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A STUDENT'S PERSPECTIVE: FRAGILE-X SYNDROME- COMMON INTELLECTUAL DISABILITY WITH GENETIC INHERITANCE

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ABSTRACT
The most prevalent inherited cause of intellectual impairment (ID) and the most prevalent monogenic cause of autism spectrum disorder (ASD) globally is fragile X syndrome (FXS), an X-linked genetic condition [1], [2]. In the 5′ untranslated region of the FMR1 gene on the X chromosome (Xq27.3), a CGG trinucleotide repeat expansion of more than 200 copies causes FXS. This expansion results in hypermethylation, transcriptional silencing, and loss of the FMR1 protein (FMRP), an RNA-binding protein necessary for synaptic development and plasticity [3], [4]. Using peer-reviewed materials published between 1991 and 2024, this review summarizes the most recent research on the genetics, epidemiology, clinical presentation, diagnosis, and treatment of FXS.

KEYWORDS: Fragile X syndrome; FMR1 gene; CGG trinucleotide repeat expansion; FMRP; intellectual disability; autism spectrum disorder; X-linked genetic disorder; genetic diagnosis; hypermethylation; clinical manifestations; epidemiology; molecular genetics; genetic counseling; targeted therapy.

INTRODUCTION

Fragile X syndrome (FXS) is the most often identified single-gene disorder among the inherited causes of intellectual impairment, which affects approximately 1-3% of the general population. It is the second most common cause of ID overall, after Down syndrome [2]. In 1943, Martin and Bell clinically diagnosed FXS as an X-linked pattern of familial mental deficit. However, it wasn't until 1991 that Verkerk and colleagues discovered the causal CGG repeat expansion inside the FMR1 gene [5].

An unstable expansion of a CGG trinucleotide repeat sequence in the 5′ untranslated region of FMR1, at Xq27.3, is the source of the condition. The area becomes hypermethylated, FMR1 transcription is suppressed, and the encoded protein, FMRP, is either absent or significantly decreased when the repeat surpasses about 200 copies (the "full mutation") [3], [6]. When FMRP is absent, synaptic pruning and plasticity are disrupted, resulting in the cognitive, behavioral, and physical characteristics of FXS [4]. FMRP normally binds several neuronal mRNAs and controls their transport and local translation at synapses.

Due to the X-linked nature of FXS, males with a single X chromosome are frequently more severely affected than females, who normally have one normal FMR1 allele on their second X chromosome [6]. Smaller CGG expansions in the premutation range (55–200 repeats) beyond the full mutation do not cause FXS, but they are linked to a unique group of later-onset conditions known as Fragile X premutation-associated conditions (FXPAC), which include FXTAS (fragile X-associated tremor/ataxia syndrome), FXPOI (fragile X-associated primary ovarian insufficiency), and FXAND (FXTAS) [1].

Because FXS demonstrates several fundamental concepts of human molecular genetics in a single disorder—trinucleotide repeat instability, genomic imprinting-like epigenetic silencing via DNA methylation, X-linked inheritance with variable penetrance, and the translation of a single-gene defect into a complex, multisystem clinical phenotype—understanding it is especially important for students studying genetics, physiology, and clinical medicine.

2. Objectives

This review's particular goals are to:

- Explain the pathophysiological process and molecular genetics of fragile X syndrome.
- Provide an overview of the prevalence and global epidemiology of FMR1 premutation alleles and FXS.
- Describe the main physical, behavioral, cognitive, and clinical characteristics of FXS throughout the course of a lifetime.
- Examine current methods for molecular and clinical diagnosis, including screening guidelines.
- Assess new targeted therapeutics as well as current pharmaceutical and non-pharmacological management techniques.

- Point out gaps in the literature, such as the underrepresentation of middle- and low-income areas in FXS studies.

3. Materials and Method / Work Plan

As is appropriate for a topic requiring synthesis of current genetic, clinical, and epidemiological information, this paper employs a narrative literature-review design as opposed to a laboratory-based experimental protocol.

3.1 Search strategy

PubMed/MEDLINE, PubMed Central (PMC), and ScienceDirect were searched systematically for literature published between 1991 (the year FMR1 was found) and 2024. Combinations of "Fragile X syndrome," "FMR1," "FMRP," "CGG repeat," "intellectual disability," "premutation," "FXTAS," "FXPOI," and "targeted treatment" were among the search phrases used.

3.2 Inclusion and exclusion criteria

- **Included:** important clinical practice reviews, systematic reviews, meta-analyses, and peer-reviewed original research publications that discuss the genetics, epidemiology, clinical characteristics, diagnosis, or treatment of FXS or FMR1 premutation disorders.
- Articles not available in English, opinion pieces without primary data, and non-peer-reviewed sources were excluded.

3.3 Data synthesis

Prevalence estimates, CGG repeat classifications, clinical checklist items, and treatment outcomes are among the pertinent data that were taken from each source and arranged thematically under the headings of genetics, epidemiology, clinical features, diagnosis, and management. These data are then narratively presented in the Results and Discussion sections that follow. No new patient data was gathered, no human or animal subjects were used, and institutional ethical approval was not necessary for this investigation.

4. RESULTS

4.1 Epidemiology

The prevalence of the FXS complete mutation is estimated to be 1 in 5,000–7,000 males and 1 in 4,000–8,000 females globally based on pooled estimates from a major systematic review and meta-analysis [2], [6]. With an estimated 1 in 250–800 males and 1 in 110–270 females affected, the premutation is much more prevalent [2]. Regional studies among people with intellectual disabilities in South Africa, Egypt, and Nigeria reported significantly higher detection rates of 4–7%, indicating that FXS may be underrecognized outside of North America and Europe due to limited awareness, diagnostic infrastructure, and genetic testing access [7]. Newborn screening programs in the United States and Canada found full-mutation rates of roughly 1 in 5,161 and 1 in 6,209 males, respectively.

4.2 Molecular genetics

At Xq27.3, the FMR1 gene is around 38 kb long and has 17 exons. It contains a polymorphism CGG trinucleotide repeat in its 5′ untranslated region. This repeat is stably transmitted at 6–44 copies in the general population. The premutation, which carries elevated but translatable FMR1 mRNA, is represented by repeats of 55–200 copies; the full mutation, which causes hypermethylation of the promoter region, transcriptional silencing, and loss of FMRP, is represented by expansions beyond 200 copies [3], [6]. Repeats of 45–54 copies form a "intermediate" or grey-zone allele that may become unstable across generations. These allele classes are summarized in Table 1.

Table 1. Classification of FMR1 CGG repeat alleles and associated phenotypes [1], [6]

Allele class	CGG repeat number	FMR1 gene status	Typical phenotype
Common / normal	6 – 44	Stable, fully active	Unaffected
Intermediate (grey zone)	45 – 54	Mildly unstable	Unaffected; may expand across generations
Premutation	55 – 200	Unstable; elevated FMR1 mRNA	Usually normal cognition; risk of FXTAS, FXPOI, FXAND
Full mutation	>200	Hypermethylated, transcriptionally silenced	Fragile X syndrome (loss of FMRP)

4.3 Clinical features

The cognitive, behavioral, and physical aspects comprise the clinical phenotype of FXS, which varies significantly depending on the degree of mosaicism and sex. In terms of cognition, affected males usually exhibit moderate to severe intellectual disability, but affected females, who still have one normal FMR1 allele, exhibit a more diverse picture, ranging from normal intelligence to mild or moderate cognitive disability, depending on the X-inactivation ratio [6], [7].

Attention-deficit/hyperactivity disorder, anxiety, sensory hypersensitivity, gaze avoidance, hand-flapping and hand-biting, and autistic spectrum traits are prevalent in behavior; up to 50–60% of boys with FXS fit the diagnostic criteria for ASD [4]. Although 30–40% of young children may not yet exhibit typical dysmorphology, physical characteristics become more noticeable after puberty and typically include an elongated face, prominent or huge ears, macroorchidism (enlarged testicles), hyperextensible finger joints, and soft, velvety skin [7]. Recurrent otitis media (associated with collapsing Eustachian tubes), seizures in approximately 10–15% of people, hypotonia, strabismus, and joint issues connected to connective tissue are examples of medical comorbidities [2], [7].

Clinical checklists, which were initially created by Hagerman and associates in 1991 and later modified for various demographics, combine behavioral and physical characteristics (such as intellectual disability, hyperactivity, poor eye contact, hand flapping, large ears, macroorchidism, hyperextensible joints, and family history of ID) to identify people who need molecular testing, especially in low-resource environments where genetic testing is not easily available [7].

4.4 Diagnosis

Molecular genetic testing of the FMR1 CGG repeat is necessary for a definitive diagnosis of FXS. This is often accomplished by combining Southern blot analysis with polymerase chain reaction (PCR), which together assess repeat length and methylation status [2]. Southern blot is crucial for verifying methylation-based silencing since PCR alone may effectively size normal, intermediate, and premutation alleles but may perform poorly for very big complete mutations. In addition to at-risk family found thru cascade testing once a proband is diagnosed, testing is advised for people who present with unexplained intellectual disability, developmental delay, or autistic spectrum disorder [2].

Fig.1 shows one Frag-X positive case observed is compiled below showing characteristic facial features and > than 200 CGG repeats found by molecular testing. The pedigree chart of the family is shown indicating the patient as a youngest boy, having elder brother who has not been tested so far for Frag-X diagnosis. However, when a mother was tested for CGG repeats, she was found to be a carrier having 92 CGG repeats indicating premutation carrier state as explained in Table-1.

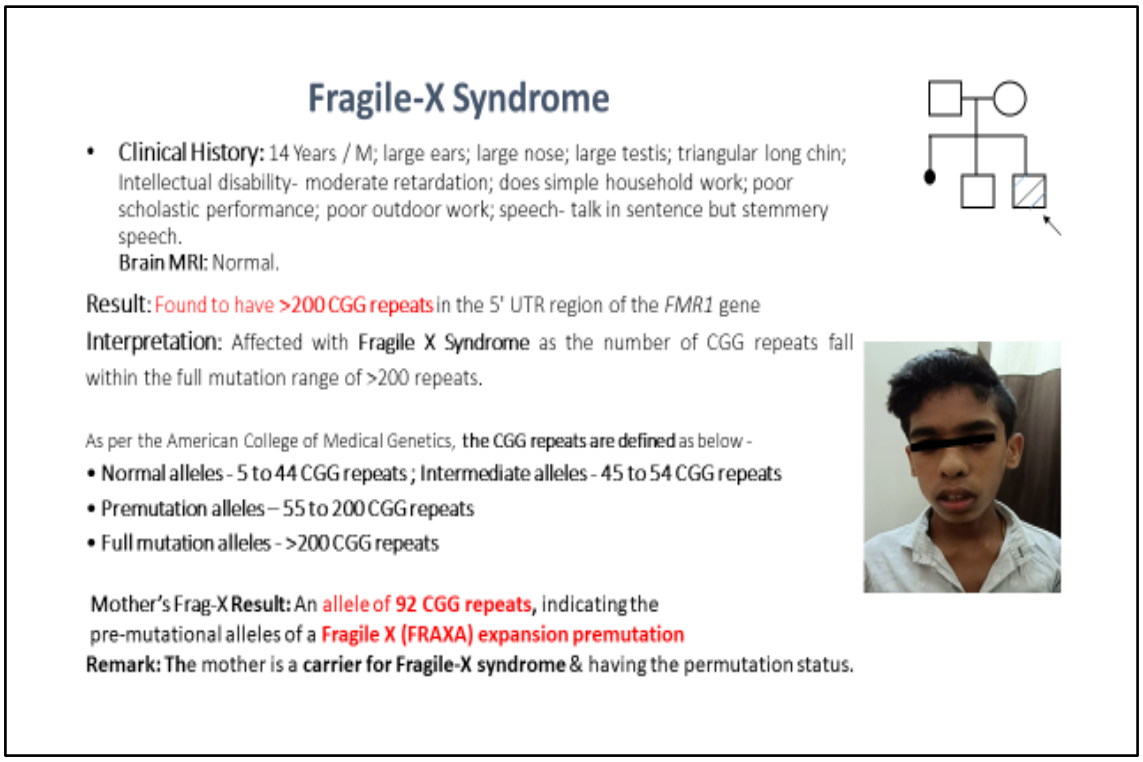

Fig.1-

4.5 Management

FXS currently has no known cure; treatment is multidisciplinary and focused on symptoms. The cornerstone of care is non-pharmacological interventions, such as early speech and language therapy, occupational therapy, physical therapy, and organized special education programs, which work best when started early in childhood [4]. Instead of addressing the underlying molecular defect, pharmacological treatment focuses on specific behavioral and medical symptoms. For example, stimulants and guanfacine are used to treat attention and hyperactivity; selective serotonin reuptake inhibitors (SSRIs) like low-dose sertraline are used to treat anxiety; atypical antipsychotics (like aripiprazole and risperidone) are used to treat aggression; and levetiracetam is used to treat seizures [7]. A number of mechanism-based, "targeted" treatments, such as metformin (which reduces elevated

mTOR pathway activity), cannabidiol, and the PDE4D inhibitor BPN14770, are currently in clinical trials due to growing knowledge of FMRP's downstream signaling pathways [4], [7]. Early-phase trials have shown improvements in cognitive and behavioral outcome measures.

5. DISCUSSION

FXS is a prime illustration of how a single trinucleotide repeat expansion can result in a complicated, multisystem neurodevelopmental illness via an epigenetic silencing mechanism rather than a structural protein deficiency, according to the literature reviewed here. This sets FXS apart from many other monogenic causes of ID and accounts for a number of its more peculiar genetic characteristics, including the anticipation phenomenon, in which premutation alleles expand preferentially during maternal transmission, and the significant sex-based variation in severity resulting from X-inactivation mosaicism in carrier females [3], [6].

The gap between the biological understanding of FXS and the availability of disease-modifying medication is a recurrent subject in all of the studied publications. Despite more than 20 years of characterization of FMRP's function in controlling synaptic mRNA translation, therapies are still primarily symptomatic and no cure is available. Larger phase 3 trials are still needed to confirm efficacy and methylation-dependent response patterns, and while the recent emergence of mechanism-based candidates like metformin and BPN14770 is encouraging, none have yet received regulatory approval as a disease-modifying therapy, as several reviews point out [4], [7].

The epidemiological data also reveal a substantial research and equity gap: the majority of large-scale prevalence and treatment studies come from North America, Europe, and Australia, whereas sub-Saharan Africa and parts of Asia report similar or higher detection rates among people with intellectual disabilities but have significantly less access to genetic testing, specialized care, and healthcare provider awareness [7]. This implies that the full burden of FXS may be underestimated by global prevalence statistics, and that funding for easily accessible and reasonably priced molecular diagnostic techniques should be a top priority for global health equality in genetic medicine.

From an educational standpoint, FXS also serves as an instructive case study connecting classical genetics (X-linked inheritance, variable expressivity) with modern molecular biology (epigenetic regulation, RNA-binding proteins, and translational neuroscience), making it a valuable model for undergraduate teaching of the genotype–phenotype relationship in neurodevelopmental disease.

Newborn screening of FXS is another alternative but effective approach to reduce the birth of FXS children and thereby reducing the “national intellectual burden”. The carrier screening of pregnant mothers or girls in the reproductive age could also be another way of reducing intellectual disability in the population till the curable therapy is available.

6. CONCLUSION

The most prevalent hereditary cause of intellectual disability and the most well-known monogenic cause of autism spectrum disorder is still fragile X syndrome with no cure available so far. It results from an amplification of the CGG trinucleotide repeat in FMR1, which silences the gene and removes FMRP, a protein necessary for proper synaptic activity. Although molecular diagnostic methods enable precise identification of carriers and affected individuals, current treatment is primarily symptomatic and combines pharmaceutical, behavioral, and educational strategies. Although there is currently no disease-modifying medication, ongoing research into FMRP's downstream signaling pathways has yielded numerous intriguing targeted treatments. The best ways to improve outcomes for people with FXS today are still multidisciplinary intervention, early detection, and ongoing research, especially to eliminate worldwide disparities in diagnostic and care access. The newborn screening for FXS and prenatal carrier screening could still be effective preventive approach to reduce the socioeconomic burden of this genetic condition.

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