Test Specific Guidelines

FMR1-Related Disorders (Fragile X) Genetic Testing

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Introduction

FMR1-related disorders (Fragile X) genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
FMR1 Expansion Analysis	81243
FMR1 Methylation Analysis	81244

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 fragile X-associated primary ovarian insufficiency (FXPOI).[1]

Prevalence

The most recent estimate for prevalence of fragile X syndrome is 16 to 25 per 100,000 in males. The prevalence of fragile X syndrome in females is predicted to be half that estimated for males. The U.S. prevalence of FXTAS in males is approximately 1/4,848. The prevalence of FXTAS in females is not well established. The U.S. prevalence of FXPOI is approximately 1/3,560.[1]

FMR1-related Phenotypes

There are three FMR1-related phenotypes.

Fragile X Syndrome

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]

Given that the mutation is on the X-chromosome, males tend to be more severely affected than females.

Fragile X-Associated Tremor/Ataxia Syndrome

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 years 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 associated with a premutation-sized repeat (55-200 CGG repeats)."[1]

Fragile X-Associated Primary Ovarian Insufficiency

FMR1-related primary ovarian insufficiency (FXPOI) occurs in approximately 20% of women who are carriers of FMR1 premutations.[1] The highest prevalence of FXPOI is seen in individuals with between 80 and 100 CGG repeats.[4]

Symptoms can include irregular menstruation, elevated follicle stimulating hormone (FSH), reduced fertility, and early menopause.[1]

Cause

FMR1-related disorders are caused by a type of genetic mutation called a triplet repeat expansion in >99% of individuals with these conditions.[1] A triplet repeat is a sequence of three nucleotide building blocks (CGG) that is variably repeated within the FMR1 gene.

Inheritance

FMR1-related disorders are inherited in an X-linked fashion.

X-Linked Inheritance

In X-linked inheritance, the mutation is carried on the X chromosome. Females have two X chromosomes, and males have one. Males typically have more severe symptoms than females. A female with a mutation has a 50% chance to pass that mutation to her children. A male with a mutation cannot pass the mutation to any sons, but will pass it to all daughters. A process called X-inactivation in females results in random inactivation of expression of one X-chromosome in each cell of the body. For females with one mutation, the percentage and distribution of cells with expression of the X chromosome carrying the mutation can influence the degree of severity.

The number of CGG repeats within the FMR1 gene can expand from one generation to the next, a property known as anticipation.[1,2,4] The type and extent of symptoms depend upon the size of the repeat expansion and the sex of the individual.[1]

Diagnosis

The diagnosis is established with molecular testing to identify the triplet repeat expansion.

The normal allele size is up to 44 repeat units.[1,4]

An intermediate allele size is 45-54 repeats.[1,4]

An intermediate size allele does not cause symptoms. These may expand into the premutation range when passed on from the mother.[1,4]

A premutation allele size is approximately 55-200 repeats.[1,4]

"Most individuals with the premutation do not show fragile X syndrome–related features; however, some with large premutation repeat sizes have been identified with learning difficulties, fragile X-associated neuropsychiatric disorders (FXAND), or even intellectual disability."[4]

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.[1,3,4] Prenatal testing is available for at-risk pregnancies.

Both male and female premutation carriers are at risk for FXTAS. The average age of onset of FXTAS is 60-65 years.[1] Approximately 40% of premutation carrier males 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 insufficiency] and simplex cases of adult males with cerebellar ataxia, the FMR1 premutation is identified in 4-6% and 2%, respectively."[4]

A full mutation (>200 repeats) usually causes the gene to be abnormally methylated, turning it off, and resulting in fragile X syndrome.[1]

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]

Treatment

Treatment of manifestations is dependent on the FMR1-phenotype and includes:

Fragile X Syndrome

Treatment for individuals with fragile X syndrome typically consists of psychopharmacologic treatment combined with therapeutic interventions.[1]

Fragile X-Associated Tremor/Ataxia Syndrome

Treatment for individuals with fragile X-associated tremor/ataxia syndrome is tailored the specific symptoms and needs of the affected individual.[1]

The following should be avoided in individuals with fragile X-associated tremor/ataxia syndrome: "Typical and atypical antipsychotics with significant anti-dopaminergic effects and metoclopramide, which can exacerbate parkinsonism; anticholinergic agents, which can exacerbate cognitive complaints; excessive alcohol, which can enhance cerebellar dysfunction and postural instability; agents with known cerebellar toxicity or side effects."[1]

Fragile X-Associated Primary Ovarian Insufficiency

Treatment for individuals with fragile X-associated primary ovarian insufficiency includes appropriate evaluations by specialists in gynecology and endocrinology.[1]

Tobacco use decreases the ovarian reserve and the age of onset of fragile X-associated primary ovarian insufficiency and thus should be avoided.[1]

Survival

In general, the life expectancy for individuals with fragile X syndrome is normal.[6] The life expectancy for fragile X-associated tremor/ataxia syndrome is 5 to 25 years after the development of motor symptoms.[7]

Test Information

Introduction

Testing for FMR1-related disorders may include CGG trinucleotide repeat expansion analysis or CGG methylation analysis.

Trinucleotide Repeat Testing

Repeat expansion genetic testing allows for the determination of the size of a repeated DNA sequence. This testing may involve more than one test methodology. Smaller repeat expansions are typically identified using certain types of polymerase chain reaction (PCR), while larger expansions may require Southern blot. More comprehensive repeat expansion testing that utilizes next generation sequencing and exome sequencing methods is under development.

The expansion in FMR1 involves a CGG repeat. Repeat number classifies results as normal, intermediate (also known as gray zone or borderline), premutation, or full mutation.[2,4] "Currently, TP-PCR [triplet repeat primed PCR] and Southern blot methods remain the gold standards for identification of expanded FMR1 alleles and CGG repeat quantification." [4] The same analysis can be used for diagnostic, carrier, and prenatal testing.

FMR1 Methylation Analysis

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.

Other Considerations

The following are special considerations regarding prenatal testing and previously utilized testing for fragile X syndrome:

Prenatal diagnosis must be undertaken with caution. Expansion analysis is 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 FRAXA 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

Introduction

The following section includes relevant guidelines and evidence pertaining to FMR1-related disorders genetic testing.

Fragile X Syndrome

Guidelines and evidence specific to fragile X syndrome include:

American Academy of Pediatrics

Consensus guidelines from the American Academy of Pediatrics (AAP, 2011) that address health supervision of fragile X syndrome stated:

"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]

American College of Medical Genetics and Genomics

Practice guidelines from the American College of Medical Genetics and Genomics (ACMG, 2005 and 2021) stated the following regarding diagnostic testing:[2,8]

Diagnostic testing is recommended 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]

"Studies have demonstrated that the diagnostic yield of FX testing in males with intellectual disability and learning delay is about 2.5% and in individuals with autism is ~1.2% suggesting that FX testing may not be indicated as a first-tier test." [8]

An ACMG (2021) educational practice resource on carrier screening stated:[8]

"All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening for autosomal recessive (Tables 1–5) and X-linked (Table 6 [gene list includes FMR1]) conditions."

ACMG (2021) stated the following regarding prenatal diagnosis:[4]

"Females who carry an FMR1 premutation should be offered prenatal diagnosis for all pregnancies."

American College of Obstetricians and Gynecologists

Practice guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2017) supported carrier screening for fragile X syndrome:[9]

"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 ACOG (2017) also supported prenatal testing for fragile X syndrome:

"Prenatal diagnostic testing for fragile X syndrome should be offered to known carriers of the fragile X premutation or full mutation."[9]

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

Guidelines and evidence specific to fragile X-associated tremor/ataxia syndrome include:

American College of Medical Genetics and Genomics

Practice guidelines from the American College of Medical Genetics and Genomics (ACMG, 2005) recommended 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."[2]

European Federation of Neurological Societies

The evidence-based guidelines from the European Federation of Neurological Societies (EFNS, 2010) stated:[10]

"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)."4 [Class B rating = "(probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence"]

The evidence-based guidelines from the European Federation of Neurological Societies (EFNS, 2014) stated:[11]

"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)."

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)

Guidelines and evidence specific to fragile X-associated primary ovarian insufficiency include:

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists committee opinion on Primary Ovarian Insufficiency in Adolescents and Young Adults (2014, Reaffirmed 2018) stated:

"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."[12]

American College of Medical Genetics and Genomics and the American College of Obstetricians and Gynecologists

Practice guidelines from the American College of Medical Genetics and Genomics (ACMG, 2005) and the American College of Obstetricians and Gynecologists (ACOG, 2017) support carrier screening for fragile X syndrome:

ACMG: Fragile X syndrome testing should be offered to "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."[2]

ACOG: Fragile X carrier screening should be offered "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."[9]

Criteria

Introduction

Requests for FMR1-related disorders genetic testing are reviewed using the following 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 primary ovarian insufficiency (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, OR**

Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic At Risk Individuals:

Age 18 years or older, and

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

Family history of primary ovarian insufficiency (cessation of menses before age of 40 years), or

Family history of movement disorder and

Cerebellar ataxia has been ruled out

Other movement disorders have been ruled out, or

Family history of undiagnosed intellectual disability, or

Prior cytogenetic test suspicious for Fragile X, AND

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

FMR1 Methylation Analysis

Genetic Counseling:

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

Previous Genetic Testing:

CGG expansion analysis result showing a premutation or full allele size (typically greater than 55 repeats), AND

Diagnostic Testing for Symptomatic Individuals:

Males and females with speech and/or language delay, motor development delay, intellectual disability (ID), or autism, or

Female with primary ovarian insufficiency (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

Introduction

These references are cited in this guideline.

Hunter JE, Berry-Kravis E, Hipp H, Todd PK. FMR1 Disorders. 1998 Jun 16 [Updated 2019 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1384/.

Sherman S, Pletcher BA, Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. *Genet Med.* 2005;7(8):584-7.

Finucane B, Abrams L. Cronister A, Archibald, A, Bennett R, McConkie-Rossell A. Genetic Counseling and Testing for FMR1 Gene Mutations: Practice Guidelines of the National Society of Genetic Counselors. J Genet Couns. 2012;21:752-760. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1007/s10897-012-9524-8.

Spector E, Behlmann A, Kronquist K, et al. Rose NC, Lyon E, Reddi HV; ACMG Laboratory Quality Assurance Committee. Laboratory testing for fragile X, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(5):799-812. doi: 10.1038/s41436-021-01115-y

Hersh JH, Saul RA; Committee on Genetics. Health supervision for children with fragile X syndrome. *Pediatrics*. 2011 May;127(5):994-100.

Fragile X syndrome. Genetic and Rare Diseases Information Center. Updated January 2015. Available at: https://rarediseases.info.nih.gov/.

Gonzalez-Usigli, HA. Fragile X- Associated Tremor/Ataxia Syndrome (FXTAS). Merck Manual Professional Edition. Updated May 2020. Available at: https://www.merckmanuals.com

Gregg AR, Aarabi M, Klugman S, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021;23(10):1793-1806. doi: 10.1038/s41436-021-01203-z. Erratum in: Genet Med. 2021 Aug 27

The American College of Obstetricians and Gynecologists. Committee on Genetics. ACOG committee opinion. Number 691. Carrier Screening for Genetic Disorders. *Obstet Gynecol*. 2017 (Reaffirmed 2020);129(3):e41-355. Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Genetics/Carrier-Screening-for-Genetic-Conditions.

Gasser T, Finsterer J, Baets J, et al.; EFNS. EFNS Guidelines on the Molecular Diagnosis of Ataxias and Spastic Paraplegias. *Eur J Neurol*. 2010 Feb;17(2):179-88.

van de Warrenburg BP, van Gaalen J, Boesch S, Burgunder JM, Dürr A, Giunti P, Klockgether T, Mariotti C, Pandolfo M, Riess O. EFNS/ENS Consensus on the diagnosis and management of chronic ataxias in adulthood. *Eur J Neurol*. 2014 Apr;21(4):552-62.

The American College of Obstetricians and Gynecologists. Committee on Genetics. ACOG committee opinion. Number 605. Primary ovarian insufficiency in adolescents and young women. *Obstet Gynecol*. 2014 (Reaffirmed 2020);124(1):193-197. doi:10.1097/01.AOG.0000451757.51964.98. Available at: https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Primary-Ovarian-Insufficiency-in-Adolescents-and-Young-Women.