
Fragile X Syndrome

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Fragile X Syndrome

Essential Evidence

Display Bottom Lines Only

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Overall Bottom Line

- Fragile X is the most commonly inherited form of mental retardation. SORT B
- The most common neurobehavioral manifestation is autism spectrum disorder, which is present in 67% of males. SORT B[2]
- Genetic testing is recommended for any individuals with mental retardation, autism, developmental delays, or a known family member with Fragile X; also consider if ataxia or tremor in individuals greater than 50 years old or fertility problems in individuals less than 40 years old. SORT C
- Amniocentesis and CVS are widely used for prenatal diagnosis; amniocentesis is accurate and reliable and may be needed if the placental CVS sample is indeterminate. SORT C
- Educational interactions and therapies are the primary mode of treatment along with occupational and speech therapy. SORT C

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Background

Fragile X Syndrome is a mutation of the FMR-1 gene located on chromosome X-q27.3 that codes for the fragile x mental retardation protein (FMRP) resulting in the most common inherited form of mental retardation.

Incidence

- Estimated frequency is approximately 1/4,000 males and 1/8,000 females. [35]

Other Impact

- Fragile X is the most commonly inherited form of mental retardation.

Causes of the Condition

- Genetic / inherited.

Pathophysiology

- Mutation of FMR-1 the gene on the long arm of the X-q27.3 chromosome resulting in a dynamic triple repeat sequence mutation (CGG). A premutation form exists that leads to two distinct disorders: fragile X associated tremors/ ataxia syndrome occurring after the fifth decade, premature ovarian failure onset before age 40. SORT C
- Fragile X follows X-linked inheritance, where women carriers transmit the syndrome to 50% of their children. Its actual transmission is dependent on premutations for coding of the FMRP. [1]
- Male carriers of the mutation transmit the syndrome to all of their daughters and none of their sons. [1]

Fragile X Syndrome

Screening and Prevention

Bottom Line

- Genetic testing is recommended for any individuals with mental retardation, autism, developmental delays, or a known family member with Fragile X; also consider if ataxia or tremor in individuals greater than 50 years old or fertility problems in individuals less than 40 years old. SORT C

Fragile X Syndrome

Diagnosis

Bottom Line

- Obtain family, medical and psychosocial histories following genetic counseling practice recommendations. SORT C Amniocentesis and CVS are widely used for prenatal diagnosis; amniocentesis is accurate and reliable and may be needed if the placental CVS sample is indeterminate. SORT C
- In postnatal diagnosis, amplification by simple PCR on modified DNA is useful for the molecular diagnosis of the Fragile X syndrome. However, the gold standard for diagnosis is the southern blot analysis. SORT C

Differential Diagnosis

Diagnosis	Features
Autism Spectrum Disorder	Mental retardation, hand flapping, social interaction impairment
Down Syndrome	Mental Retardation, congenital heart diseases, epicanthal folds, flattened nasal bridge, low set ears, fifth finger dinodactyly, simian crease
Asperger's Syndrome	Can look like autism, but language is in tact, higher functioning than autism
Angelman Syndrome and Prader-Willi syndrome	Both of these syndromes are chromosomal disorders, resulting in mental retardation with varying dysmorphic features
Cerebral Palsy	Hypertonicity, microcephaly, strabismus, mental retardation

Using the History and Physical

- A comprehensive exam is warranted in any child with an intellectual disability to find the etiology. Treatment, prognosis and genetic risk, along with improved health and functional outcomes, are improved with a specific etiology. A comprehensive exam includes medical and developmental history, family history for three generations, dysmorphologic exam, and neuroimaging. [3]
- Obtain family, medical, and psychosocial histories following genetic counseling practice recommendations.
- Fragile X has many distinguishing physical and clinical features. Dysmorphic features include macrocephaly, large ears, long face, broad forehead, prominent jaw, strabismus, and macro-orchidism.
- Behavioral features include mental retardation, developmental delays, learning disabilities, hand flapping, and mild to severe behavioral problems.
- Neurologic features include late onset progressive tremor, ataxia, dementia, and memory loss.
- Gynecological features may include fertility problems with premature ovarian failure.
- The most common neurobehavioral manifestation is autism spectrum disorder, which is present in 67% of males. [2] Attention deficit/ hyperactivity disorder ADHD is present in 73% of Fragile X boys. [2]

Selecting Diagnostic Tests

- Fragile X is characterized by a triple repeat sequence mutation CGG in the x-linked gene coding for Fragile X mental retardation protein. If the protein is freely expanded, Fragile X syndrome results.
- Amniocentesis and CVS are widely used for prenatal diagnosis; amniocentesis is accurate and reliable and may be needed if the placental CVS sample is indeterminate.
- In postnatal diagnosis, amplification by simple PCR on modified DNA is useful for the molecular diagnosis of the Fragile X syndrome. However, the gold standard for diagnosis is the southern blot analysis.
- MRI shows large caudate nucleus with a small posterior cerebellar vermis.

Approach to the Patient

- Screen persons of either sex with mental retardation, autism, or developmental delay or physical stigmata of Fragile X, as well as individuals with a family history of mental retardation or Fragile X.
- Order Southern blot analysis to assess the number of trinucleotide repeats CGG to assess for premutation or full mutation. If the analysis shows premutation, monitor for premature ovarian failure and Fragile X Tremor/Ataxia Syndrome. If the analysis shows full mutation, monitor for mental retardation and autism spectrum disorders.
- Premutation and full mutation patients will need genetic counseling for manifestations and future risks and educational interventions. [3]

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Treatment

Bottom Line

- Stimulant medications are well established treatments for ADHD; however, if ADHD is associated with Fragile X, the stimulant medication may cause mood instability. SORT B[2]
- Educational interactions and therapies are the primary mode of treatment along with occupational and speech therapy. SORT C

Drug Therapy

- Folic acid therapy and L-Leucovorin 15mg/day have questionable benefits, but there are no major side effects noted. [4]
- Consider L-acetylcarnitine 20-50 mg/kg/day. This is the acetylated form of carnitine and is abundant in cerebral tissue. Its administration in patients with Fragile X and ADHD may reduce hyperactivity and improve learning.
- Methylphenidate is a well established stimulant for the treatment of ADHD. While it may improve irritability, anxiety, moodiness, and hyperactivity, there is an increase in motor tics, social isolation, and mood instability with outbursts.

Other Treatment

- Using a family network is the goal. A key family member is the first to tell relatives at risk, with follow up by a genetic counselor. [1]
- Reproductive alternatives are discussed including adoption, egg donation, foster care, or raising a fragile x child. [1]
- Psychiatrists may be consulted to assist in controlling behavior, such as temper tantrums, self injurious behavior, screaming, head banging, using a behavior modification technique.
- Depending on the degree of mental retardation, educational intervention therapy may be the main approach to maximizing their intellectual outcome, as well as social support.
- Speech therapy is indicated if there is speech delay.

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Prognosis

Bottom Line

- Patients with Fragile X can have a normal life expectancy. Comorbid conditions and behaviors may impact on this, such as the degree of mental retardation, degree of behavioral problems and the degree of self injurious behavior. SORT C
- With premutation, watch for tremor, gait ataxia and dementia after the age of 50 in males. SORT B
- In females less than 40, monitor for increased levels of FSH and premature ovarian failure. SORT B
- Low quality of life and high stress were the common concerns among the family unit, but the degree of child behavior problems accounted for the varying degrees of stress, depression, anxiety, and anger within the family. SORT C
- Prognosis for a stable home environment is decreased with comorbid autism or ADHD. SORT C

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Management of Special Populations

The Elderly

- In men over age 50 years with ataxia and tremor or women over 40 with premature ovarian failure, consider Fragile X premutations.

Pregnancy

- Reproductive counseling is recommended for female carriers of the Fragile X gene and affected males.

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References and Additional Resources

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Additional Resources

- National Fragile X Foundation [http://www.fragilex.org]
- FRAXA Research Foundation [http://www.fraxa.org]
- The Archs Q&A on Fragile X Syndrome [http://www.nichd.nih.gov/health/topics/fragile_x_syndrome.cfm]
- Your Genes your Health: Fragile X Syndrome [http://www.ygyh.org/fragx/whatisit.htm]

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Practice Guidelines

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