FMR1 Key Biomarker in Fragile X Syndrome- A Comprehensive Review

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ABSTRACT

Fragile X Syndrome (FXS) is a complicated neurodevelopmental condition that causes intellectual disabilities, behavioural issues, and a variety of physical symptoms. Central to understanding FXS is the Fragile X Mental Retardation 1 (FMR1) gene, pivotal in the disorder's pathogenesis. This review examines FMR1 as a key biomarker in FXS, drawing on recent research insights. The FMR1 gene, situated on the X chromosome, encodes the fragile X mental retardation protein (FMRP), which is essential for synaptic function and brain development. Mutations in FMR1, including CGG repeat expansions, cause FXS, resulting in cognitive and behavioural impairments. Advances in molecular genetics elucidate FMR1 dysfunction and its roles in FXS phenotypes. DNA testing for FMR1 mutations is used in diagnostic techniques, which is critical for accurate diagnosis and genetic counselling. FMR1 serves as a biomarker for disease monitoring and treatment evaluation. Emerging therapies targeting FMR1-related pathways offer promise for FXS intervention, highlighting FMR1 as a therapeutic target. Understanding FMR1's roles in FXS pathophysiology informs precision medicine approaches. Elucidating FXS's molecular basis and leveraging FMR1 as a biomarker aim to advance diagnostics, refine therapies, and improve outcomes. This review underscores FMR1's pivotal role in FXS research and clinical practice, emphasizing its potential as a key biomarker for guiding precision medicine interventions.

Keywords: Fragile X Syndrome, FMR1 (Fragile X Mental Retardation 1) gene, Biomarker, Neurodevelopmental disorder, Precision medicine

INTRODUCTION

Fragile X syndrome (FXS), recognized as the most prevalent form of hereditary intellectual disability and a monogenic etiology of autism spectrum disorders, primarily arises from the amplification of CGG trinucleotide repeats within the 5′ untranslated region of the FMR1 gene [1]. Current estimates indicate that FXS afflicts approximately 1 in every 2,500 to 5,000 males and 1 in every 4,000 to 6,000 females. Males affected by this condition exhibit a spectrum of symptoms ranging from mild to severe. Due to the compensatory effects of the unaffected X chromosome, only one-third of female carriers possessing a full mutation (FM) exhibit intellectual disability; the majority maintain normal intellectual quotient, although they frequently encounter learning difficulties and emotional challenges [2]. In exceedingly rare instances, constituting less than 1%, FXS may manifest due to alternative defects that result in the loss of gene function, such as deletions or point mutations. The FMR1 gene is responsible for coding the fragile X mental retardation protein (FMRP); hence, the silencing of this gene culminates in the abrogation of protein expression. FMRP functions as an RNA-binding protein that participates in multiple processes, including neuronal plasticity and the operation of neuronal networks. Individuals in good health typically exhibit fewer than 45 CGG repeats. An expansion to 46–54 repeats is classified as the gray zone, while individuals with 55–200 repeats are designated as having the premutation (PM) [3]. Carriers of the PM may present with various conditions, such as fragile X-associated primary ovarian insufficiency (FXPOI) in females, and neuropsychiatric disorders including anxiety and depression, which have recently been identified as fragile X-associated neuropsychiatric

disorders (FXAND) along with fragile X-associated tremor/ataxia syndrome (FXTAS). This review shall concentrate on FXTAS, a movement disorder characterized by tremor and/or ataxia, cognitive impairment, neuropathy, and autonomic dysfunction in individuals possessing the PM [4]. Taking into account the X-linked nature of the mutation, males frequently exhibit more pronounced clinical manifestations than females [4]. FMRP is regarded as the most significant biomarker for FXS, as it serves to identify individuals with fragile X syndrome and to predict, to a certain extent, their cognitive capabilities [5].

ETIOLOGY

FXS is caused by loss of-function mutation of FMR1 gene, located in Xq27.3, which corresponds to the position of the folate-sensitive fragile site FRAXA observed cytogenetically in affected males. The gene contains 17 exons spanning 38 kb with a CpG island and an unstable CGG repeat sequence in the upstream promoter region and it encodes an RNA binding protein. In normal population this triplet is composed of 5–55 repeats, allowing transcription and translation of the gene; within this size range the gene is transmitted stably over generations. When the CGG repeat stretches from 56 and 200 (premutation), the gene continues to produce (additional) messenger RNA, while the premutated repeat becomes meiotically unstable. [6]. The presence of AGG interruptions within the repeat region seems to stabilize the trinucleotide repeat, while their absence results in increased size variability upon meiotic transmissions. Although premutation carriers do not have FXS, the significantly increased transcription of FMR1 mRNA sometimes results in a gain-of-function phenotype associated with early menopause in women and with a tremor-ataxia neurodegenerative syndrome in male. The localisation of the brain-expressed FMR-7 gene to this EcoRl segment shows that this gene is involved in the phenotypic expression of Fragile X syndrome [7].

STRUCTURE OF FMR1 GENE

The FMR1 gene, which becomes inactivated due to the methylated CGG expansion in individuals affected by fragile X syndrome, encompasses approximately 40 kilobases and comprises 17 exons, encoding a messenger RNA of 3.9 kilobases and structure of FMR1 gene are shown in figure 1. The CGG repeat is situated within the initial exon, corresponding to the 58 untranslated region. This sequence is an integral component of the CpG island that extends upstream of the transcription initiation site and is instrumental in the expression of FMR1. The transcript of the FMR1 gene undergoes alternative splicing, which influences the inclusion of exons 12 and 14 and the selection of acceptor sites within exons 15 and 17 [8]. The protein encompasses various domains, including the RNA-binding domains KH and RGG box, as well as nuclear localization and nuclear export signals (NLS and NES), which facilitate its transport between the nucleus and cytoplasm [9]. Typically, premutation alleles remain unmethylated and yield normal levels of FMRP [10]. Females with premutation alleles have demonstrated a greater likelihood of being diagnosed or treated for attention-related issues, anxiety, depression, and developmental delays [11]. FMRP is the protein encoded by the FMR1 gene; it serves as the principal regulatory protein for the translation of numerous RNAs implicated in synaptic plasticity [12]. The observed reduction in FMRP levels, despite an elevation in mRNA, indicates that the increased levels of FMR1 may signify a feedback mechanism responding to impaired translation, which results in a deficit of FMRP [13]. The interaction of FMRP with ribosomes is contingent upon mRNA through large ribonucleoprotein (RNP) particles, which comprise several additional proteins, including FXR1P and FXR2P, nucleolin, YB-1, NUFIP1, CYFIP1, and CYFIP2 [14]. The absence of the 4.4 kilobase FMR1 transcript in the majority of fragile X patients (2), the evident scarcity of other genes both proximal and distal to the FRAX(A) locus (10), and the recent identification of fragile X patients with FMR1 deletions and a point mutation unequivocally establish FMR1 as playing a crucial role in the syndrome [15].

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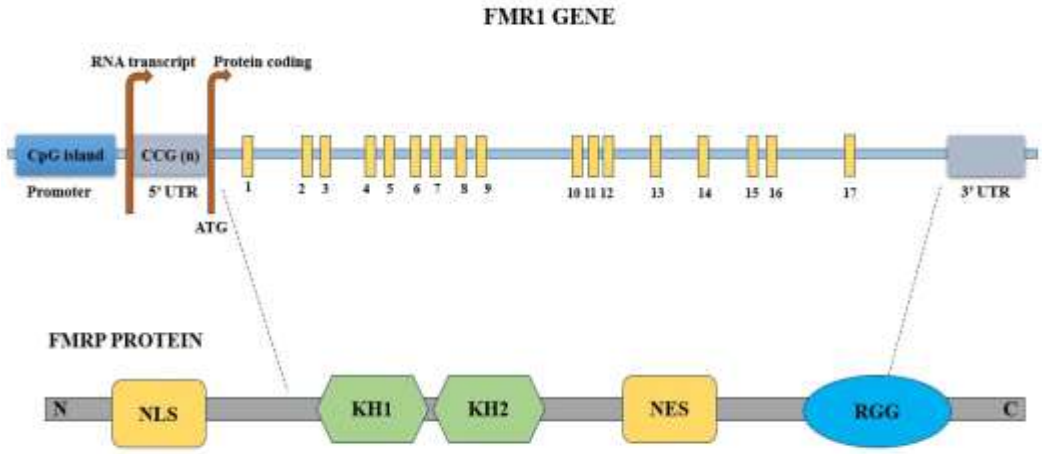

Fig 1: Structure of FMR1 gene

CLINICAL PRESENTATION OF FRAGILE-X SYNDROME

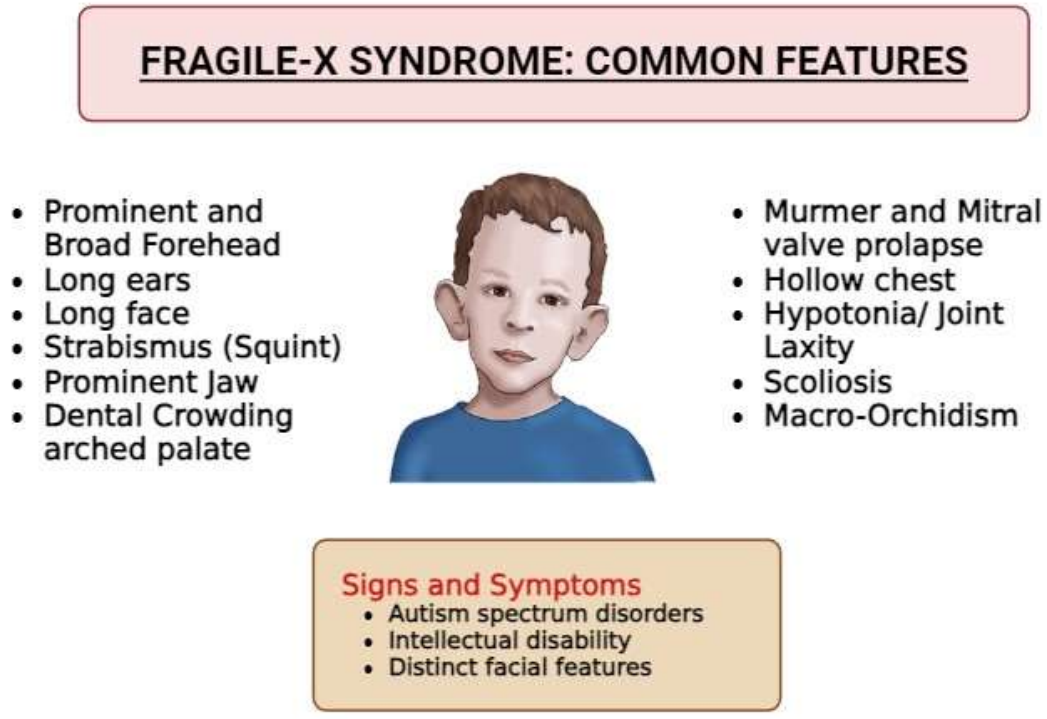

Fig 2: Clinical presentation of Fragile-X Syndrome

The prevalent characteristics encompass an elongated facial structure, prominent auricles, lax connective tissue, and enlarged testes, which become evident post-puberty [16]. Movement

disorders are frequently observed in Fragile X syndrome, primarily manifesting as stereotypical behaviors, such as hand flapping [17]. Fragile X syndrome ought to be considered in a male exhibiting developmental delays and hypotonia during early childhood. Cognitive impairments often lead to moderate-to-severe intellectual disability; the mean IQ is estimated to be around 40 in an adult male possessing a fully methylated full mutation [18]. Sleep disturbances are commonly reported among children diagnosed with attention-deficit hyperactivity disorder (ADHD) [19]. Females diagnosed with Fragile X syndrome (FXS) may exhibit considerable physical, neuropsychological, and emotional involvement [20]. Carriers of the Fragile X premutation experience the cessation of menstruation prior to the age of 40 years more frequently than their noncarrier counterparts or control women, when all women over the age of 21 years are taken into account [21]. Individuals diagnosed with FXS exhibit a broad spectrum of anxiety symptoms that align with various anxiety disorders as classified by the Diagnostic and Statistical Manual IV (DSM IV) [22]. Those affected by the full mutation of the FMR1 gene present distinct phenotypic traits, which include an elongated facial structure, large and prominent ears, joint hypermobility, and macroorchidism. Over 90% of affected children experience developmental delays, and approximately 50-60% receive a diagnosis of autism spectrum disorder (ASD) [23]. Gender differences undoubtedly influence the severity of the FXS phenotype; indeed, intellectual and developmental disabilities are observed in 85% of males, whereas only 25% of females are similarly affected [24]. Clinical presentations of Fragile-X Syndrome are shown in figure 2.

PATHOGENESIS

FXS represents the most prevalent variant of heritable intellectual disability (ID) and the monogenic etiology of autism spectrum disorder (ASD). The estimated prevalence of FXS is approximately 1 in 5000 males and 1 in 8000 females [23]. This condition is attributed to the full mutation (FM) of the FMR1 gene, which is characterized by the excessive amplification

of CGG trinucleotide repeats (≥ 200) within the 5' untranslated region (UTR) of the gene. These expanded CGG triplet repeats undergo hypermethylation, resulting in transcriptional gene silencing, thereby inhibiting gene expression and leading to a diminished or absent production of FMRP. While this phenomenon is regarded as the primary etiology of FXS, numerous molecular mechanisms involving FMRP and the physiological ramifications manifesting as FXS remain to be elucidated [24]. It is widely acknowledged that mild to moderately reduced levels of FMRP correlate with less severe manifestations, such as moderate emotional dysregulation and learning challenges, frequently accompanied by a normal IQ, as observed in certain females with FXS. Insufficient levels of FMRP or the absence of its synthesis are linked to more severe manifestations of ID, as commonly seen in males with FXS. The quantity of CGG trinucleotide repeats escalates with each subsequent generation, transitioning from premutation in females (PM; 55–200 repeats) to a full mutation in their progeny [25]. For PM alleles comprising more than 99 CGG repeats, the probability of transitioning from PM to FM approaches 100%. Individuals exhibiting PM typically possess a normal IQ, although it is noted that female PM carriers harbour a significant likelihood of bearing a child with FXS. Furthermore, it has been demonstrated that neurons with PM experience premature cell death in vitro, displaying increased sensitivity to toxins. For instance, these neurons exhibit heightened vulnerability to environmental toxins such as alcohol and pesticides, resulting in a greater propensity for cell death in culture. The "gray zone" or intermediate alleles of the FMR1 gene (45–54 CGG repeats) may be regarded as precursors to PM alleles. The propensity for trinucleotide repeats to expand across generations accounts for the designation of this genetic alteration as a 'dynamic mutation' [25,26]. Illustrations of the pathogenesis of Fragile X Syndrome are shown in figure 3.

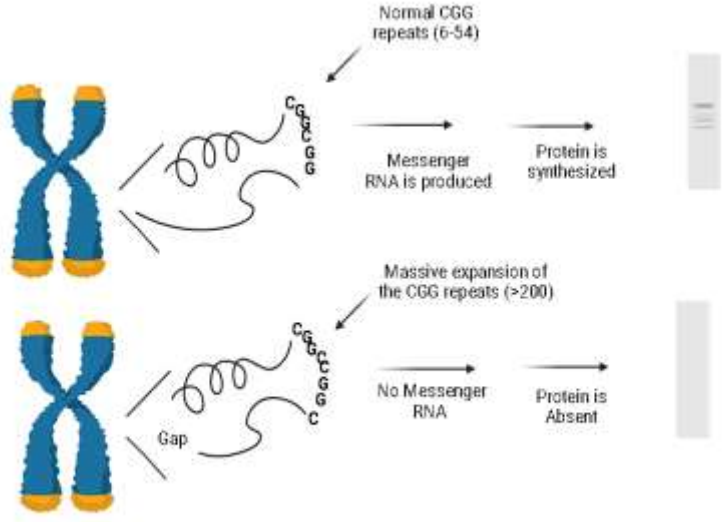

Figure 3: Illustration of the Pathogenesis of Fragile X Syndrome.

DIAGNOSIS

DNA analysis is regarded as the most suitable methodology for the assessment of Fragile X Syndrome (FXS) and the associated trinucleotide repeat expansion within the FMR1 gene. It is imperative in instances of isolated cognitive impairment, wherein DNA analysis ought to be incorporated into an exhaustive genetic evaluation, which should also encompass routine cytogenetic analysis. This necessity arises from the fact that constitutional chromosome abnormalities are frequently identified, if not more so, than fragile X mutations in individuals with mental impairments who are referred for fragile X testing. For individuals possessing a familial background of FXS, DNA testing in isolation is adequate. Prenatal testing should be extended to known carrier mothers to ascertain the fetal FMR1 gene status, ideally through amniocentesis conducted after 15 weeks' gestation. Although DNA testing can be conducted on chorionic villi procured by CVS at 10 to 12 weeks' gestation, prudence is advised due to the potential absence of established methylation status in chorionic villi samples, necessitating subsequent amniocentesis to clarify ambiguous results [23,26].

Recent advancements in the domain of molecular diagnosis have revolutionized the diagnostic process for FXS since the identification of the FMR1 gene in 1991. Previously, the preferred diagnostic approach for FXS involved culturing cells in a folate-deficient medium followed by cytogenetic analysis; however, this method faced limitations, particularly regarding the visualization of fragile sites on the X chromosome, especially in females. As time has progressed, research has shifted towards more sensitive molecular methodologies, predominantly polymerase chain reaction (PCR)-based techniques. The diagnosis of FXS entails the measurement of CGG repeat size and the evaluation of FMR1 gene methylation status employing PCR-based methods. These advancements have markedly improved diagnostic precision and facilitated the development of more effective management strategies for FXS [26,27].

The evaluation of the risk associated with Fragile X Syndrome (FXS) necessitates an assessment of the presence of mutations within the Fragile X Mental Retardation 1 (FMR1) gene. This evaluation is critical for identifying individuals who are at risk of either developing FXS or carrying the mutated gene, thereby informing suitable management strategies. Typically, risk assessment commences with a comprehensive genetic evaluation that includes an analysis of family history and diagnostic testing for FXS. DNA analysis serves as the principal method for detecting trinucleotide repeat expansions in the FMR1 gene, with PCR-based techniques being favored due to their enhanced sensitivity and specificity [27, 28].

Individuals possessing a familial history of FXS or exhibiting symptoms indicative of the condition, such as developmental delay, intellectual disability, or behavioral challenges, may be subjected to genetic testing to either confirm or exclude the presence of FXS. Prenatal testing may likewise be proposed to pregnant women with a family history of FXS or established carrier status to evaluate the risk of transmitting the mutated gene to their

progeny. Furthermore, genetic counseling assumes a vital role in risk assessment by equipping individuals and families with pertinent information regarding the inheritance pattern of FXS, the probability of transmitting the mutated gene to subsequent generations, and the available testing and management alternatives. Counseling sessions also address the psychosocial ramifications of FXS on individuals and families, assisting them in making informed decisions concerning family planning and reproductive options [28].

TREATMENT

Pharmacological Therapy

Pharmacological intervention for Fragile X Syndrome (FXS) encompasses a diverse array of pharmacological agents aimed at addressing various symptoms and underlying mechanisms associated with the disorder. Sertraline, a selective serotonin reuptake inhibitor (SSRI), is frequently prescribed to mitigate anxiety manifestations in individuals diagnosed with FXS, with treatment often commencing as early as the second or third year of life. The justification for its utilization is rooted in the documented serotonin deficiencies observed in the cerebral structures of young children with autism spectrum disorders (ASD), including FXS. Research has indicated a downregulation of enzymes responsible for synthesizing serotonin from tryptophan in ASD, thereby reinforcing the potential effectiveness of sertraline as a targeted intervention for anxiety related to FXS [22,28]. Metformin, a biguanide antihyperglycemic agent primarily indicated for the management of type 2 diabetes mellitus (DM) and weight reduction, has surfaced as a promising therapeutic alternative for FXS. Its mechanism of action encompasses both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent pathways. Despite its primary indication for type 2 DM, the mechanisms of metformin may possess broader implications for the symptomatology associated with FXS [23,25]. Acamprosate, which is sanctioned for the maintenance of alcohol abstinence, has

attracted attention for its potential impact on glutamate and GABA neurotransmission. While its precise mechanism remains partially elucidated, it is postulated to modulate multiple receptors, potentially including mGluR5 antagonism. Acamprosate is proposed as a preferred targeted intervention for individuals with FXS who also experience comorbid alcohol dependence [27,28].

Investigations suggest that lovastatin, an HMG-CoA reductase inhibitor utilized in the treatment of hyperlipidemia, may possess therapeutic relevance for FXS. It acts by inhibiting the RAS-MAPK-ERK1/2 activation pathway, normalizing protein synthesis, and potentially averting epileptogenesis in animal models of FXS [24,28]. Minocycline, an antibiotic predominantly prescribed for acne, has been explored for its potential in the treatment of FXS. It inhibits the activity of MMP-9, which is elevated due to FMRP deficiency in FXS, consequently enhancing synaptic connectivity and ameliorating cognitive deficits in animal models [28]. Oxytocin, a neuropeptide with multifaceted effects, has demonstrated promise in enhancing social communication skills across various disorders, including FXS. Intranasal administration of oxytocin modulates GABAergic neurotransmission, thereby contributing to its therapeutic influence on social behavior and anxiety [29]. These pharmacological interventions embody a diverse spectrum of treatment modalities aimed at addressing distinct facets of FXS pathology, thereby providing optimism for improved symptom management and quality of life among individuals afflicted with FXS.

Non-Pharmacological therapy

Non-pharmacological therapy (shown in figure 4) plays a pivotal role in enhancing the quality of life for individuals with Fragile X Syndrome (FXS), focusing on addressing behavioral and cognitive characteristics through various interventions. Drawing from strategies commonly employed in intellectual disability (ID) and autism populations,

environmental and behavioral approaches are tailored to suit the unique needs of individuals with FXS. These encompass a range of interventions, including psychological evaluations and interventions such as positive behavioral support, functional behavioral analyses, relaxation training, and desensitization techniques to target specific phobias. Additionally, speech and language therapy is utilized to provide communication supports, while occupational therapy focuses on sensory assessments, treatments, and establishing daily structures to enhance functional abilities. Social and welfare support, along with special educational interventions and vocational guidance, further contribute to comprehensive care. However, while non-pharmacological interventions form the cornerstone of FXS management, the judicious use of medications may complement these approaches, albeit with limited understanding of their efficacy in this population. Selective serotonin reuptake inhibitors (SSRIs) are sometimes prescribed to manage anxiety symptoms, while methylphenidate may be used to address attention deficits, particularly in young males with FXS, though further research is required to establish their effectiveness definitively [24,30].

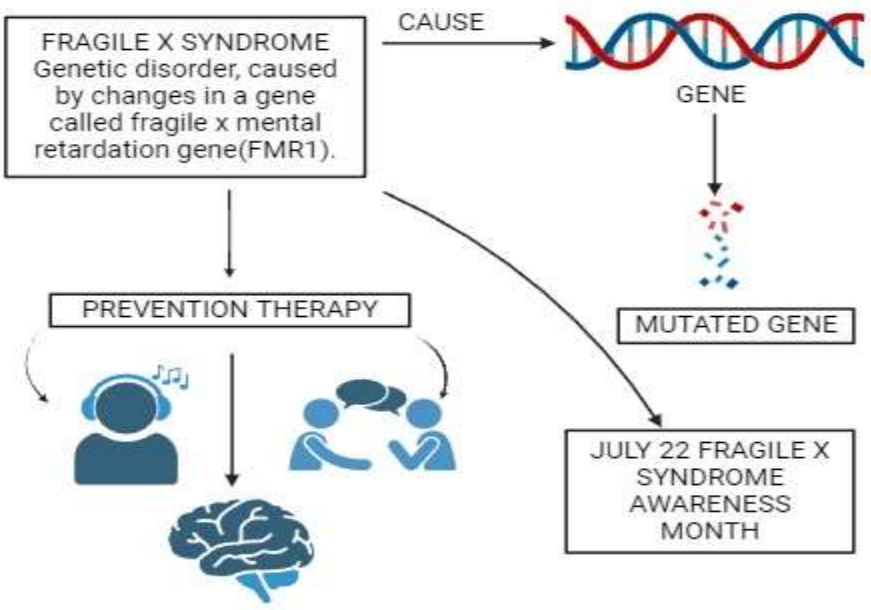

Fig 4: Non-pharmacological therapy of Fragile X Syndrome

CURRENT ADVANCEMENTS IN TARGETING FMR1 IN FRAGILE-X SYNDROME

Fragile X Syndrome (FXS) research is currently undergoing a rapid evolution, which is contributing significantly to the advancement of potential therapeutic interventions for individuals who are affected by this complex genetic condition; this progress is being driven by innovative methodologies that specifically target the deficiency of the Fragile X Mental Retardation Protein (FMRP) that results from a mutation located within the FMR1 gene [1]. Gene therapy strategies, which encompass both gene augmentation techniques as well as gene editing methodologies such as CRISPR-Cas9, are designed with the primary goal of directly tackling the fundamental causes of FXS by enhancing the production of FMRP and rectifying the underlying genetic mutations responsible for this disorder. This innovative approach not only holds considerable promise for the restoration of normal gene functionality but also presents the potential for alleviating the myriad symptoms that are associated with this syndrome [30]. Furthermore, researchers are actively exploring the role of mGluR5 Positive Allosteric Modulators (PAMs), which have the potential to augment the functionality of any remaining FMRP protein, thereby possibly mitigating the cognitive and behavioural impairments that are characteristic of the disorder [31]. The exploration of the intricate gut-brain connection, particularly regarding the modulation of gut microbiota, could pave the way for novel microbiome-based therapeutic interventions aimed at enhancing neurological health, thereby further expanding the therapeutic landscape available for FXS [32]. Additionally, the endeavour to unravel the complex and multifaceted network of signaling pathways with which FMRP interacts within the brain is crucial, as it significantly aids in the development of targeted pharmacological agents that are intended to restore normal physiological functions [33]. The integration of advanced artificial intelligence (AI) technologies into the realm of FXS research serves to facilitate the meticulous analysis of

vast datasets generated from brain imaging studies, genetic assessments, and comprehensive patient histories, thereby enabling the formulation of personalized treatment regimens meticulously tailored to the unique genetic and molecular profiles of individual patients [34]. Moreover, non-invasive methodologies such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are currently under investigation, as they offer the potential to modulate neural activity in a way that may improve clinical outcomes without necessitating invasive surgical procedures [35]. The amalgamation of diverse therapeutic modalities, which includes gene therapy, pharmacological interventions, and non-invasive brain stimulation techniques, presents a more holistic and comprehensive strategy for the treatment of FXS, thereby providing synergistic benefits that are likely to exceed those achieved through any singular treatment approach.

In spite of a historical background characterized by a series of “negative” clinical trials related to FXS, the relentless quest for effective targeted therapeutic agents continues unabated. As of October 2018, the database ClinicalTrials.gov documented a total of 71 studies pertaining to FXS, which are currently at various stages of development and activity, with notable involvement from the pharmaceutical industry in the pursuit of promising targeted therapeutic agents such as OV101/gaboxadol, ZYN002/cannabidiol, BPN14770, and Bryostatin-1 [31]. Nevertheless, the clinical trials associated with these therapeutic agents have encountered significant complications attributed to the presence of subgroups of responders, which complicates the demonstration of efficacy across entire cohorts. In this challenging context, the identification of biomarkers—such as specific electroencephalogram (EEG) findings or responses observed in induced pluripotent stem cell (iPSC)-derived neuronal cell cultures—may prove instrumental in discerning potential treatment responses for individual patients, thus facilitating patient stratification and selection processes for future clinical trials [36]. Addressing the myriad challenges that arise from the inherent

heterogeneity within the FXS population, enhancing the development of improved outcome measures, and identifying reliable biomarkers for monitoring treatment responses are among the primary priorities that researchers are currently focusing on. Various gene therapy approaches, which may include the reactivation of the silenced FMR1 gene or the introduction of a healthy copy of the gene, represent another promising avenue for potential intervention [37]. Ongoing research efforts are also dedicated to the identification of alternative therapeutic targets that lie downstream of the FMR1 gene, which could serve as viable candidates for future therapeutic strategies. This comprehensive and multifaceted approach directed at targeting the FMR1 gene holds substantial promise for advancing the treatment of FXS and for ultimately enhancing the clinical outcomes for those individuals who are affected by this condition. Clinical trials of drugs for Fragile X Syndrome are shown in table 1.

Table 1: Clinical Trials of Drugs for Fragile X Syndrome

Drug	Type	Target	Clinical Trials	Trail Results	Approval Status	References
Zatolmilast	PDE inhibitor	Modulating cAMP	Phase 2	Safe, well-tolerated; Some improvement in cognition.	Phase 3 ongoing development	[38]
Arbaclofen	GABA-B agonist	Influencing GABA signaling and FMRP protein	Phase 3	Didn't improve social avoidance; Not FDA-approved.	Not FDA-approved for FXS	[39]

CHALLENGES IN TARGETING FMR1 IN FRAGILE-X SYNDROME

Efficient delivery of therapeutic genes poses a significant challenge in gene therapy for Fragile X Syndrome (FXS), given the FMR1 gene's location on the X chromosome, which complicates access to affected cells [40]. Additionally, Epigenetic Silencing resulting from

the CGG repeat expansion adds complexity to restoring normal gene function [41]. Identifying Effective Compounds for pharmacological reactivation that can reverse FMR1 gene silencing without off-target effects remains a major hurdle, exacerbated by the lack of reliable biomarkers for assessing treatment efficacy in FXS. Moreover, the heterogeneous nature of FXS, with varying degrees of FMRP expression and therapeutic responses, complicates the development of effective treatments across various therapeutic modalities [42].

Challenges persist in Patient Selection for clinical trials, necessitating strategies to navigate FXS's heterogeneity. The absence of reliable biomarkers further complicates the evaluation of treatment efficacy, requiring innovative approaches to quantify disease modification over time and across symptom domains. Understanding FXS is impeded by its phenotypic heterogeneity, epigenetic modifications of the FMR1 gene, and the gene's high conservation, highlighting the need for collaborative efforts to address these challenges and advance FXS research and therapeutic development [43].

FUTURE DIRECTION

The prospective future of targeting the FMR1 gene within the context of Fragile X Syndrome (FXS) reveals a highly intricate and exceptionally promising landscape, wherein researchers are diligently investigating a plethora of innovative methodologies designed to effectively address the fundamental pathology underlying this disorder. Gene therapy distinctly emerges as a crucial strategic approach, concentrating on two primary methodologies that are of significant importance in this field: gene augmentation and gene editing. Gene augmentation entails the precise delivery of healthy copies of the FMR1 gene into the affected cells, with the objective of elevating the production levels of Fragile X Mental Retardation Protein (FMRP), thereby counteracting the detrimental effects associated with FMRP deficiency and leading to noticeable improvements in cognitive and behavioral outcomes, a phenomenon

that has been substantiated through various preclinical animal studies. Conversely, gene editing exploits the revolutionary CRISPR-Cas9 technology to rectify the pathological CGG repeat expansion present in the FMR1 gene, with successful correction being demonstrated in cells derived from patients, which paves the way for future applications within living organisms (in vivo). Moreover, the pharmacological reactivation of the previously silenced FMR1 gene exhibits considerable promise, as scientists meticulously target specific signaling pathways and proteins that play a crucial role in the process of gene silencing. High-throughput screening methodologies have yielded a variety of promising compounds, and targeted transcriptional activation has successfully achieved selective reactivation of the FMR1 gene in human embryonic stem cells, contributing to the advancement of therapeutic options.

In addition to these innovative strategies, researchers are diligently unraveling the highly complex and intricate network of signaling pathways that the FMRP engages with in the cerebral context, with the aim of developing targeted pharmaceuticals that can effectively restore normal physiological functions. The incorporation of artificial intelligence (AI) into the domain of FXS research significantly enhances the potential for the formulation of personalized treatment plans, as it enables the comprehensive analysis of vast amounts of data derived from brain imaging, genetic information, and detailed patient histories, thereby facilitating predictions regarding treatment responses and the identification of novel drug targets. The strategic combination of multiple therapeutic approaches, which includes gene therapy, pharmacological reactivation, and a diverse array of other innovative strategies, presents a comprehensive and synergistic framework for the treatment of FXS. This holistic approach not only promises enhanced therapeutic benefits that extend beyond the efficacy of single treatment modalities but also paves the way for the development of more effective and personalized interventions tailored to the unique needs of individuals. In conclusion, the

future trajectory of treatment modalities for FXS is characterized by a diverse array of innovative approaches that are poised to fundamentally revolutionize the treatment landscape, ultimately leading to improved outcomes for individuals afflicted with Fragile X Syndrome, thus significantly transforming the lives of those who are impacted by this challenging and complex condition.

CONCLUSION

Current research in Fragile X Syndrome (FXS) treatment aims to address problems in gene therapy delivery and the discovery of effective pharmaceutical agents. Because of the variety of FXS presentations, clinical trials face challenges in patient selection and outcome monitoring. Understanding the many symptoms and epigenetic changes in FXS is critical for creating tailored treatments. Despite challenges, advances in molecular diagnostics and risk assessment show promise for improving FXS management and patient outcomes.

Conflict of interest: None.

Financial support: None.

Ethics statement: None

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