FMR1-Related Disorders (Fragile X) Genetic Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What are FMR1-related disorders

Definition

FMR1-related disorders are a group of disorders caused by mutations in the FMR1 gene. These include fragile X syndrome, fragile X-associated tremor/ataxia syndrome (FXTAS), and FMR1-related primary ovarian insufficiency (POI).¹

FMR1-related phenotypes

• Fragile X Syndrome
  o Fragile X syndrome is the most common cause of inherited intellectual disability, affecting approximately 1 in 4,000 males and 1 in 8,000 females.²,³
  o Given that the mutation is on the X-chromosome, males tend to be more severely affected than females.
  o Symptoms of Fragile X syndrome vary widely and may include the following: intellectual disability, autism, large head, long face, prominent forehead and chin, protruding ears, loose joints, large testes in postpubertal males, motor and language delays, and behavioral differences.¹,³

• Fragile X-associated tremor/ataxia Syndrome
  o Fragile X-associated tremor/ataxia syndrome (FXTAS) is a neurodegenerative disorder characterized by progressive cerebellar ataxia and/or intention tremor usually presenting after age 50 in individuals with a premutation allele in the gene for fragile X (FMR1).¹
Other neurologic findings of FXTAS include short term memory loss, executive function deficits, cognitive decline, dementia, Parkinsonism, peripheral neuropathy, and lower limb proximal weakness.\(^1\)

A diagnosis of FXTAS “is confirmed by the presence of a FMR1 premutation and white matter lesions on MRI in the middle cerebellar peduncles and/or brain stem, with intention tremor and/or gait ataxia.”\(^1\)

- FMR1-related premature ovarian failure
  - FMR1-related primary ovarian insufficiency occurs in women who are carriers of FMR1 premutations. “Females with premutations (usually >80 CGG repeats) are at ~20% risk for premature ovarian insufficiency (POI).”\(^4\)
  - Symptoms can include irregular menstruation, elevated follicle stimulating hormone (FSH), reduced fertility, and early menopause.\(^1\)

**Inheritance**

- FMR1 related disorders are caused by a type of genetic mutation called a triplet repeat expansion in >99% of individuals with these conditions. A triplet repeat is a sequence of three nucleotide building blocks (CGG) that is variably repeated within the FMR1 gene. The normal allele size is up to 44 repeat units.\(^1\) A premutation ranges from approximately 55 repeats to 200 repeats.\(^1\) A full mutation (>200 repeats) usually causes the gene to be abnormally methylated, turning it off. The number of CGG repeat copies within the FMR1 gene can expand from one generation to the next, a property known as anticipation.\(^1,2,4\)
- Predictive (carrier) testing can be performed for at-risk relatives when there is a family history of fragile X syndrome, intellectual disability of unknown etiology, or other characteristic features.\(^3\)
- A woman carrying a premutation or full mutation is at risk to have a child affected with fragile X syndrome. The actual risk depends on the number of repeats in her FMR1 gene.\(^1,3\) Prenatal testing is available for at-risk pregnancies.
- “Most individuals with the premutation do not show fragile X syndrome–related features; however, some with large repeat sizes (>100 repeats) have been identified with learning difficulties, emotional problems, or even intellectual disability.”\(^4\)
- Both male and female premutation carriers are at risk for FXTAS. Approximately 40% of premutation carrier males over the age of 50 will develop FXTAS. The risk to female premutation carriers appears to be lower.\(^1\) “The penetrance of FXTAS increases with age and with premutation repeat length.”\(^5\)
- “Among females with POI [premature ovarian failure] and simplex cases of adult males with cerebellar ataxia, the FMR1 premutation is identified in 4-6% and 2%, respectively.”\(^4\)
Test information

- FMR1 CGG expansion analysis measures the number of CGG repeat copies within the FMR1 gene. Repeat number classifies results as normal, intermediate (also known as gray zone or borderline), premutation, or full mutation.\(^2,4\) The same analysis can be used for diagnostic, carrier, and prenatal testing.

- FMR1 CGG methylation analysis is typically assessed in those with a premutation or full mutation.\(^1,4\) Abnormal methylation, causing a disruption in FMR1 protein production, is the mechanism responsible for features of Fragile X syndrome. Non-classic clinical presentations due to size and methylation mosaicism have been reported.

- Prenatal diagnosis must be undertaken with caution. Expansion analysis is equally accurate on fetal samples from amniocentesis and chorionic villus sampling (CVS). However, methylation analysis on a CVS sample may yield an ambiguous result and amniocentesis may be needed for follow up.\(^4\)

- Testing for the fragile site FXA at Xq27 is no longer an acceptable diagnostic method as test sensitivity and specificity are both insufficient. Families with a diagnosis from this method should be eligible for trinucleotide repeat expansion and/or methylation studies.\(^2\)

Guidelines and evidence

Fragile X Syndrome

- Consensus guidelines from the American Academy of Pediatrics (AAP, 2011) that address health supervision of fragile X syndrome:
  - “Because children with fragile X syndrome may not have apparent physical features, any child who presents with developmental delay, borderline intellectual abilities, or mental retardation or has a diagnosis of autism without a specific etiology should undergo molecular testing for fragile X syndrome to determine the number of CGG repeats (Fig 1). Fragile X testing should also be considered in patients in whom there is suspected, but not molecularly proven, Sotos syndrome or Prader-Willi syndrome. On the other hand, fragile X testing, is not routinely warranted for children with isolated attention-deficit/hyperactivity disorder.”\(^5\)

- Practice guidelines from the American College of Medical Genetics (ACMG, 2005) recommend diagnostic testing for fragile X syndrome for “Individuals of either sex with mental retardation, developmental delay, or autism, especially if they have (a) any physical or behavioral characteristics of fragile X syndrome, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation.”\(^2\)

- Practice guidelines from the American College of Medical Genetics (ACMG, 2005)\(^2\) and the American College of Obstetricians and Gynecologists (ACOG, 2017)\(^6\) support carrier screening for fragile X syndrome:
ACMG: Fragile X syndrome testing should be offered to:
- “Individuals seeking reproductive counseling who have (a) a family history of fragile X syndrome or (b) a family history of undiagnosed mental retardation.”

ACOG: Fragile X carrier screening should be offered to:
- “Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome and who are considering pregnancy or are currently pregnant.”

Practice guidelines from the American College of Medical Genetics (ACMG, 2005) and the American College of Obstetricians and Gynecologists (ACOG, 2017) support prenatal screening for fragile X syndrome:
- ACMG: Fragile X testing is appropriate in “Fetuses of known carrier mothers.”
- ACOG: “Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation gene.”

Fragile X-associated tremor/ataxia syndrome (FXTAS)

Evidence-based guidelines from the European Federation of Neurological Societies (EFNS, 2014) state:
- “In the case of sporadic ataxia and independent from onset age, we recommend routine testing for SCA1, SCA2, SCA3, SCA6 and DRPLA (in Asian patients) (level B), the step 1 panel of the recessive ataxia work-up, i.e. mutation analysis of the FRDA gene (level B), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, CK and α-fetoprotein.
- If negative and if age at onset is above 45 years, we recommend screening for the FMR1 permutation [sic] in male patients (level B).”

Evidence-based guidelines from the European Federation of Neurological Societies (EFNS, 2010) state:
- “Recommendations for FXTAS genetic testing: Genetic testing for the X-linked FXTAS is recommended when there is a clinical suspicion, and it is readily available in many laboratories (Class B).” [Class B rating = “(probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence”]

Practice guidelines from the American College of Medical Genetics and Genomics (ACMG, 2005) recommend FXTAS testing for the following individuals:
- "Men and women who are experiencing late onset intention tremor and cerebellar ataxia of unknown origin, especially if they have (a) a family history of movement disorders, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation.”
Primary Ovarian Insufficiency (POI)

- Practice guidelines from the American College of Medical Genetics and Genomics (ACMG, 2005)\(^2\) and the American College of Obstetricians and Gynecologists (ACOG, 2017)\(^6\) support carrier screening for fragile X syndrome:
  - ACOG: Fragile X carrier screening should be offered to:\(^6\)
    - "If a woman has unexplained ovarian insufficiency or failure or an elevated follicle-stimulating hormone level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation."
  - ACMG: Fragile X syndrome testing should be offered to\(^2\)
    - "Women who are experiencing reproductive or fertility problems associated with elevated follicle stimulating hormone (FSH) levels, especially if they have (a) a family history of premature ovarian failure, (b) a family history of fragile X syndrome, or (c) male or female relatives with undiagnosed mental retardation."
- ACOG committee opinion on Primary Ovarian Insufficiency in Adolescents and Young Adults (2014, Reaffirmed 2018) states:\(^9\)
  - "If a woman has a personal or family history of ovarian failure or an elevated follicle-stimulating hormone (FSH) level before age 40 years without a known cause, fragile X premutation carrier testing should be offered."

Criteria

Targeted mutation analysis for CGG trinucleotide repeat expansion in FMR1

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous molecular genetic testing of FMR1, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Males and females with unexplained speech and/or language delay, motor development delay, intellectual disability (ID), or autism, or
  - Female with premature ovarian failure (cessation of menses before age of 40 years), or
  - Males and females 50 years of age or older with progressive intention tremor and cerebellar ataxia of unknown origin, or
o Males and females 50 years of age or older with white matter lesions on MRI in the middle cerebellar peduncles and/or brain stem, or
o Males and females 50 years of age or older with FXTAS-related neurologic, cognitive, or behavioral difficulties, OR

• Prenatal Testing for At-Risk Pregnancies:
  o CGG trinucleotide repeat expansion in FMR1 identified in biologic mother,** OR

• Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic At Risk Individuals:
  o Age 18 years or older, and
  o Known CGG trinucleotide repeat expansion in FMR1 in 1st, 2nd, or 3rd degree biologic relative and the individual is at risk for inheriting the familial FMR1 expansion based on an X-linked inheritance pattern, or
  o Family history of premature ovarian failure (cessation of menses before age of 40 years), or
  o Family history of movement disorder and
    ▪ Cerebellar ataxia has been ruled out
    ▪ Other movement disorders have been ruled out, or
  o Family history of undiagnosed intellectual disability, or
  o Prior cytogenetic test suspicious for Fragile X, AND

• Possibility of X-linked inheritance has not been ruled out by male to male transmission

Methylation analysis

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o CGG expansion analysis result showing a premutation or full allele size (typically greater than 55 repeats), AND

• Diagnostic Testing for Symptomatic Individuals:
  o Males and females with speech and/or language delay, motor development delay, intellectual disability (ID), or autism, or
Female with premature ovarian failure (cessation of menses before age of 40 years), or
Males and females 50 years of age or older with progressive intention tremor and cerebellar ataxia of unknown origin, or
Males and females 50 years of age or older with white matter lesions on MRI in the middle cerebellar peduncles and/or brain stem, or
Males and females 50 years of age or older with FXTAS-related neurologic, cognitive, or behavioral difficulties, OR

- Prenatal Testing for At-Risk Pregnancies:

- CGG trinucleotide repeat expansion in FMR1 identified in biologic mother**

** Note: CVS must be interpreted with caution. The number of CGG repeats in the fetus can be accurately determined; however, often the methylation status of FMR1 is not yet established in chorionic villi at the time of sampling. CVS results may lead to a situation in which follow-up amniocentesis is necessary to resolve an ambiguous result.

References


