unstable allele length
Epigenetic state	Methylation of 5' region/promoter	FMR1 silencing
RNA	Reduced FMR1 transcription	Less FMR1 mRNA
Protein	Reduced FMRP	Dysregulated synaptic translation
Cell phenotype	Impaired synaptic plasticity	Cognitive/behavioral effects

Historical cytogenetics is not the modern test

Former cytogenetic approach

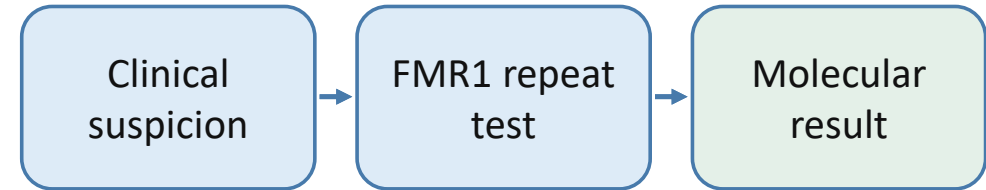
- Cultured cells under folate-deficient conditions.
- Looked for a Giemsa-negative gap/constriction.
- Provided a visible “fragile site” phenotype.

Molecular approach

- Analyzes CGG repeat length directly.
- Connects test to the disease-causing allele.
- Has replaced fragile-site microscopy for diagnosis.

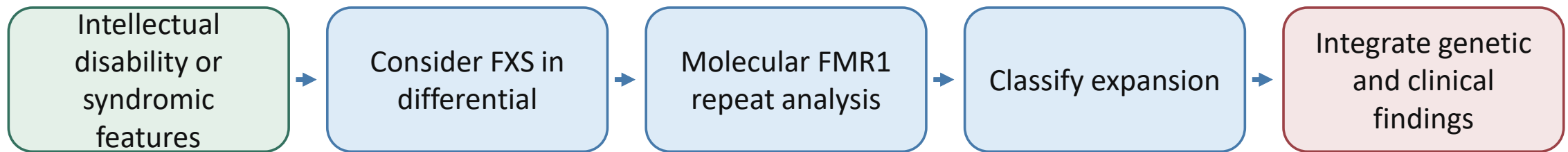
PCR-based repeat analysis establishes the lesion

- PCR-based repeat detection as the preferred diagnostic approach.
- The test interrogates the FMR1 CGG tract rather than an unrelated phenotype marker.
- Interpretation requires correlation with repeat class, clinical findings and inheritance.



DNA-based confirmation replaces fragile-site culture

Molecular diagnosis and clinical recognition



The defining lesion is molecular; Physical features direct suspicion.

Premutation is not the same as FXS full mutation

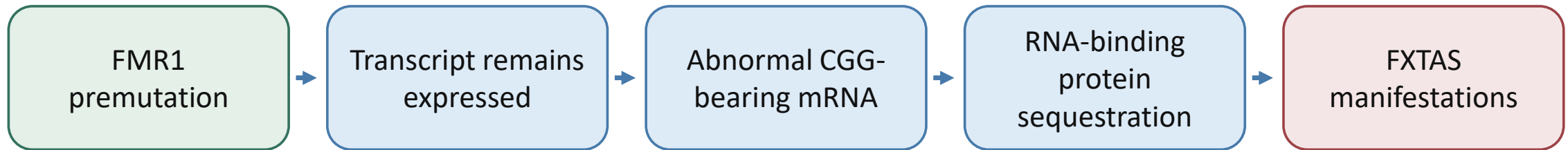
Full mutation: Classic FXS

- Large CGG expansion.
- 5' region/promoter becomes methylated.
- Reduced FMRP: Loss-of-function pathogenesis.

Premutation carrier

- Smaller expanded CGG tract.
- FMR1 transcription can persist.
- Possible risk of distinct RNA-mediated disorders.

Premutation RNA toxicity contributes to FXTAS



Ovarian disease also occurs in carriers, but its exact molecular pathogenesis is less certain.

FXTAS differs clinically from classic FXS

Fragile X syndrome

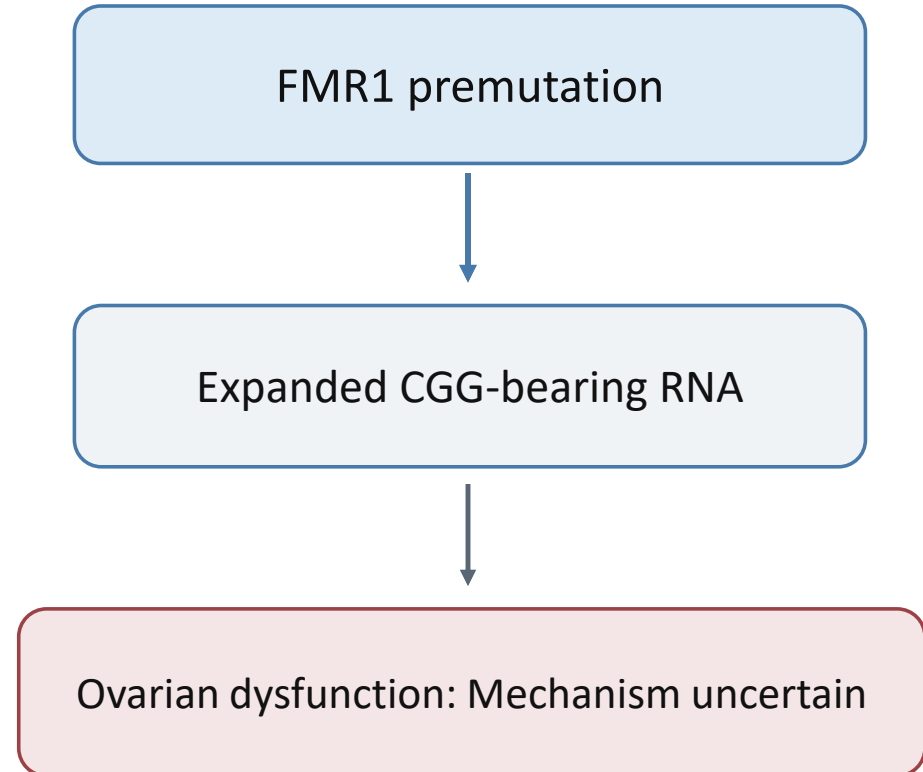
- Primarily neurodevelopmental presentation.
- FMRP deficiency.
- Intellectual disability and behavioral manifestations.

FXTAS in premutation carriers

- Typically later-life neurologic syndrome.
- Intention tremor and cerebellar ataxia.
- Toxic RNA-mediated mechanism.

Ovarian dysfunction is a premutation association

- A subset of female premutation carriers develop primary ovarian insufficiency.
- Reduced fertility, menstrual irregularity and early menopause are described.
- FSH may rise and anti-Müllerian hormone may fall as ovarian function declines.
- The precise role of RNA aggregates in follicular loss remains uncertain.



Case: Intellectual disability and somatic signs

A postpubertal male has intellectual disability, large everted ears, a long face and macroorchidism. What molecular lesion should be investigated?

Mechanistic interpretation

A large CGG-repeat expansion in the 5' untranslated region of FMR1.

Case: Explain the gene-expression result

A boy carries a full FMR1 CGG expansion. Why may the encoded FMRP be absent despite no amino-acid–coding variant?

Mechanistic interpretation

The noncoding expansion promotes promoter methylation and transcriptional silencing.

Case: A girl with a full mutation

Two girls have full FMR1 expansions, but their cognitive findings differ. Which source-discussed mechanism may contribute to the variable phenotype?

Mechanistic interpretation

Differences in X-inactivation patterns may change the proportion of cells expressing the altered X.

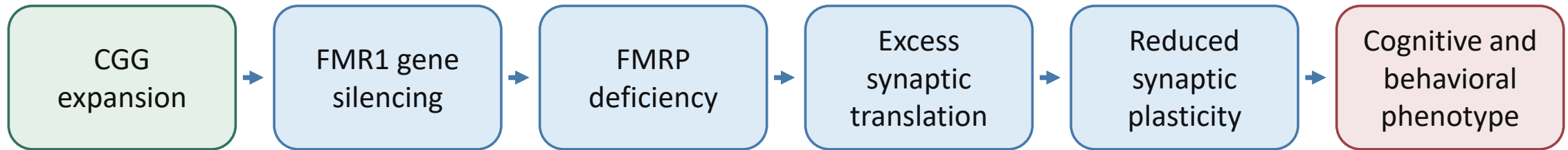
Case: Expanded repeats without childhood FXS

A male relative with an FMR1 premutation is neurologically well in youth. Why should the premutation not be considered equivalent to a full mutation?

Mechanistic interpretation

Premutations can remain transcribed and have distinct intergenerational and later-life implications.

Mechanism integration: From DNA to behavior



Each arrow represents the mechanistic sequence emphasized.

Interpretation pitfalls to avoid

- A classic appearance does not establish a molecular diagnosis.
- An absent physical sign does not exclude an FMR1-associated condition.
- A premutation is not interchangeable with a full mutation.
- The inheritance pattern changes because repeat length may expand in maternal transmission.

Synthesis: Five points to retain

- CGG expansion in the 5' UTR of FMR1 is the underlying genetic lesion.
- Full mutations commonly silence FMR1 through abnormal methylation.
- FMRP loss disturbs neuronal mRNA transport and synaptic translation.
- Cognition, behavior and somatic findings vary across affected individuals.
- Maternal repeat expansion explains anticipation and unusual pedigrees.

Primary textbook source

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 5, Genes and Human Diseases: Fragile X Syndrome and related trinucleotide-repeat mechanisms.
- Lecture content is based on the supplied textbook Markdown extraction; original chapter PDF was unavailable for image/caption verification.