Chapter 10

Fragile X Syndrome: A Comprehensive Review of Etiology, Pathophysiology, and Management

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Abstract

Fragile X syndrome (FXS) is the most common inherited single-gene cause of intellectual disability and a significant genetic cause of autism spectrum disorder. The disorder shows variable expressivity and reduced penetrance, especially in females due to X-chromosome inactivation. Clinically, FXS is associated with intellectual disability, behavioral problems, anxiety, and autism-related features. Diagnosis is mainly performed using molecular genetic tests such as PCR and Southern blot analysis to detect CGG repeat expansion and methylation status.

Keywords: FMR1; Gene therapy, treatment, fragile X messenger ribonucleo protein (FMRP);

1. Introduction

Fragile X syndrome (FXS), also known as Martin-Bell syndrome in the past, is a non-Mendelian trinucleotide repeat disorder [1]. Fragile X syndrome (FXS) is the most common single-gene cause of inherited

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intellectual disability. FXS is caused by an expanded trinucleotide repeat (CGG) on the 5′ untranslated region of the fragile x mental retardation 1 (*FMR1*) gene. A normal range is between 6 and 44 repeats. Individuals with 45 to 54 repeats are considered to have a gray zone or intermediate expansion. Those with 55 to 200 repeats have the permutation, which is likely to become unstable in future generations. Affected individuals with the full mutation FXS have >200 repeats [3]. However, the biological mechanism responsible for the presentation of FXS is not fully understood. Approximately 30% of girls and 90% of boys with the full mutation have intellectual disability, and 60% of boys are diagnosed with autism spectrum disorder (ASD). Anxiety disorders occur in 70–80% of individuals with FXS [4]. FXS testing should be a consideration in the differential diagnosis of any individual with intellectual disabilities, impaired development, or autism of unknown etiology. In addition, all individuals older than 50 years with ataxia and tremors or females with premature ovarian insufficiency should be tested for this premutation. Molecular genetic tests, rather than cytogenetics, are now used to diagnose FXS. There is no cure for the disease, but early diagnosis and intervention can improve patients' and families' prognosis and quality of life and aid them in their future reproductive decisions[1]. Unfortunately, clinicians frequently do not diagnose this condition due to several factors, including similar clinical features as other syndromes, various presenting phenotypes, and frequent absence of clinical features at birth. Therefore, FXS is underdiagnosed, leading to suboptimal management and patient outcomes[9].

2. Etiology

FXS is an X-linked dominant condition with variable expressivity and reduced penetrance[5]. One reason is the differing number of CGG repeats in the *FMR1* gene in affected individuals. Those without the disorder have 5 to 44 CGG repeats. However, individuals with abnormal alleles are classified according to their expanded number of CGG repetitions[6]. Furthermore, due to X-inactivation in females and genetic anticipation, the inheritance of FXS does not follow standard X-linked dominant inheritance. Females with full FMR1 mutations have a milder phenotypic presentation than males, secondary to the protection provided by an additional unaffected X chromosome [6][7].

3. Epidemiology

FXS with a full mutation allele occurs in approximately 1 in 7000 males and 1 in 11,000 females; however, the exact frequency is unknown[10]. However, it is essential to note that the carrier frequency can vary greatly based on the diagnostic testing used and the population of interest, with specific populations showing significantly higher or lower disease prevalence[11-13]. For instance, the prevalence in Columbian males is reported to be 1 in 20, which is 343 times higher than the rest of the world[14].

4. Pathophysiology

FXS is indirectly the result of the expansion of the CGG triplet repeat within the fragile X mental retardation 1 gene (*FMR1*) located on the X chromosome, which silences *FMR1* expression[15]. This CGG expansion is due to abolished or greatly diminished fragile X mental retardation protein (FMRP) and is the direct cause of FXS**[16].** Point mutations or deletions may also be a cause of reduced functional

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FMRP[17]. FMRP is a master regulator that directs protein translation, impacting neuronal connections, synaptic plasticity, and ovarian functions[18].

5. Treatment

5.1 Supportive therapies

There is no cure for FXS; therefore, management primarily involves symptomatic treatment, including speech therapy, behavioral therapy, sensory integration, occupational therapy, and special education[15][22]. Furthermore, providing occupational therapy and tailored training for individuals affected by the condition can help them achieve greater independence, improve their self-care skills, and receive vocational training[14].

5.2 Pharmacologic therapies

Medications used for symptom-based treatment aim to minimize some behavioral and mental health challenges associated with FXS. Stimulants may target hyperactivity, impulsivity, and attention issues. Antidepressants (eg, bupropion, buspirone, or selective serotonin and norepinephrine reuptake inhibitors) may treat anxiety, obsessive-compulsive behaviors, and mood disorders. Drugs targeting the metabotropic glutamate receptors linked with synaptic plasticity have been demonstrated to be particularly beneficial[14]. Adverse effects specific to the FXS population may occur with most of the abovementioned agents. Therefore, medication management is best done by the practitioner's familiarity with the drug and the FXS population[14].

6. Differential diagnosis

Differential diagnoses to be considered in cases of suspected FXS include [1]:

- Sotos syndrome
- Prader-Willi syndrome
- Klinefelter syndrome
- Rett syndrome
- Trisomy 21
- Metabolic disorder
- Autism

7. Search Terms and Inclusion/Exclusion Criteria by Topic Area

Topic Area	Search Terms	Search Dates	Other Search Criteria
Full mutation phenotype	Fragile X syndrome, fragile X–associated disorders, fragile X premutation, fragile X carrier, fragile X–associated tremor/ataxia syndrome, or fragile X–associated primary ovarian insufficiency and phenotype, clinical presentation, description, neurocognitive, cognitive, behaviour, social-emotional, or language, communication	2008–2014	English language Human United States only
Developmental trajectories across the life span	Fragile X syndrome or fragile X and lifespan, developmental, longitudinal, adolescent, adult, services, or transition to adulthood	1991–2014	English language Human

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Topic Area	Search Terms	Search Dates	Other Search Criteria
Available interventions and treatments	Fragile X syndrome or fragile X and treatment, intervention, pharmacological, educational, behavioral, medication, or clinical trial	1991–2014	English language Human
Impact on family	Fragile X syndrome or fragile X and family adaptation, family impact, family outcomes, burden, or cost of care	1991–2014	English language Human United States only

8. Conclusion

Despite the progress in many areas of FXS research, work remains to address gaps in clinical and public health knowledge. We pose 3 main areas of focused research, including early detection and diagnosis, determinants of health, and development and implementation of targeted

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