

Fragile X–Associated Tremor/Ataxia Syndrome and Fragile X–Associated Primary Ovarian Failure

Molecular pathology · neurological and reproductive phenotypes

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Learning outcomes

- Explain why an FMR1 premutation causes disease without classic FMR1 silencing.
- Relate toxic FMR1 RNA to late-onset neurological dysfunction and ovarian insufficiency.
- Recognize FXTAS and FXPOI presentations, diagnostic clues, and family implications.

Three phenotypes, one gene

Disorder	Molecular context	Defining phenotype
Fragile X syndrome (FXS)	Full mutation, FMR1 silencing, deficient FMRP	Usually childhood-onset neurodevelopmental phenotype
FXTAS	Premutation, toxic RNA-associated mechanism	Late-onset progressive tremor–ataxia phenotype
FXPOI	Premutation, ovarian dysfunction	Hypergonadotropic ovarian insufficiency before 40

Premutations are not phenotypically silent

- A CGG premutation can be transmitted without classic fragile X syndrome.
- Some carriers later develop neurologic disease; Some females develop ovarian insufficiency.
- Clinical risk is incompletely penetrant: Carrier status does not guarantee either outcome.

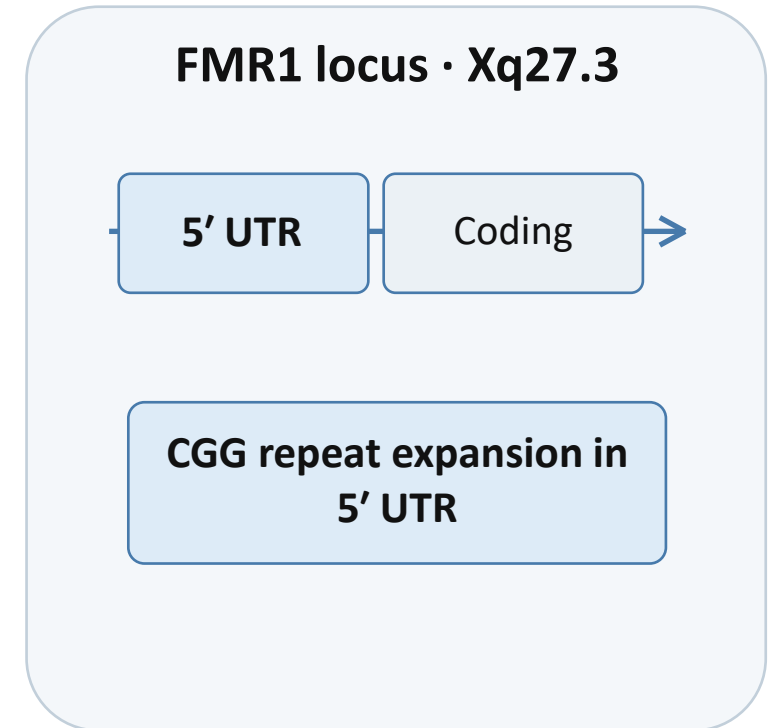
Premutation carrier

Risk of FXTAS or FXPOI

Some remain without these syndromes

FMR1 is located on the X chromosome

- The FMR1 gene lies at Xq27.3.
- CGG repeats are in the 5' untranslated region—not the protein-coding sequence.
- The expansion can alter transcriptional regulation or RNA behavior depending on repeat range.



What is a CGG repeat expansion?

- CGG is a three-nucleotide sequence repeated in tandem within FMR1.
- Repeat lengths are unstable across some generations.
- Increased repeat size can cause distinct molecular outcomes—not simply a graded form of one disease.

FMR1 DNA repeat tract

CGG

CGG

CGG

CGG

Repeat number varies by allele
and across generations

Interpret repeat ranges carefully

Allele class	CGG repeats	Clinical interpretation
Typical/normal	<45	Generally stable, not the premutation phenotype
Intermediate	45–54	Borderline stability; not FXTAS or FXPOI by itself
Premutation	~55–200	Associated with FXTAS and FXPOI risk
Full mutation	>200	Usually hypermethylated; associated with FXS

Repeat-size boundaries are operational

- Repeat classification is based on allele size plus methylation and family context.
- GeneReviews emphasizes that boundaries at the margins are not absolute.
- For smaller premutations, AGG interruptions affect maternal expansion risk.

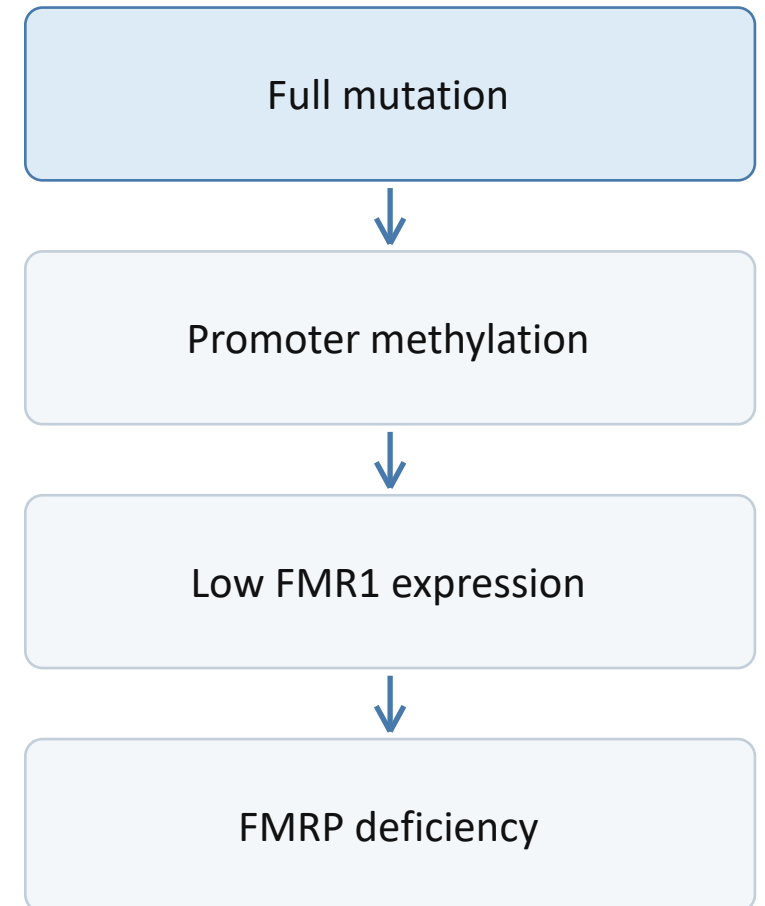
Repeat count

Methylation / AGG pattern

Family and phenotype

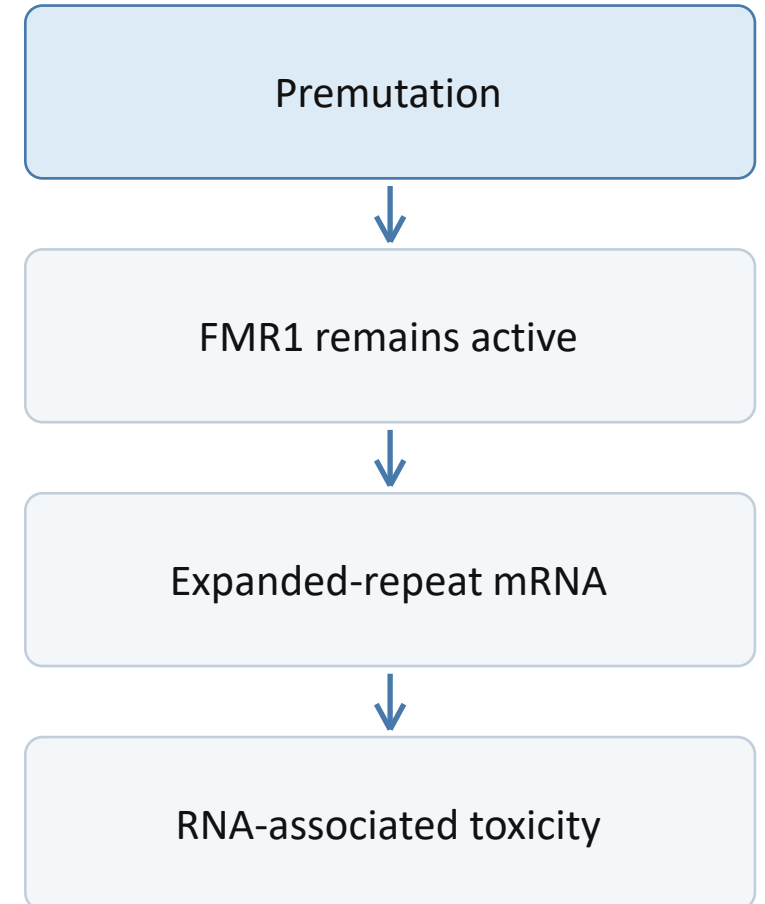
Full mutation: Gene silencing dominates

- A large CGG expansion usually triggers methylation involving the FMR1 promoter.
- Methylation suppresses FMR1 transcription and reduces FMRP production.
- The primary phenotype is fragile X syndrome—not the canonical premutation phenotype.



Premutation: Transcription persists

- The premutation is generally not associated with the full-mutation hypermethylation pattern.
- Expanded-repeat FMR1 transcripts continue to be produced; Levels can be increased.
- RNA-mediated toxicity is a proposed principal mechanism of premutation disorders.



Loss of protein versus toxic RNA

Phenotype	Repeat category	Gene behavior	Main pathogenic model
FXS	Full mutation	Transcriptional silencing	Loss of functional FMRP
FXTAS / FXPOI	Premutation	FMR1 RNA remains expressed	Toxic gain of function (proposed)

The expanded repeat is noncoding

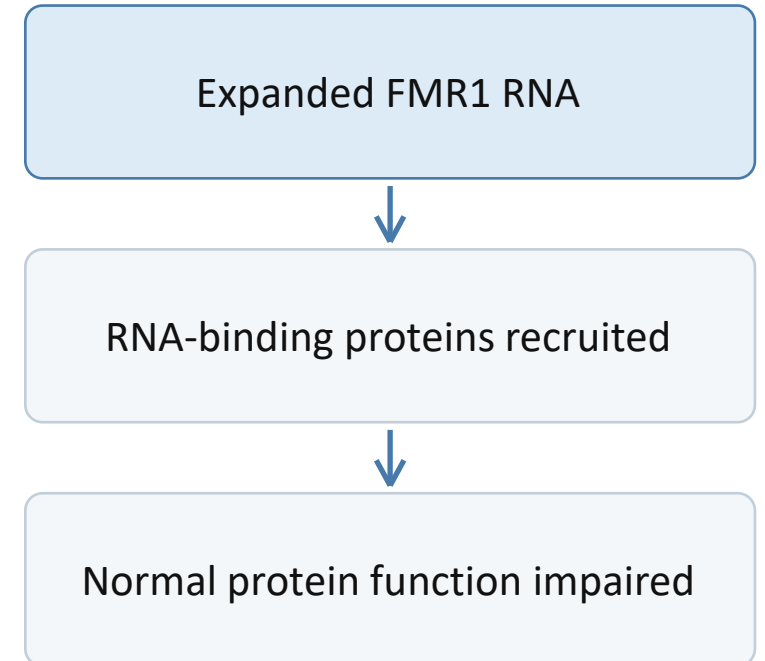
- A CGG expansion in the 5' UTR is not a polyglutamine expansion.
- Its pathogenic effect is linked to gene regulation and the behavior of abnormal RNA.
- This differs mechanistically from coding-region CAG expansion disorders such as Huntington disease.

**Noncoding CGG: RNA /
regulation**

Coding CAG: Abnormal protein

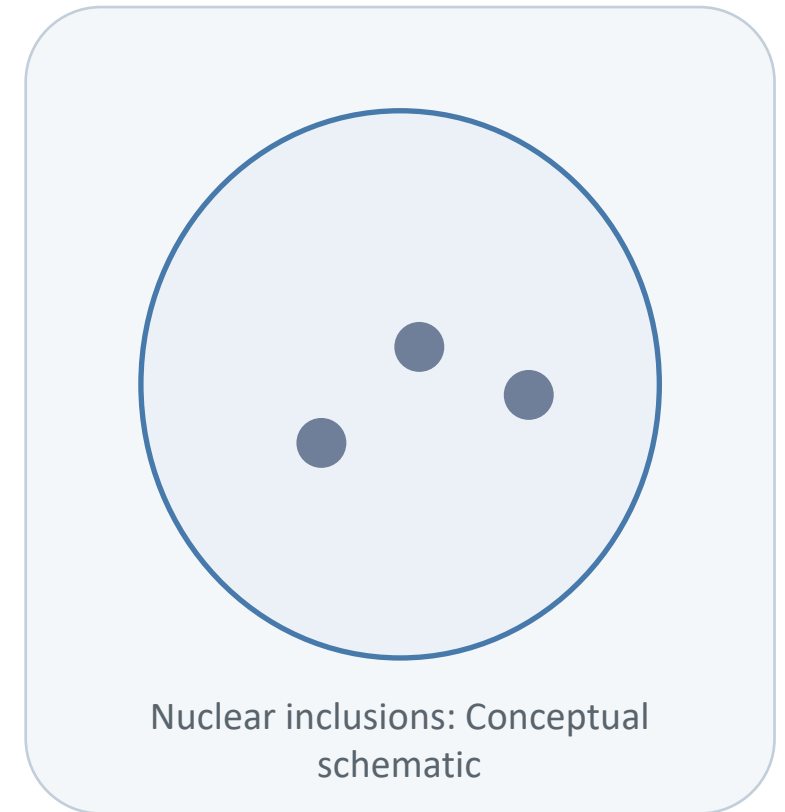
A molecular model of RNA sequestration

- Expanded FMR1 RNA can bind and sequester RNA-binding proteins.
- Sequestration reduces the availability of these proteins at their normal functional sites.
- The resulting disruption is a proposed link between RNA expansion and tissue injury.



Intranuclear inclusions are a tissue clue

- Abnormal FMR1 RNA and recruited proteins can aggregate in nuclei.
- Nuclear inclusions in central and peripheral nervous systems.
- The presence of inclusions supports a tissue-level manifestation of RNA-associated toxicity.



What intranuclear inclusions do—and do not—prove

- Inclusions are a characteristic neuropathologic finding in FXTAS.
- They support the molecular diagnosis in appropriate tissue and clinical context.
- A visible aggregate does not, by itself, establish every downstream injury mechanism.

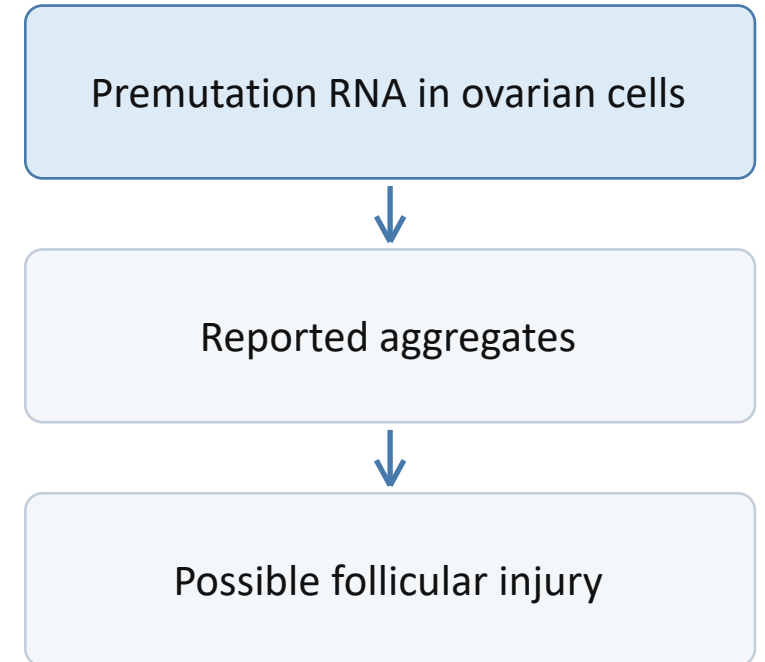
Observed inclusion

Molecular association

Causal interpretation remains
qualified

The ovarian mechanism is less settled

- FMR1 RNA-containing aggregates have been reported in granulosa and ovarian stromal cells.
- Premature follicular loss has been proposed as a consequence.
- Robbins explicitly presents this ovarian injury mechanism as a hypothesis, not a confirmed complete pathway.



Same premutation: Organ-selective phenotypes

Affected system	Primary dysfunction	Typical clinical window
Nervous system	Progressive motor, cognitive and other neurological changes	Late-adult expression of disease
Ovary	Impaired ovarian function / depleted reserve	Reproductive-age expression of disease

Why premutation testing has broad meaning

- It may explain a neurological syndrome, an ovarian syndrome, or both patterns across a family.
- It also informs the potential for repeat expansion in the next generation.
- The laboratory result should be interpreted together with phenotype and reproductive history.

Individual diagnosis

Family segregation

Reproductive counseling

FXTAS: A late-onset neurodegenerative syndrome

- FXTAS stands for fragile X-associated tremor/ataxia syndrome.
- It is associated with a premutation-sized FMR1 allele.
- The hallmark clinical presentation combines progressive intention tremor and cerebellar ataxia.

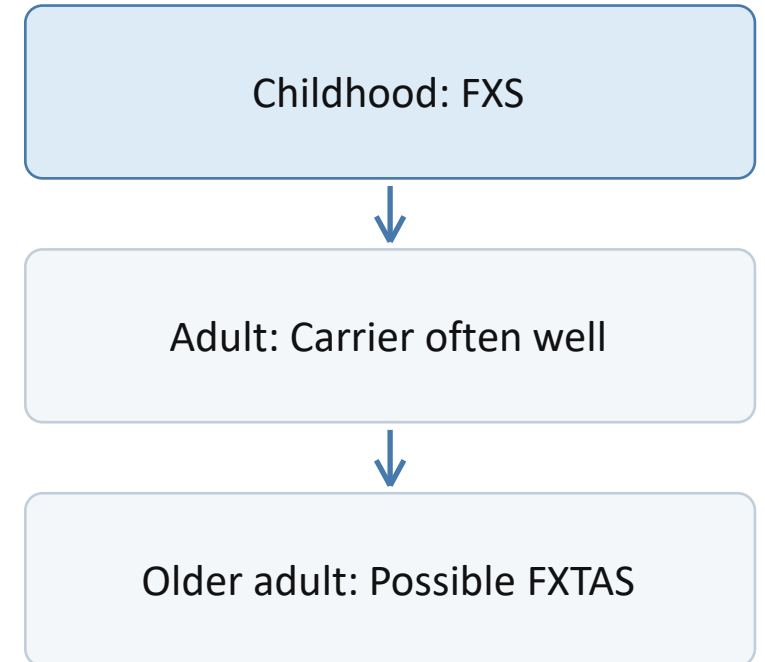
FMR1 premutation

Later-life neurological onset

Progressive tremor / ataxia

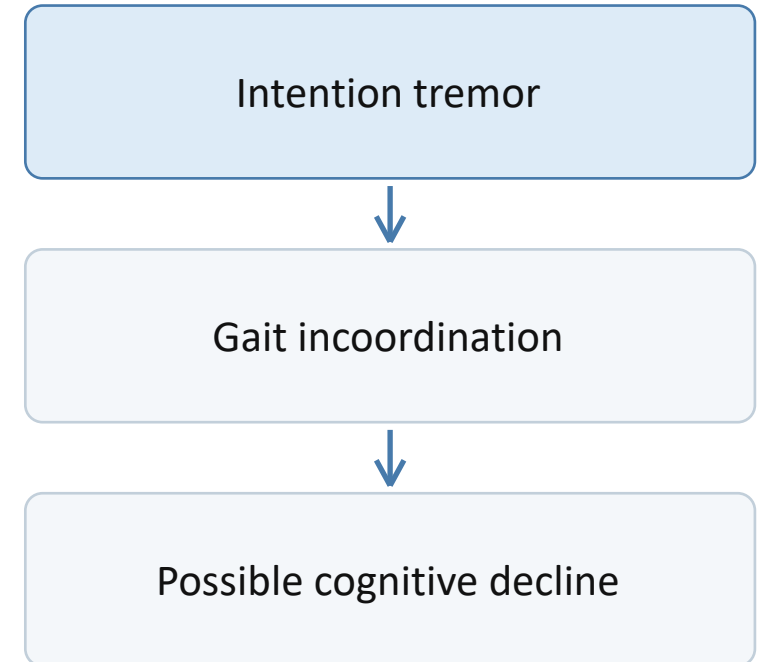
Age at presentation matters

- Typical onset beginning in the sixth decade of life.
- GeneReviews gives a usual onset around 60–65 years, with wide individual variation.
- A late-onset neurological disorder in a premutation carrier differs from childhood FXS.



FXTAS often begins with action tremor

- Intention tremor is a major clinical criterion for FXTAS.
- Tremor may precede clinically obvious gait ataxia.
- The combination and progression are more informative than the presence of tremor alone.



Intention tremor: The clinical concept

- The tremor appears or increases during goal-directed movement.
- It is consistent with dysfunction in cerebellar motor control pathways.
- Do not equate any tremor, particularly an isolated rest tremor, with FXTAS.

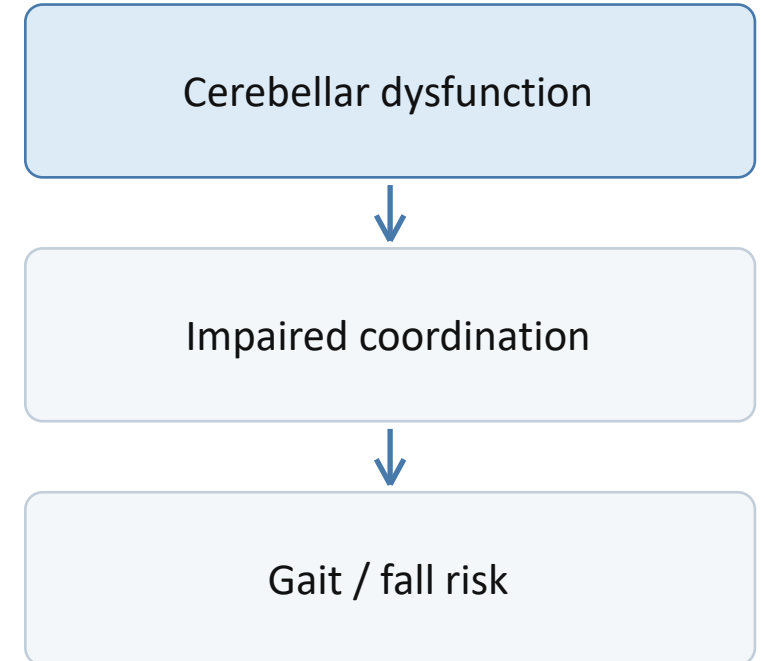
Goal-directed movement

Tremor near target

Evaluate accompanying ataxia

Cerebellar gait ataxia is a major sign

- Cerebellar gait ataxia is a second major clinical criterion.
- Impaired gait and postural stability are important causes of functional decline.
- Progressive imbalance in an older premutation carrier warrants neurological evaluation.



Motor manifestations extend beyond ataxia

- Parkinsonism may develop as FXTAS progresses.
- Lower-extremity neuropathy can coexist with central movement dysfunction.
- Phenotypic overlap with other neurodegenerative syndromes can complicate diagnosis.

Tremor and ataxia

Parkinsonian features

Peripheral nerve findings

Parkinsonism is not the defining sign

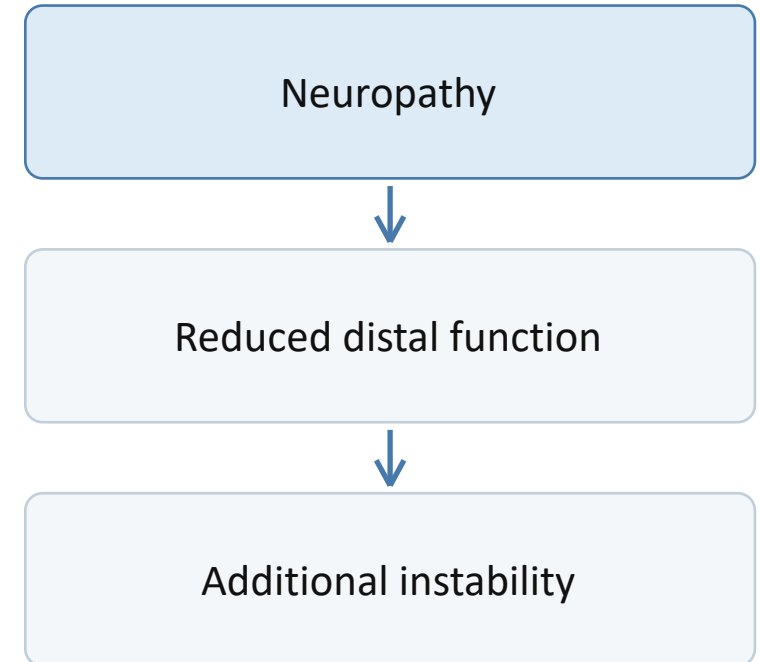
- Parkinsonism is classified as a minor clinical criterion in established FXTAS criteria.
- Tremor and cerebellar gait ataxia are the major clinical findings.
- An apparent Parkinson disease phenotype alone is not sufficient to diagnose FXTAS.

**Major: Intention tremor / gait
ataxia**

Minor: Parkinsonism

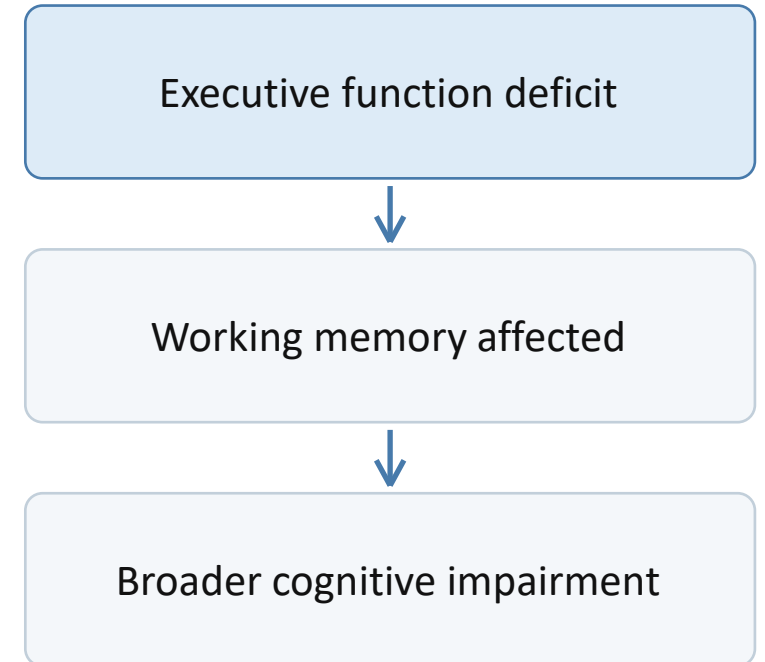
Peripheral neuropathy adds disability

- Neuropathy in the lower extremities is a minor clinical feature.
- Sensory or motor impairment may aggravate balance difficulty.
- Both central cerebellar and peripheral nerve contributions deserve examination.



Executive dysfunction is an early cognitive pattern

- Cognitive decline can begin with executive function difficulties.
- Working memory and processing speed may subsequently be involved.
- Cognitive manifestations should be assessed rather than assumed to be age-related.



Short-term memory loss in FXTAS

- Moderate-to-severe short-term memory deficiency is a minor clinical criterion.
- Cognitive findings often accompany a motor syndrome rather than defining it alone.
- Dementia in an older person with ataxia or tremor is a reason to consider FMR1 testing.

Motor syndrome

Memory / executive findings

Consider genetic explanation

Psychiatric symptoms may coexist

- Anxiety, depression, irritability and apathy have been reported in FXTAS.
- These symptoms can add clinically meaningful impairment.
- Their presence is supportive context, not a specific diagnostic substitute for motor findings.

Mood and behavior

Neurological phenotype

Whole-person assessment

Autonomic and other neurological findings

- Autonomic dysfunction and lower-limb proximal weakness are among reported associated features.
- Neuropathic pain may occur with peripheral neuropathy.
- These findings widen the clinical assessment but are not uniquely diagnostic of FXTAS.

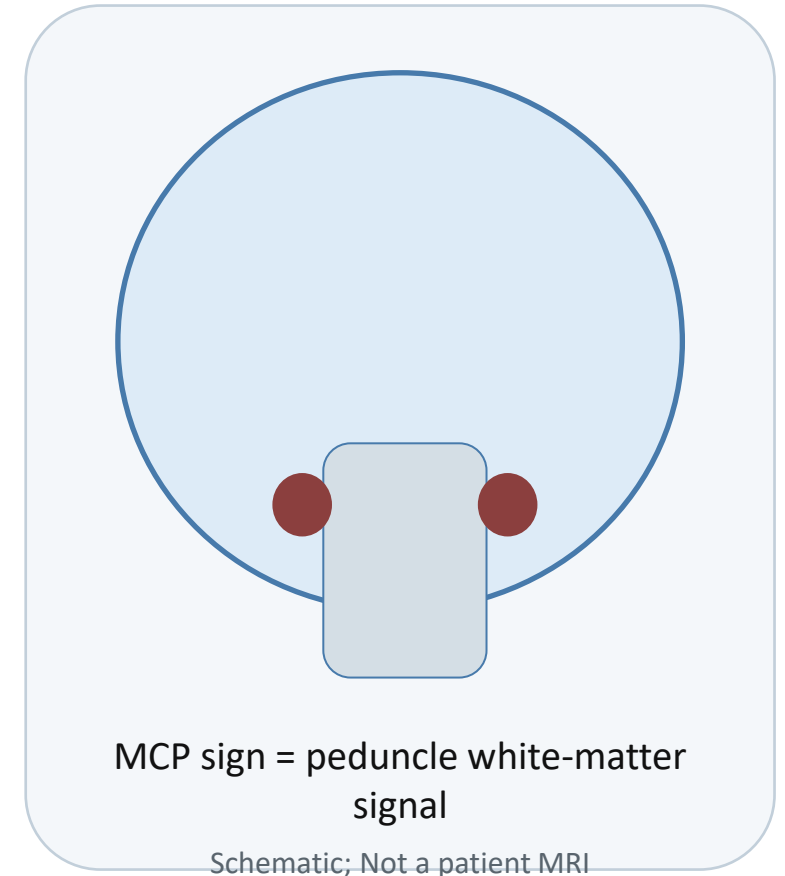
Autonomic dysfunction

Weakness / neuropathic pain

Motor / cognitive syndrome

MRI: Middle cerebellar peduncle sign

- White-matter lesions in the middle cerebellar peduncles constitute the major radiologic criterion.
- This pattern is commonly called the MCP sign.
- The sign must be interpreted in clinical and genetic context; It is not an isolated proof of FXTAS.



Other MRI abnormalities are minor criteria

- White-matter lesions in cerebral white matter may be observed.
- Splenial white-matter lesions are included among minor radiologic findings.
- Moderate-to-severe generalized brain atrophy is also a minor criterion.

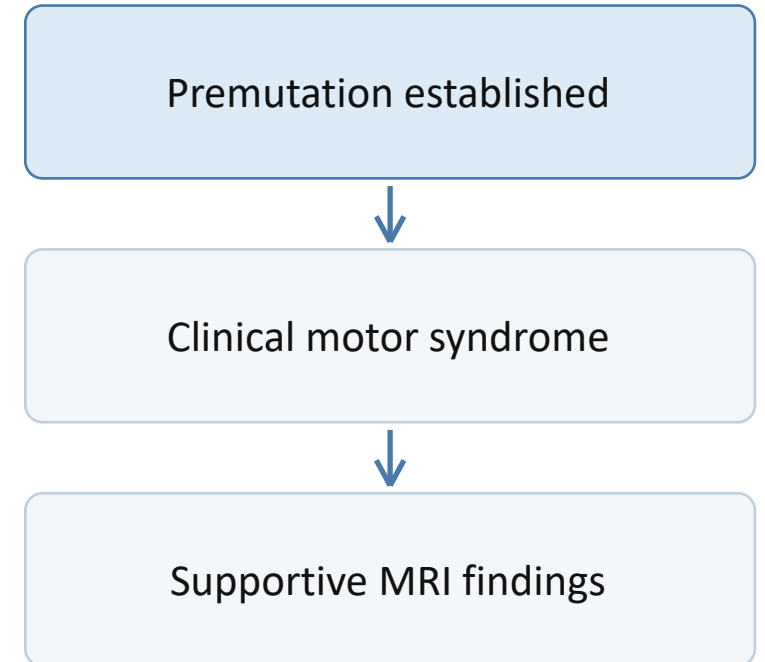
Cerebral white-matter lesions

Splenium lesions

Generalized atrophy

Clinical–radiologic convergence is essential

- The premutation establishes susceptibility, not by itself clinical FXTAS.
- Progressive clinical signs must be weighed alongside imaging patterns.
- Alternative causes of tremor, ataxia and white-matter abnormalities require assessment.

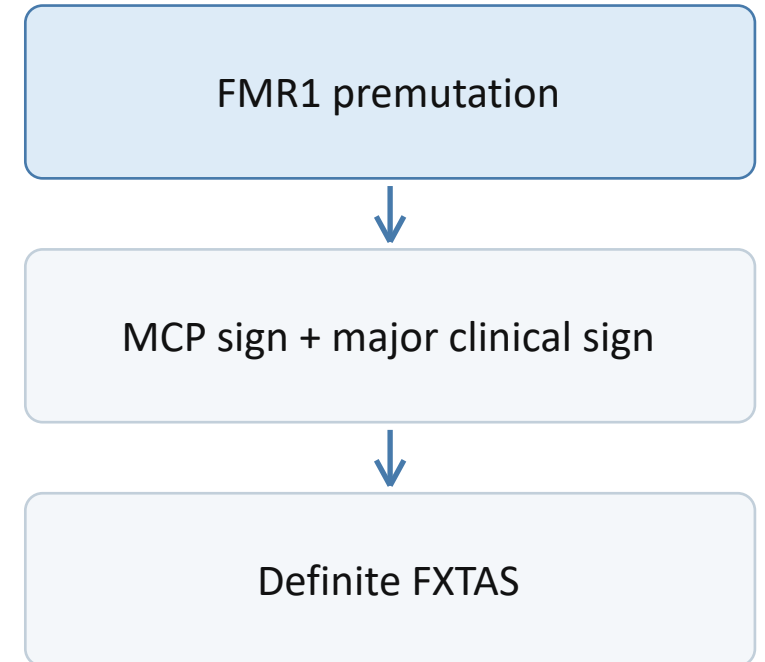


Diagnostic criteria: Major and minor signs

Class	Findings
Clinical major	Intention tremor; cerebellar gait ataxia
Clinical minor	Parkinsonism; memory deficiency; executive dysfunction; leg neuropathy
Radiologic major	MCP white-matter lesions
Radiologic minor	Cerebral white-matter lesions; splenial lesions; generalized atrophy

Definite FXTAS: Accepted pathways

- A premutation carrier can meet definite criteria with one major radiologic plus one major clinical sign.
- A characteristic neuropathologic inclusion finding also qualifies in the defined criteria.
- The criteria describe diagnostic confidence, not a stand-alone imaging screening result.



Probable FXTAS: Two combinations

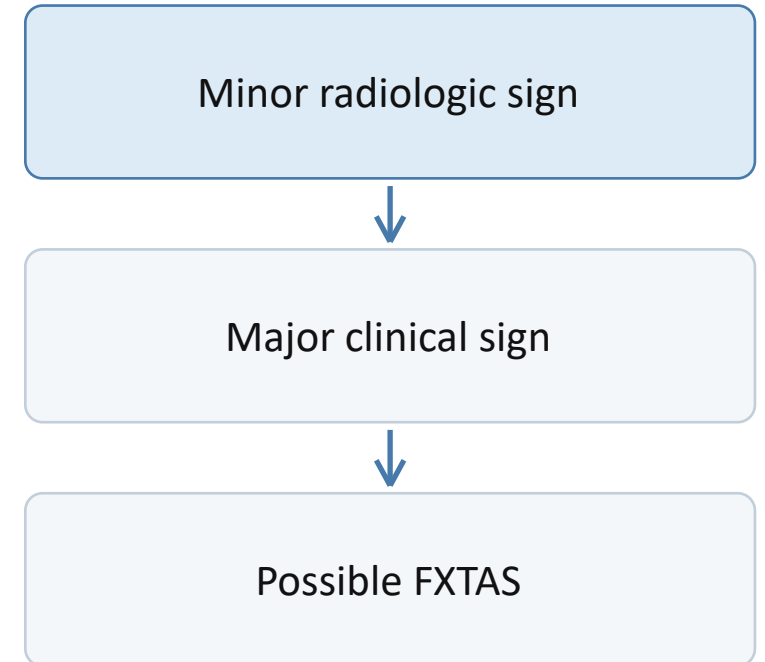
- One major radiologic sign plus one minor clinical sign meets probable criteria.
- Alternatively, two major clinical signs meet probable criteria.
- The latter pattern allows a probable diagnosis without the major radiologic sign.

Major MRI + minor clinical

Two major clinical signs

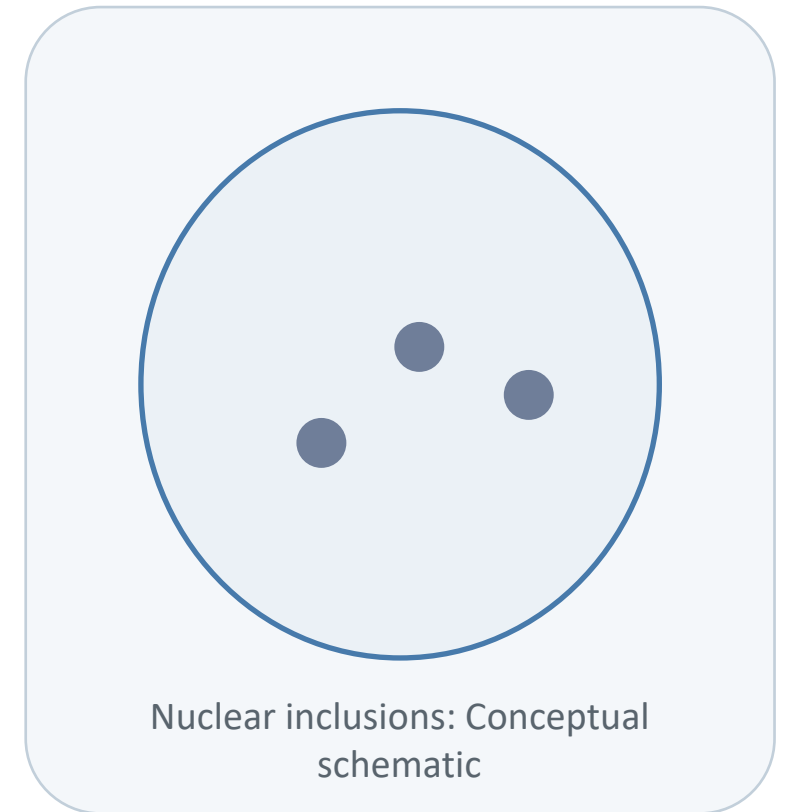
Possible FXTAS: One specified combination

- One minor radiologic sign plus one major clinical sign meets possible criteria.
- This category expresses lower certainty than definite or probable.
- It should be interpreted with molecular testing and exclusion of competing causes.



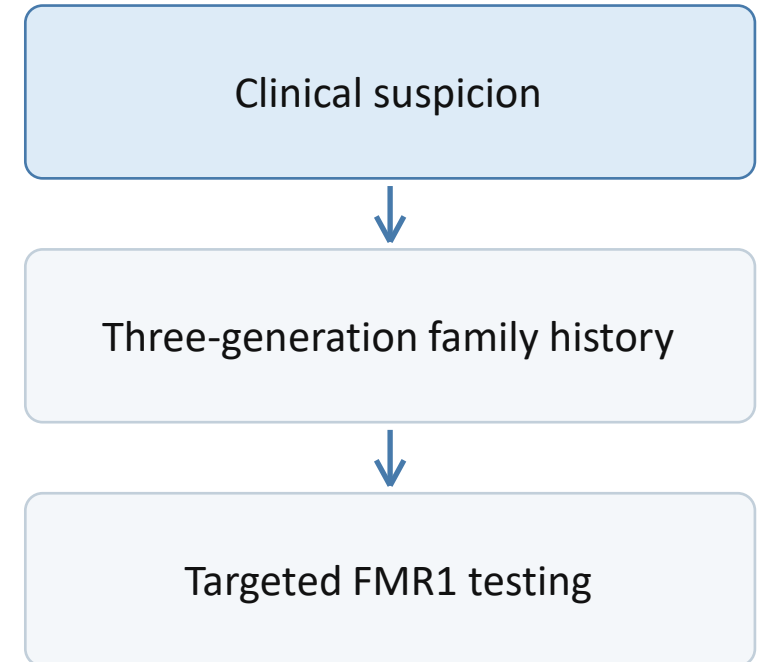
The neuropathologic hallmark is nuclear

- FXTAS inclusions are found within cell nuclei, including neuronal and astrocytic nuclei.
- GeneReviews describes characteristic eosinophilic, ubiquitin-positive intranuclear inclusions.
- These are genuine morphologic criteria; The slide schematic is not a photomicrograph.



A diagnostic work-up is phenotype driven

- Consider FXTAS in adults with otherwise unexplained intention tremor and gait ataxia.
- Review family history for fragile X syndrome and premature ovarian insufficiency.
- Confirm premutation status with specialized FMR1 CGG repeat testing.



Differential diagnosis: Motor syndromes

- Common alternative diagnostic categories include parkinsonism, essential/other tremor syndromes and hereditary ataxias.
- Multiple system atrophy, cerebellar subtype, can resemble FXTAS.
- Evaluate the chronology, phenotype, imaging and genetic result together.

Tremor disorders

Ataxia syndromes

Parkinsonian syndromes

Differential diagnosis: Cognition and white matter

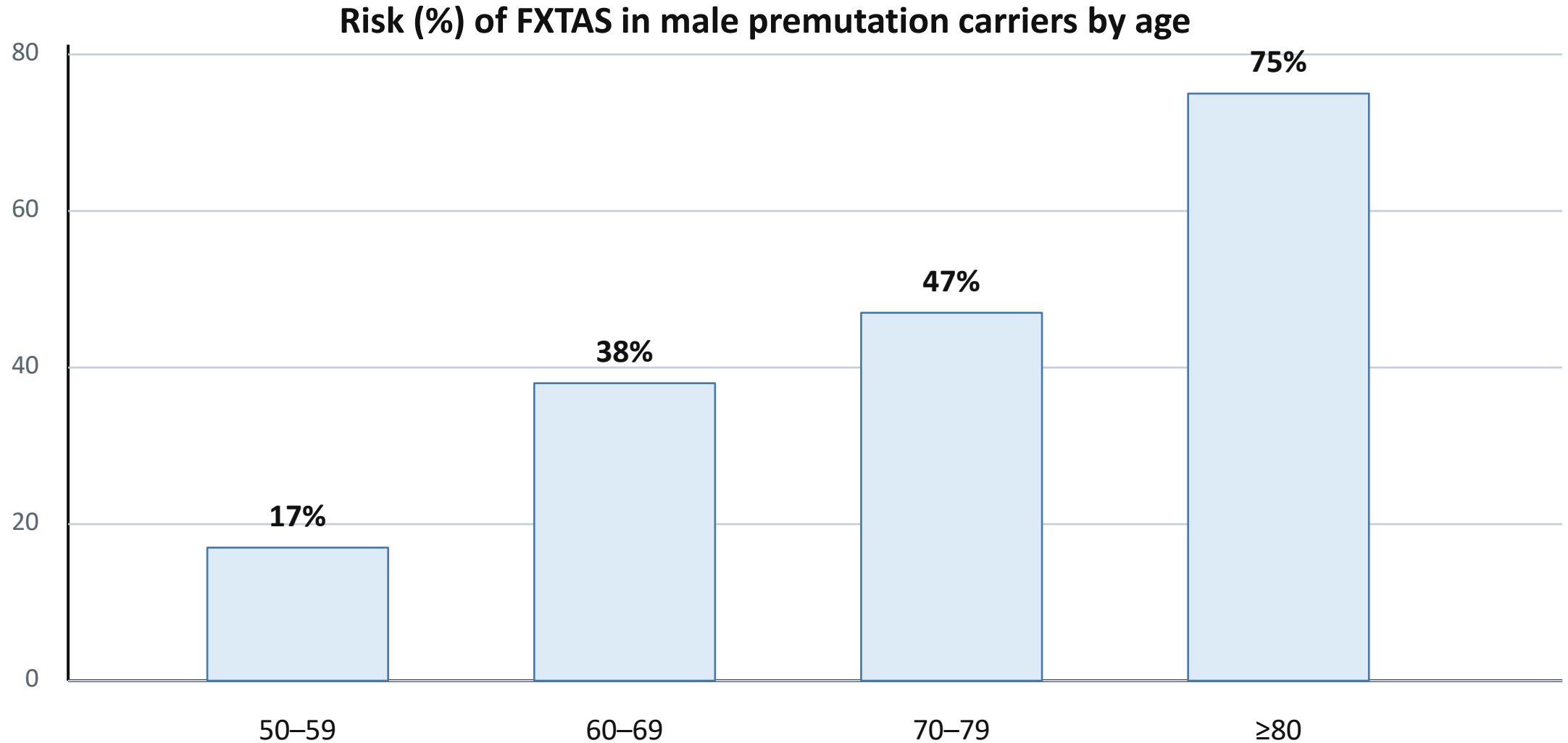
- Dementia, cerebrovascular disease and other leukoencephalopathies may overlap clinically or radiologically.
- The MCP sign is helpful but not independently pathognomonic.
- A premutation plus compatible clinical evidence strengthens attribution.

Motor / cognitive phenotype

MRI white-matter findings

Rule out alternatives

FXTAS penetrance increases with age



Estimated FXTAS risk by age among males with an FMR1 premutation (GeneReviews, Table 2; Adapted from Grigsby et al).

Sex modifies FXTAS penetrance

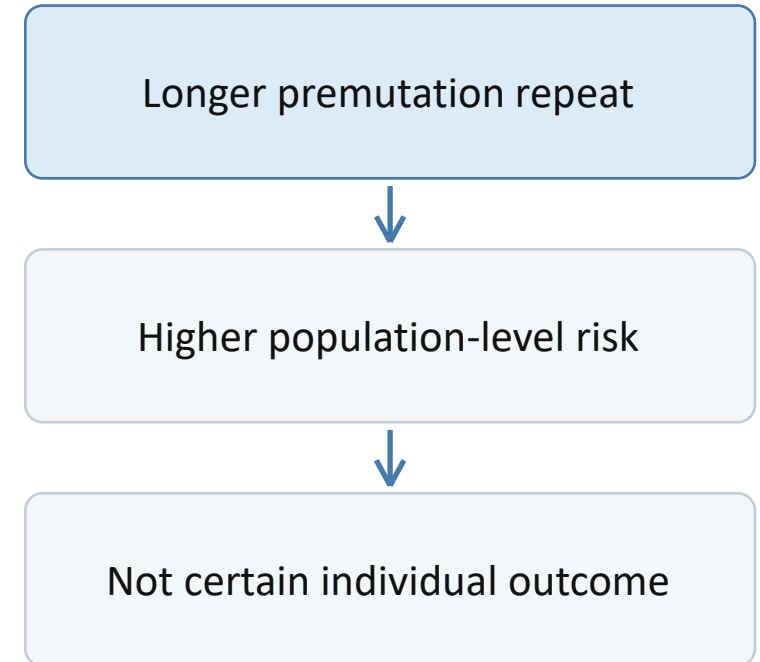
- Premutation-carrying males are more frequently affected than females.
- GeneReviews reports about 40% among males older than 50 and 16%–20% among female carriers.
- Age and ascertainment affect prevalence estimates; Sex is not an absolute determinant.

Males: Higher penetrance

Females: Lower, nonzero risk

Repeat length also modifies neurological risk

- Higher CGG repeat size within the premutation range correlates with increased FXTAS risk and severity.
- Reported associations include earlier onset and greater motor impairment.
- Genotype–phenotype correlation is probabilistic, not a deterministic forecast for one person.



Functional consequences of progressive FXTAS

- Gait and postural instability can lead to need for walking aids.
- Cognitive impairment can compromise complex daily activities.
- Therapeutic priorities emphasize symptom control, falls prevention and multidisciplinary support.

Motor / cognitive decline



Safety and independence affected



Supportive care needs

FXTAS management is supportive

- No established therapy reverses the underlying FMR1 RNA-associated process.
- Management addresses tremor, ataxia, neuropathic symptoms and cognitive/psychiatric complications.
- Rehabilitation and individualized fall-risk assessment are clinically important.

Symptom management

Rehabilitation and safety

Cognitive / mental health support

FXPOI: The reproductive phenotype of a premutation

- FXPOI is ovarian insufficiency attributable to an FMR1 premutation.
- It occurs before age 40 and is associated with elevated gonadotropin concentrations.
- Not every premutation-carrying woman develops the ovarian phenotype.

Premutation carrier

Reduced ovarian function

Possible FXPOI before 40

Why “ovarian insufficiency” is preferred

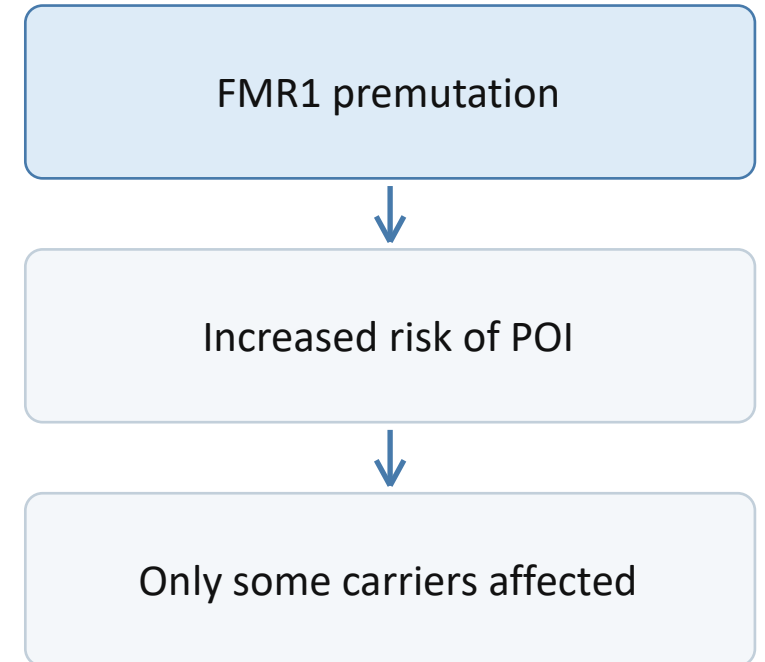
- The Robbins section uses “primary ovarian failure”; Current terminology favors “primary ovarian insufficiency.”
- Ovarian activity can be intermittent rather than completely or permanently absent.
- The newer terminology avoids implying inevitable and absolute sterility.

Older: Ovarian failure

Preferred: Ovarian insufficiency

FXPOI affects only a subset of carriers

- Premature ovarian failure in approximately one-fifth of female premutation carriers.
- A carrier result alone does not diagnose ovarian insufficiency.
- Clinical menstrual history and biochemical assessment are necessary.



Age threshold distinguishes primary ovarian insufficiency

- FXPOI is defined by ovarian insufficiency before 40 years of age.
- The relevant phenotype is hypergonadotropic hypogonadism.
- Earlier menopause by itself is not interchangeable with confirmed FXPOI.

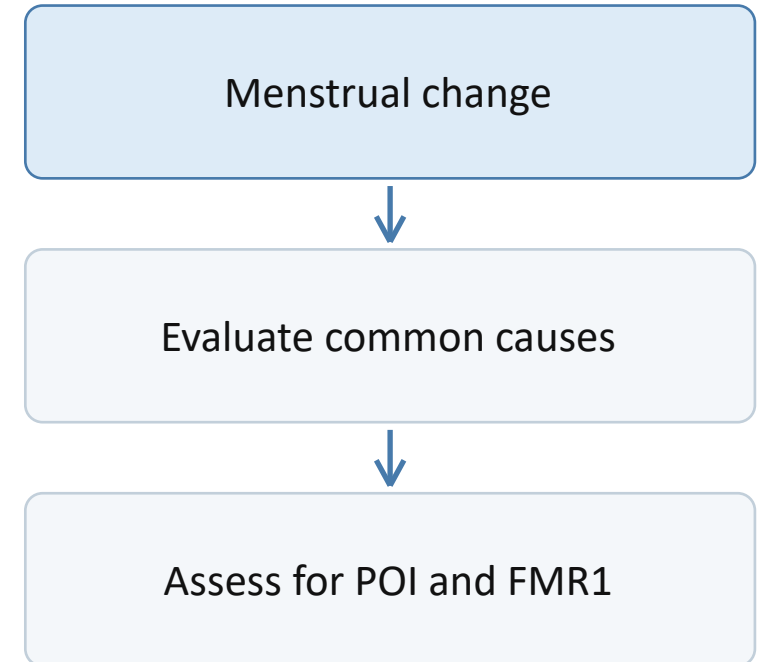
Age <40

Ovarian functional decline

Gonadotropin elevation

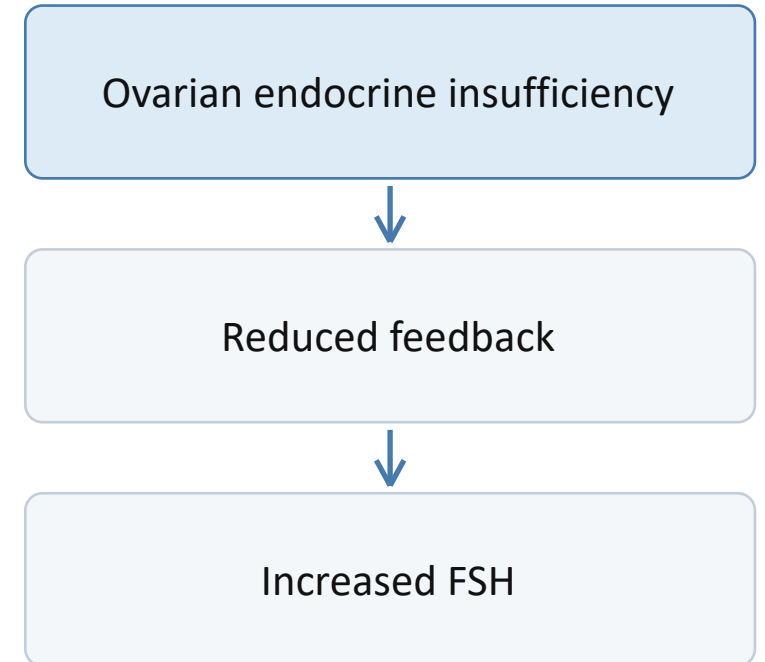
Menstrual changes are a clinical entry point

- Cycle irregularity, oligomenorrhea or amenorrhea may prompt evaluation.
- Irregular menses in a carrier should not automatically be attributed to FXPOI.
- Pregnancy and other endocrine or gynecologic causes must still be considered.



Elevated FSH reflects reduced ovarian feedback

- Follicle-stimulating hormone can rise when ovarian endocrine feedback declines.
- Elevated FSH as a marker of declining ovarian function in affected carriers.
- Interpreting FSH requires clinical and reproductive context rather than an isolated value.



AMH gives information about ovarian reserve

- Anti-Müllerian hormone is often decreased as ovarian reserve declines.
- Reduced AMH in affected premutation carriers.
- Low AMH supports diminished reserve, but NFXF cautions that it is not independently diagnostic of POI.

FSH: Gonadotropic response

AMH: Ovarian reserve marker

Ovarian dysfunction has a continuum

- An individual may first develop menstrual irregularity and evidence of diminished reserve.
- Persistently elevated FSH may accompany hypergonadotropic ovarian insufficiency.
- Some spontaneous ovarian activity may remain even after POI diagnosis.

Diminishing ovarian reserve



Irregular cycles / endocrine change



Clinical POI; Activity can vary

FXPOI affects fertility—but is not absolute infertility

- Premutation carriers with FXPOI have reduced fertility.
- Spontaneous ovulation and pregnancy may still occur after POI diagnosis.
- Counseling should address both fertility planning and contraception as appropriate.

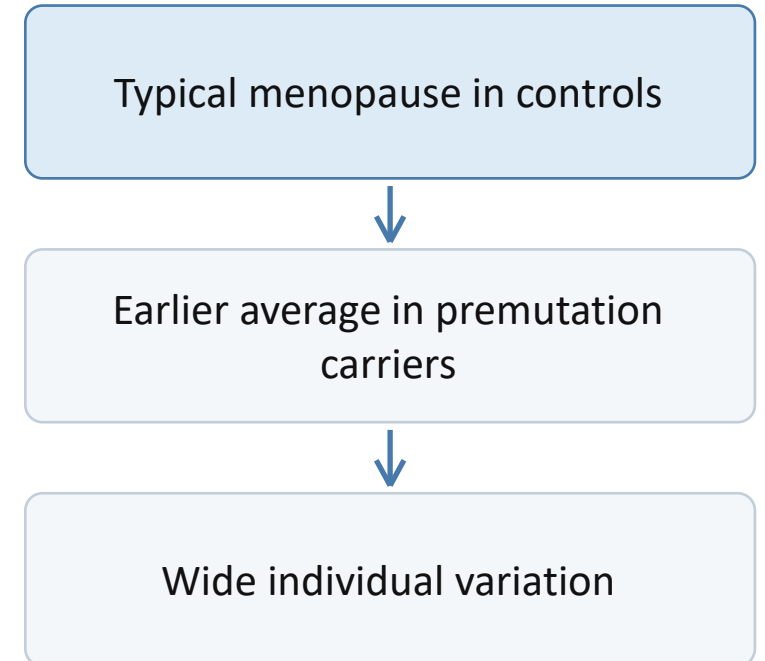
Reduced fertility

Intermittent ovarian function
possible

Individualized family planning

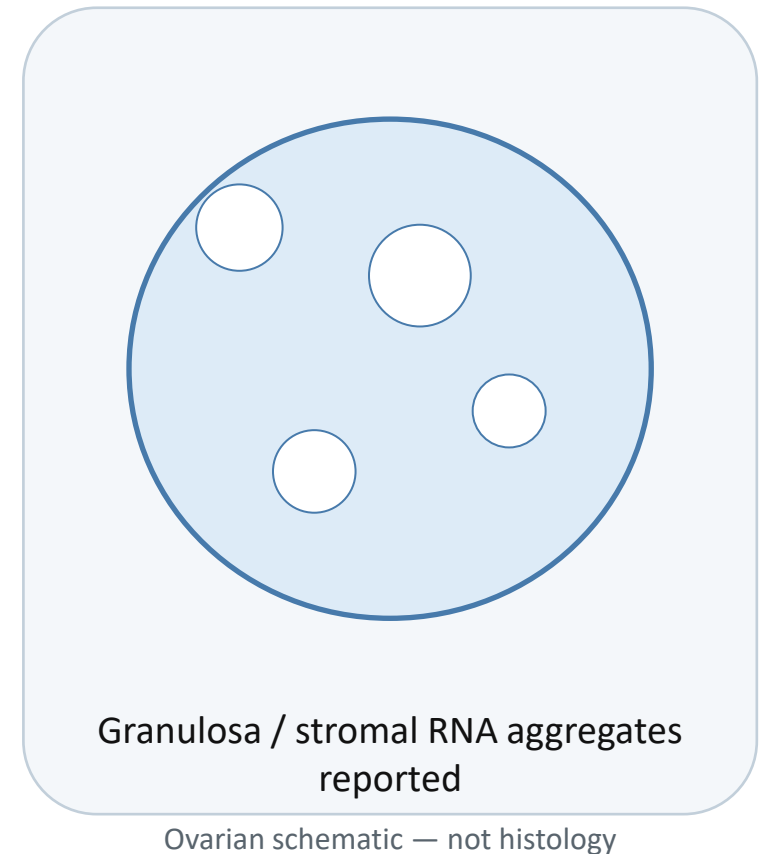
Menopause may occur earlier in carriers

- Menopause approximately five years earlier than in controls on average.
- The finding describes a population comparison, not the expected age for every carrier.
- Premutation carriers without diagnosed FXPOI may nevertheless experience altered reproductive timing.



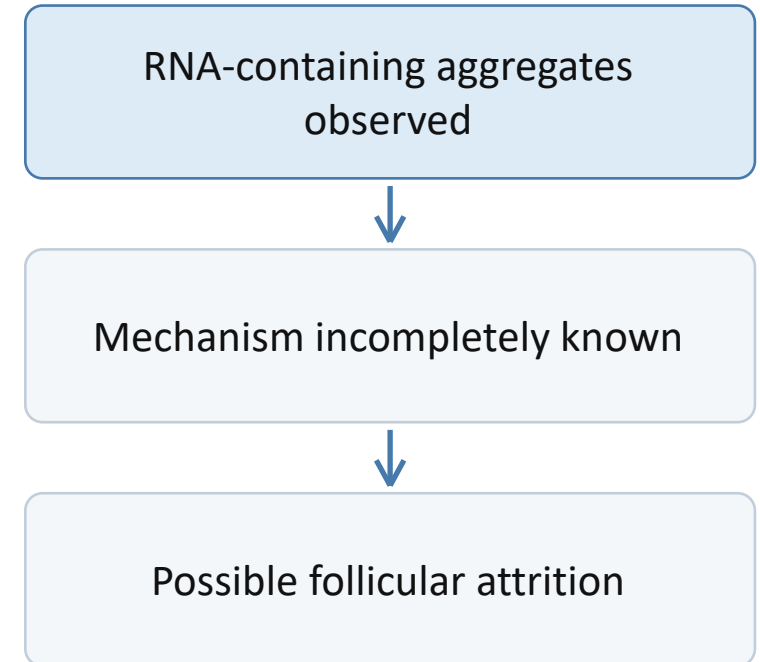
Ovarian cellular inclusions: Cautious interpretation

- Expanded FMR1 RNA-containing aggregates have been detected in granulosa cells.
- Ovarian stromal cells can also contain aggregates.
- These reports suggest a tissue correlate but do not prove the complete sequence of follicular injury.



Premature follicle loss remains a hypothesis

- That abnormal RNA aggregates might trigger premature follicular death.
- The available textbook discussion does not establish all intermediate molecular pathways.
- Separate demonstrable histopathologic observation from a proposed causal mechanism.



Clinical consequences of hypoestrogenism

- Estrogen deficiency may produce vasomotor symptoms, vaginal dryness and sexual discomfort.
- Long-term health concerns include reduced bone mineral density.
- Attention to cardiovascular and overall health belongs in POI management.

Symptoms

Bone health

Cardiovascular risk

Current FXPOI diagnostic approach

- 2025 NFXF guidance describes absent menstrual periods for at least four months before age 40.
- A serum FSH value in the menopausal range (>25 IU/L) is part of that guidance.
- Guidelines have evolved; Confirm locally applicable criteria before using a threshold clinically.

Age <40 + amenorrhea ≥ 4 months



FSH >25 IU/L



Evaluate cause, including FMR1

The literature uses differing FSH criteria

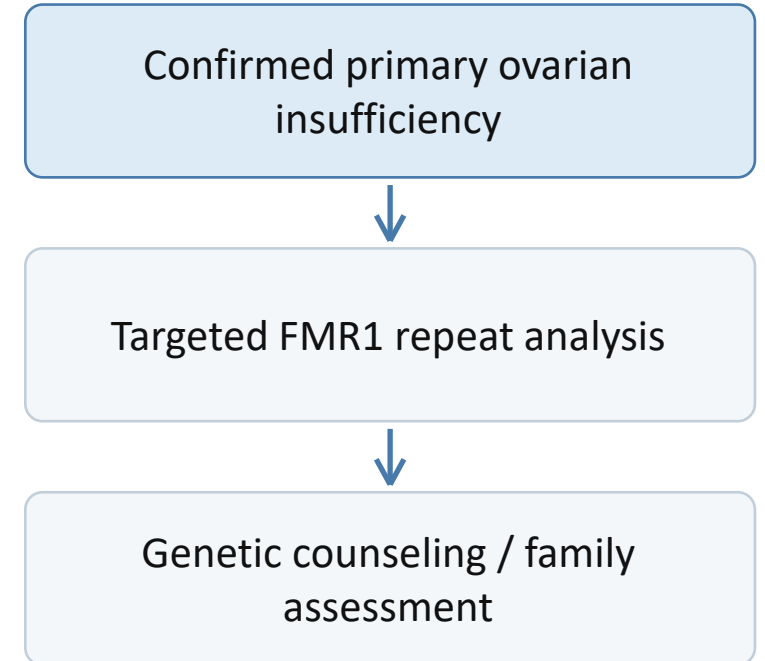
- GeneReviews (2024) describes earlier criteria requiring two elevated FSH levels at least one month apart.
- The NFXF 2025 consensus description uses a single menopausal-range FSH level.
- These criteria should be identified by publication and date rather than merged.

**GeneReviews 2024: 2 FSH
samples**

NFXF 2025: 1 menopausal-range
FSH

Screen for FMR1 premutation in POI

- NFXF 2025 recommends premutation testing in women diagnosed with POI.
- A negative family history does not exclude an inherited FMR1 premutation.
- A positive result also creates implications for other relatives and future pregnancies.



Other causes of amenorrhea remain relevant

- Evaluate pregnancy, thyroid disease, hyperprolactinemia and hypothalamic causes when clinically indicated.
- Polycystic ovary syndrome can also produce irregular menses.
- Not all irregular menses in a premenopausal carrier is caused by FXPOI.

Pregnancy / hypothalamic causes

Thyroid / prolactin disorders

PCOS / other gynecologic disorders

Alternative causes of established POI

- Other POI etiologies include chromosome disorders such as Turner syndrome.
- Autoimmune causes and prior gonadotoxic treatment require consideration.
- The molecular diagnosis of FXPOI should be made in the context of the full clinical work-up.

Chromosomal causes

Autoimmune causes

Iatrogenic injury

FXPOI care addresses long-term health

- Gynecologic or reproductive endocrine specialist input is appropriate.
- Hormone replacement is generally recommended for POI when no contraindication exists.
- Bone-density assessment, cardiovascular considerations and psychosocial support may be relevant.

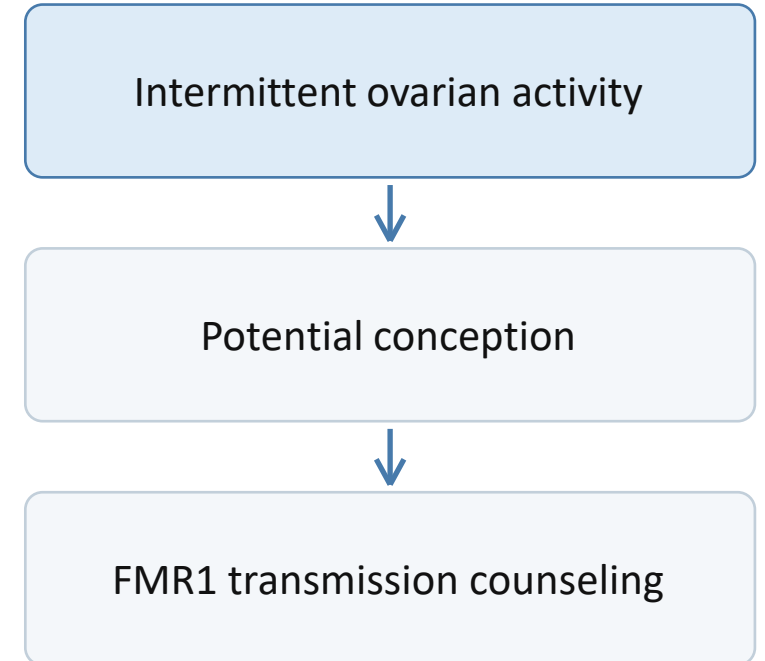
Hormonal health

Bone / vascular health

Fertility and psychosocial care

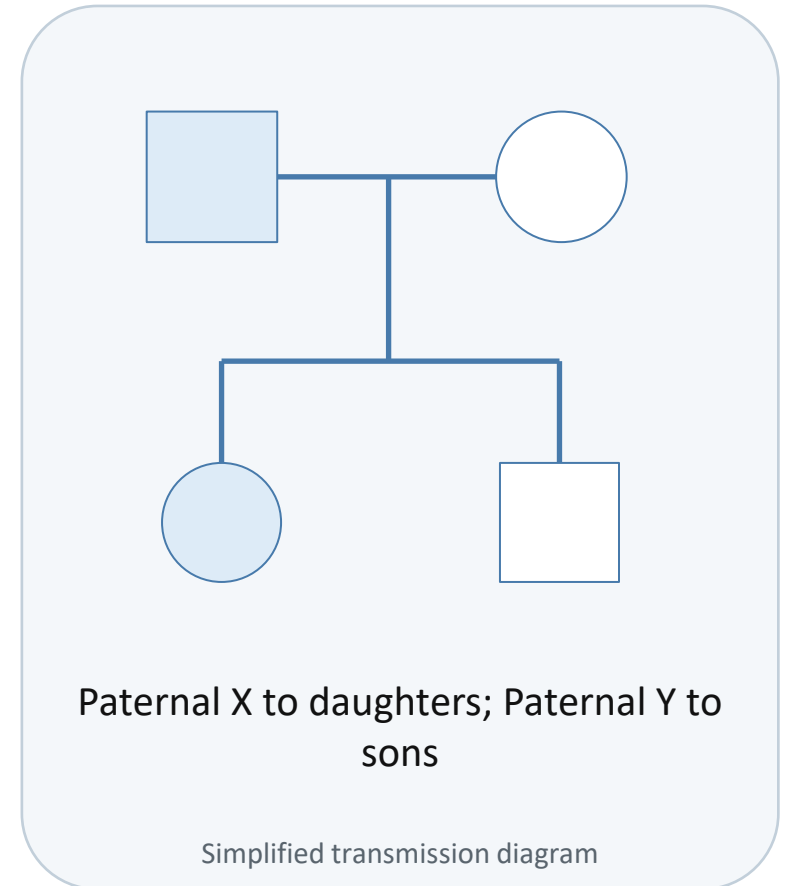
Counseling must preserve reproductive nuance

- An FXPOI diagnosis does not rule out spontaneous conception.
- Genetic transmission risk persists if conception occurs.
- Preconception discussion can include molecular counseling and reproductive options.



X-linked inheritance creates multi-generation risk

- FMR1 is an X-linked locus: Sex of the transmitting parent affects inheritance.
- Premutation transmission by a mother may involve CGG expansion to a full mutation.
- A transmitting male passes his FMR1 premutation to all daughters, not sons.



Transmission is not equivalent to disease

- Inheriting a premutation conveys risk of FXTAS/FXPOI and repeat expansion; It does not guarantee disease.
- An expanded maternal premutation may cause FXS in a child if it becomes a full mutation.
- Phenotype and molecular repeat size must be kept separate in pedigrees.

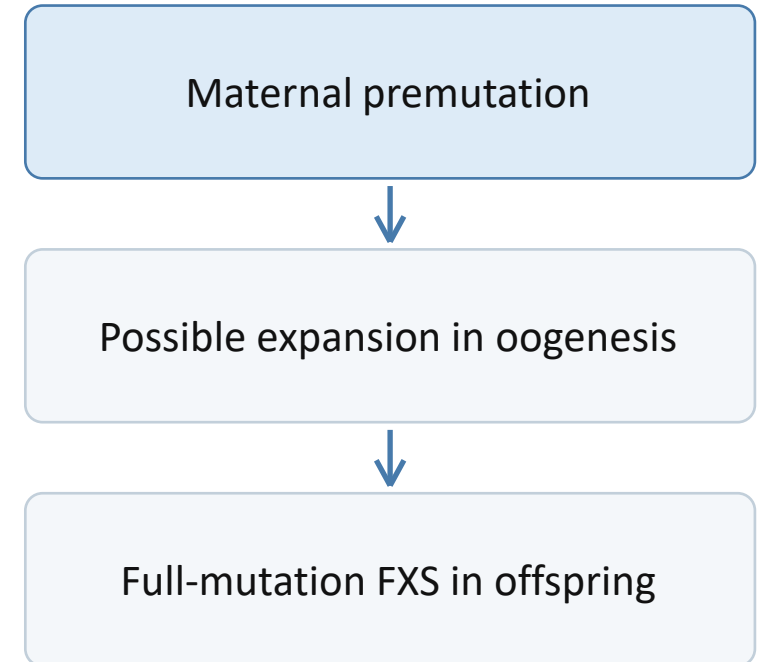
Allele transmission

Repeat stability / expansion

Clinical expression

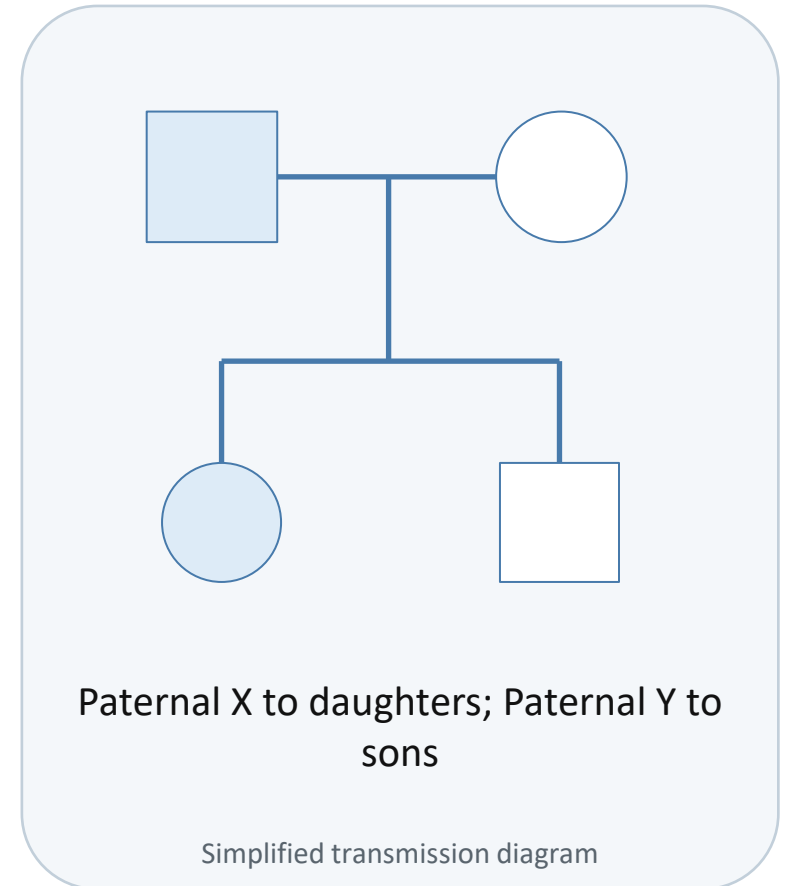
Maternal expansion: Why anticipation matters

- Premutation-to-full-mutation amplification during oogenesis.
- This helps explain why classic FXS may emerge in later generations.
- Risk is influenced by repeat size and sequence interruptions; A counseling assessment is individualized.



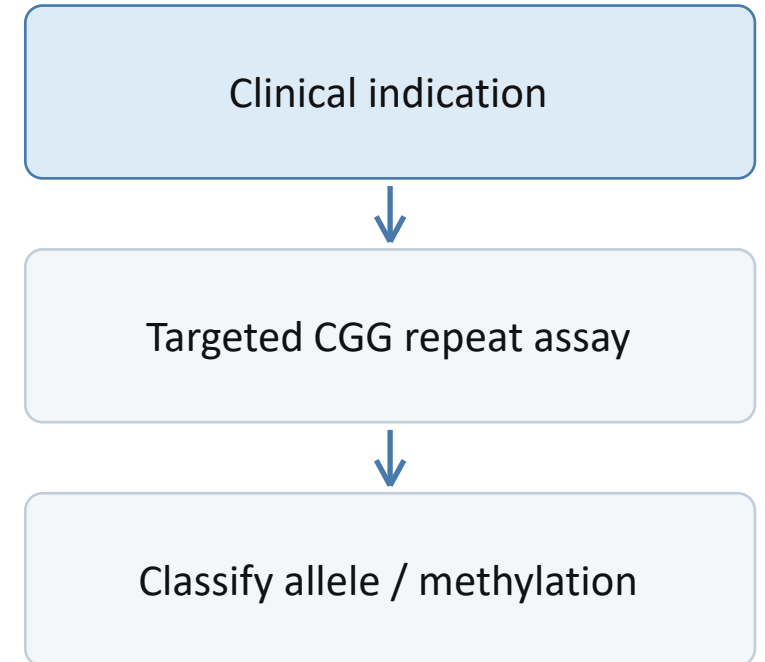
Paternal premutations follow a different pattern

- A hemizygous premutation-carrying father transmits the allele to daughters.
- He transmits his Y chromosome—not the FMR1-bearing X chromosome—to sons.
- Paternal transmission typically does not generate a full-mutation expansion.



FMR1 testing is not routine sequencing

- Diagnostic evaluation requires repeat-sizing methods targeted to FMR1 CGG expansions.
- Repeat-primed PCR can identify the expanded-repeat locus and AGG interruptions.
- Methylation testing is particularly relevant to classifying a full mutation.



Why a standard exome may miss an expansion

- Routine exome or gene panels may not adequately characterize FMR1 CGG repeat length.
- GeneReviews recommends specialized molecular analysis for suspected FMR1-associated disorders.
- Do not interpret an unrevealing generic panel as exclusion of FXTAS or FXPOI.

Targeted repeat assay: Indicated

Ordinary exome alone:
Insufficient

Molecular result versus clinical diagnosis

Evidence	What it contributes	Interpretation
Premutation detected	Establishes genotype and susceptibility	Does not alone confirm FXTAS or FXPOI
Clinical syndrome documented	Establishes phenotype	Requires appropriate differential diagnosis
Both together	Connects genotype and phenotype	Supports FMR1-associated diagnosis

Case: Older adult with progressive imbalance

- A 68-year-old man develops intention tremor and progressive cerebellar gait ataxia.
- MRI shows middle cerebellar peduncle white-matter lesions.
- A targeted test detects an FMR1 premutation.

Which diagnostic category is supported by these findings?

Interpretation: Definite FXTAS: One major radiologic sign (MCP sign) plus at least one major clinical sign, in a premutation carrier.

Case: No major MRI abnormality

- A premutation-carrying older adult has intention tremor and cerebellar gait ataxia.
- MRI does not demonstrate an MCP lesion.
- No neuropathologic examination has been performed.

Is definite FXTAS established by the given criteria?

Interpretation: No. Two major clinical signs meet probable FXTAS criteria; An MCP lesion or inclusions are not shown.

Case: Reproductive-endocrine presentation

- A 32-year-old woman presents with persistent amenorrhea and elevated FSH.
- Molecular testing identifies a premutation-sized FMR1 allele.
- She reports a family member affected by fragile X syndrome.

What two dimensions of care are required?

Interpretation: Evaluate/manage primary ovarian insufficiency and provide reproductive genetic counseling for FMR1 transmission risk.

Case: Do not equate a low AMH with POI

- A premutation-carrying woman has decreased AMH but continues regular menstrual cycles.
- She has no reported amenorrhea meeting POI criteria.
- A low ovarian-reserve marker is not sufficient as a stand-alone diagnosis.

Can FXPOI be diagnosed solely from low AMH?

Interpretation: No. AMH may indicate diminished reserve, but a clinical/biochemical POI evaluation is still required.

Comparative clinicopathologic diagnosis

Condition	Clinical domain	Characteristic presentation	Supporting evaluation
FXTAS	Neurological	Intention tremor + cerebellar ataxia	MRI / selected neuropathology + repeat test
FXPOI	Reproductive-endocrine	POI before age 40	Menstrual/FSH evaluation + repeat test
FXS	Neurodevelopmental	Childhood developmental impairment	Full-mutation/methylation testing

Five errors to avoid in interpretation

- Premutation $\neq$ full mutation; Gain-of-function model $\neq$ transcriptional silencing.
- Carrier status $\neq$ inevitable penetrance of FXTAS or FXPOI.
- MRI signal $\neq$ standalone FXTAS diagnosis; Low AMH $\neq$ standalone POI diagnosis.
- Reported ovarian aggregates $\neq$ fully established causal mechanism.
- An FMR1 phenotype can have genetic implications beyond the index patient.

Genotype $\neq$ phenotype

Supportive test $\neq$ stand-alone
proof

Observation $\neq$ complete causal
model

Integrated mechanism and phenotype

Genotype	Transcription	Pathogenesis	Phenotype
FMR1 full mutation	Promoter hypermethylation	Reduced FMRP	Fragile X syndrome
FMR1 premutation	Expanded RNA remains expressed	RNA-associated toxicity	FXTAS / FXPOI

Core teaching synthesis

- FXTAS and FXPOI result from FMR1 premutation-associated disease risk, not from the classical FXS silencing mechanism.
- FXTAS is a late-onset motor–cognitive syndrome with characteristic clinical and MRI clues.
- FXPOI is ovarian insufficiency before 40 with reproductive, endocrine and familial consequences.
- Specialized molecular testing and pedigree interpretation link both disorders.

Selected references

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