Fragile X Syndrome

Disease Overview

Fragile X syndrome (FXS), the most common heritable form of intellectual disability (ID) and autism, is caused by full FMR1 gene mutations. Individuals with an FMR1 gene premutation may develop fragile X-associated tremor/ataxia syndrome (FXTAS), FX-associated neuropsychiatric disorder, or primary ovarian insufficiency (POI).

Diagnostic testing should be offered to individuals with unexplained intellectual disability (ID), developmental delay, autism spectrum disorder, late-onset cerebellar ataxia and intention tremor, POI, or infertility associated with elevated follicle-stimulating hormone (FSH) levels.

Screening for FXS should be offered to women with a positive family history of FXS, FXTAS, unexplained ID, or autism. Fetal testing should be offered to women who carry a fragile X premutation or full mutation.

Symptoms of FXS

- Moderate ID (median IQ of 40-45 but ranges from <10 to normal range)
- Autism in 50-70%
- Perseverative speech
- Behavioral issues: hand flapping/biting, attention deficit hyperactivity disorder (ADHD), social anxiety, poor eye contact, tactile defensiveness, aggressiveness, and irritability
- Large ears, long face, large jaw, prominent forehead, and large testes

Symptoms of FXTAS

- Cerebellar gait ataxia
- Intention tremor
- Parkinsonism; muscle rigidity, unbalanced shuffling gait, slowed movement and speech
- Moderate to severe short-term memory loss
- Executive function deficit
- Incontinence/ impotence

Prevalence

FXS:

- 1/4,000 males
- 1/8,000 females

Premutation allele in U.S.:

- 1/1,000 males
- 1/350 females
Genetics

Gene

FMR1

Inheritance

X-linked

Structure/Function

FMR1 codes for fragile X mental retardation protein (FMRP), an RNA-binding protein expressed in many tissues

Mutations

Caused by FMR1 variants

- 99% caused by expansion of the FMR1 gene CGG repeat
- Less than 1% caused by FMR1 sequence variants or partial/full FMR1 gene deletions
- Risk for CGG repeat expansion is dependent on sex of transmitting parent and size of repeat

CGG repeat sizes:

- Normal alleles: 5-44 CGG repeats (unmethylated)
  - Stably transmitted
- Intermediate alleles: 45-54 CGG repeats (unmethylated)
  - Unstable but will not expand to a full mutation in one generation
- Premutations: 55 to ~200 CGG repeats (unmethylated)
  - Females:
    - At risk for having offspring with FXS-transmission of CGG repeats to offspring is unstable
      - Premutations of <56 repeats have not expanded to full mutation in a single generation\(^1,2\)
      - Stability of alleles <90 CGG repeats is influenced by the number of AGG interspersions within the CGG repeat sequence
      - Premutations >90 repeats nearly always expand to full mutation in offspring
    - 21% risk for POI (before age 40)
    - At risk for fragile X-associated neuropsychiatric disorders
    - 17% risk for FXTAS in women>50 years of age
  - Males:
    - Transmission of CGG repeats is stable
    - All of their daughters and none of their sons will inherit the premutation
    - 47% risk for FXTAS in men >50 years of age
- Full mutations: typically >200 CGG repeats (methylated)
  - Males are affected with FXS
  - 50% of females have moderate ID
  - Disease symptom severity cannot be predicted based on:
    - Size of CGG repeat
    - Degree of methylation
    - Pattern of X-inactivation (in females)

Test Interpretation

Sensitivity/Specificity
Clinical sensitivity/specificty: 99%
Analytic sensitivity/specificty: 99%

Results

<table>
<thead>
<tr>
<th>Result</th>
<th>Number of CGG Repeats</th>
<th>Clinical Significance</th>
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<tbody>
<tr>
<td>Full mutation</td>
<td>~200 (methylated)</td>
<td>Male: FXS with ID</td>
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<td>Female: Variable expression of FXS; 50% have ID</td>
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<tr>
<td>Premutation</td>
<td>55 to ~200 (unmethylated)</td>
<td>Male: 47% risk for FXTAS in men &gt;50 years of age</td>
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<tr>
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<td>Female: At risk for POI; At risk for FX-associated neuropsychiatric disorders; 17% risk for FXTAS in women &gt;50 years of age</td>
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<tr>
<td>Indeterminate</td>
<td>45 to ~54</td>
<td>Offspring at risk for inheriting premutation</td>
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<tr>
<td>Negative</td>
<td>5 to ~44</td>
<td>Normal; not affected with nor a carrier of FXS</td>
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Limitations

- Estimated CGG repeat number is not provided for full mutations (alleles with >200 repeats)
- Sizing precision of CGG premutation alleles is within two-three CGG repeats
- Methylation patterns are not fully established in the first trimester of pregnancy; thus, CVS is not recommended for prenatal diagnosis. A small, full mutation may be distinguished from a large premutation in amniocytes
- Rare FMR1 variants unrelated to trinucleotide expansion will not be detected
- Diagnostic errors can occur due to rare sequence variations
- AGG trinucleotide interruptions within the FMR1 CGG repeat tract are not assessed

References


Additional Resources