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# RESEARCH ARTICLE

# AN EMPIRICAL STUDY OF FRAGILE X SYNDROME USINGBIOINFORMATICS TOOLS

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**ABSTRACT**

The objectives of this paper are to examine general knowledge of FXS as well as knowledge of FXS pharmacotherapy. This overview may help pave the road for greater knowledge and understanding of NDDs, with a focus on FXS.Intellectual incapacity and behavioural abnormality, consisting of fear, ADHD symptoms, and Bio Neurological Disorder traits, are all linked to Fragile X syndrome (FXS). We noticed that a large number of patients with FXS had High-density lipoprotein cholesterol and low-density lipoprotein readings while following up on them, therefore we started a systematic chart analysis of drug molecules development This study has implications for evaluating one's health with FXS, treatments .Therefore, his study identifies additional risks associated with FXS, such as genetic and environmental variables that contribute to increased brain dysfunction in addition to the FMR1 mutation.



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# INTRODUCTION

Intellectual impairment, behavioral and learning difficulties, and a variety of physical traits are all symptoms of this hereditary disorder. Though both genders are afflicted by FXS, males are affected more frequently and with higher severity than females. It's also the most common and well-known cause of autism caused by a single gene (Latham, 2012) A "full mutation" of the Fragile X gene is present in people with FXS. The most common X-linked hereditary illness is Fragile X Syndrome because the FMR1 gene on the X-chromosome is silenced, the condition causes intellectual impairment. This gene is charge of producing the FMRP protein. FMRP is a protein that has a role in gene regulation, mRNA translocation, RNA processing, the creation and maintenance of neural synaptic connections, and most likely the developmental maturity of brain neurons (Latham, 2012) As a result, the protein is also called Synaptic functional regulator FMR1 or RNA binding protein, and the condition is called trinucleotide repeat disorder (Fig1). FXS is anautistic disease characterised by a full mutation in the fragile X mental retardation 1 gene, as well as epigenetic silencing of the gene, resulting in fragile X mental retardation protein deficit or absence. With an estimated frequency of 1:4000 in men and 1:6000 in females, FXS is the most common particular gene cause of autism spectrum disease and hereditary intellectual impairment. Reduced FMRP levels contribute to the ASD phenotype as well as being a cause of FXS since they lead to ID.FMRP expression in the brain is the most important predictor of neurobehavioral phenotype severity, with men with severe ID or severe ASD having the lowest FMRP levels.

This isn't surprising, given that FMRP is an RNA-binding protein involved in synaptic and dendritic development as well as synaptic plasticity (Hoeft, 2011). No pharmaceutical has been approved by the US Food and Drug Administration to treat FXS, symptom-based care is the sole choice. Male carriers might expect a more severe phenotype because the FMR1 gene is on the X chromosome. On the other hand, the symptoms of ADHD did not follow this trend.

## CHARACTERISTICS OF THE DISEASE

### The physical feature of FXS include

- Ears that protrude from the head, a large face, flat feet, hyper extensible finger joints, double-jointed thumbs, and soft skin.
- Although not all individuals have changed physical characteristics, macro-orchidism occurs around the time of puberty.

These characteristics are linked to growth and connective tissue alterations, including elastin fiber anomalies. (3)Hernias, joint dislocation, and flat feet with pronation are further FXS symptoms associated to connective tissue loss. Certain people with a high end premutation have a minor FMRP deficiency as well as some FXS characteristics. Certain people with a high end premutation have a minor FMRP deficiency as well as some FXS characteristics, such as large ears, attention deficit hyperactivity disorder (ADHD), motor co-ordination issues, anxiety, and social difficulties (Small, 1976)


**Figure1 (a)**

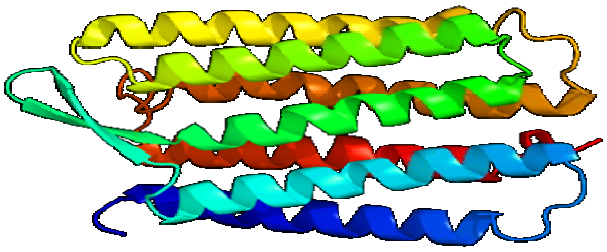


**Figure1 (b)**

## DIAGNOSTIC CHARACTERISTICS

**The features of FXS are different at different stages of life.**

### Infancy

- Poor suck
- Hypotonia
- Emesis
- Reflux

### Crawling

- Mild motor delays

### Walking

- Recurrent otitis media
- Sensory hyperarousal
- Emergence of anxiety
- Language delays
- Hyperactivity
- Seizures

### Early childhood

- Anxiety
- Tantrums
- Poor eye contact
- Autism symptoms
- Aggression
- Impulsivity

### Adolescence

- Perseveration
- Poor attention
- Hyperactivity
- Impulsivity
- Anxiety
- More aggression

### Adulthood

- Perseveration
- Anxiety
- Poor attention
- Episodic dyscontrol

### Ageing

- Parkinsonism symptoms and cognitive decline in some

**Reason of the disease:** FXS is caused by the deficiency of the Fragile X mental retardation 1 protein. (FMRP)( Chonchaiya et al., 2010). A trinucleotide repeat expansion of CGG in the promoter region of FMRl, situated at Xq27.3, is the most prevalent cause of FXS, which results in to methylation, transcriptional silence, and the lack of FMRP.

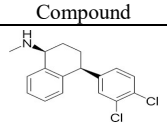
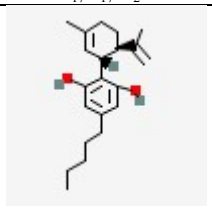
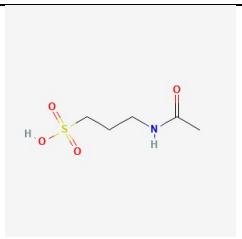
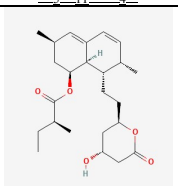
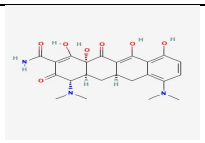
**Treatments for FXS**

**The following therapies may help children with FXS, according to research and clinical experience:**

- Starting at low dosages and progressively increasing the amount until the intended benefit is achieved or severe side effects occur is a key general guideline with any drug therapy in Fragile X syndrome. If adverse effects arise, the medicine may need to be stopped with the doctor's approval (Angkustsiri, 2008).
- Adults (ages 18 and above) and kids (children and teens between the ages of 5 and 18) can use the drugs listed below at different dose levels. Some children aged 3 to 5 may be given drugs under the supervision of their doctor (Angkustsiri et al., 2008)
- The appropriate dose level should be determined with the patient's physician. Without consulting the individual's doctor, make no modifications to drugs or supplements (raising OR lowering) (Berry-Kravis, 2015)
- If dose amounts for a medicine are not supplied, it is because the medication is not indicated for use in people with Fragile X syndrome (Table1) Medications are only included in such cases where they are recommended by a doctor (Berry-Kravis, 2015)
- it's critical to avoid adding new drugs every time an adult has a crisis, and to make every effort to prevent overmedicating people with excessive doses and several medications at once (Berry-Kravis, 2015)
- Program for early diagnosis
- Cognitive and dialectical behaviour therapy
- Psychological interventions
- Education for people with disabilities
- Treatments for particular symptom issues including anxiety, ADHD, seizures, and so on.
- 11. Educational options that help adolescents and adults with FXS learn adequate living skills are also beneficial.
- These programmes might start in high school and go all the way through adulthood. And they should include employment, social engagement, recreation, and sexuality education and advice.
- The NFXF Consensus Documents can assist you and your doctors in deciding on the most effective therapy options.

**Mapping**: Using a somatic cell hybrid mapping panel and fluorescence in situ hybridization, the FXR1 gene was mapped to chromosome 12 and to 12q13. This localisation, however, was determined to be an intron less pseudo gene.(8) They discovered the functional FXR1 gene on chromosome 3q28 using FISH. The FXR1 gene was localised to chromosome 3q27 using BAC analysis. They discovered that mouse Fxr1 is located in the proximal region of chromosome 1. In a family with mental retardation and cleft lip and palate, linkage analysis yielded a maximum lod score of 2.78 (theta = 0.0) for the DXS441 locus, which was flanked by the markers DXS337 and DXS990, defining the Xp11.3-q21.3 region. Juberg-Marsidi syndrome was diagnosed after linking to a probe at the DXS441 locus mapped the disease locus to Xq12-q21; maximal lod = 3.24 at theta = 0.0. The JMS gene was shown to be inside the interval specified by DXS159 and DXYS1X using multipoint linkage analysis. The XLMR syndrome in the family they reported has a relationship to a locus at Xq11-q22, according to linkage analyses.

**Table1. Medicineused for FragileX Syndrome:**

| Medicine | Source | Purpose | Compound |
|---|---|---|---|
| Sertraline. | Hydride of a terrain. | Depression, anxiety disorders, and obsessive-compulsive disorder (OCD) are all treated with psychotherapy. |  $C_{17}H_{17}Cl_2N$ |
| **Cannabidiol (CBD)** | **hemp plant**, and cousin of marijuana | Neurological condition. |  C21H30O2 |
| **Acamprosate** | Ethanol | cognitive therapy |  $C_5H_{11}NO_4S$ |
| **Lovastatin** | As a secondary metabolite, it's found in a range of filamentous fungi, including Penicillium species, Monascus ruber, and Aspergillus terreus. | cholesterol |  C24H36O5 |
| **Minocycline** | tetracyclines | Acne, rosacea, respiratory tract infections, urinary tract infections, and certain sexually transmitted illnesses are treated with it. |  $C_{23}H_{27}N_3O_7$ |
| Ambra grisea | abdomens of dead sperm whales | skinny, nervous patients and hyperactive, nervous children | |
| Alumina | **bauxite** | Relieves pain and dryness in the throat while also lowering headaches. |  Al2O3 |
| Anacardium orientale | *Anacardium* plants | gastrointestinal problems | |
| Cannabis indica | phenolic compounds | activities that are psychotropic | |
| Thuja | Arbor vitae or white cedar, | Used to treat bronchitis, bacterial skin infections, and cold sores in the respiratory tract. | |

The disease locus was narrowed in a follow-up investigation of the same family to a region between Xp11.3 and Xq23 (highest lod score of 2.53 at numerous markers).

**Molecular Genetics**

**FMR1 expansions can take three forms: intermediate, premutation, and complete mutation.**

- **Intermediate:** This form of enlargement is prevalent in the general population, with one out of every three people experiencing it. Intermediates aren't linked to any medical conditions and people with this range's extensions aren't at danger of having Fragile X syndrome children. Intermediates alter slightly in the following generation in a limited percentage of families, this might result in premutations in subsequent generations (Gothelf, 2008)
- **Premutation:** An estimated 1.5 million citizens of the United States have a FMR1 premutation. When transferred from a mother to her kid, premutations can become unstable and grow into complete mutations, resulting in FXS. Infertility, early menopause, and other ovarian problems are all risks for females with premutations (FXPOI). FXTAS is an adult-onset neurological illness that affects men who have permutations (Gothelf, 2008)
- **Full mutation:** Males with FMR1 complete mutations often develop FXS. An estimated 100,000 people in the United States have a full mutation. FXS affects around half of all females with complete mutations. Others may experience minor learning or behavioural issues. When the FMR1 gene is fully mutated, it "turns off" and stops working normally. (10) This is accomplished by a process known as methylation, which acts as a switch to turn off the 4 gene. (Normally, the gene is turned on or "unmethylated."). This indicates that the gene does not create any or enough FMRP, a protein that is thought to be required for optimal evolution of the brain Mosaicism is a condition that affects a limited percentage of people with FXS. This indicates that they contain a combination of cells with varying amounts of CGG repeats and/or methylation status. A kid, for example, may have a variety of cells, some with complete mutations in FMR1 and others with premutations.

The growth and methylation of a CGG tract in the 5' untranslated region of the FMR1 gene causes Fragile X syndrome. In the United States, the estimated frequency of enlarged alleles (55 repetitions) is 1:257-1:382, however these values are not based on unbiased

populations (11). A homozygous 4-bp deletion at the 3-prime end of exon 15 of the FXR1 gene, predicted to result in a frameshift and premature termination, was discovered in a male infant and his affected foetus sibling, conceived of consanguineous Egyptian parents (family 1), with congenital myopathy, respiratory insufficiency, and bone fractures (Arg588SerfsTer37). The mutation, which was discovered by whole-exome sequencing and validated through Sanger sequencing, was found to be associated with the condition in the family.Truncated 82- and 84-kD proteins were found in primary myoblasts from one of the patients with the delACAG mutation, indicating escape from nonsense-mediated mRNA degradation (NMD) (Hunter, 2014) These aberrant proteins were found in cytoplasmic granules that held mRNA and were ring-shaped. Similar abnormalities were seen in the skeletal muscle of mutant mice with a corresponding 4-bp deletion.

**Clinical Features:** Polymerase chain reaction and Southern blotting are used to determine the genetic/medical diagnosis of FXS. Furthermore, Amplidex's next-generation FMR1 gene-specific PCR technique identifies the whole range of fragile X expanded alleles, reducing the requirement for Southern blotresearch (Bagni, 2012). The development ofexact responses which included FMRP synthesis enabled for further precise FMR1–FMRP correlations, allowing for the detection of new FMRP deficiency's clinical connections not previously described in significant investigations.

**Fragile X testing should be indicated in three broad approaches**

Indications in the clinic suggestive of FXAD, (ii) FXAD in the family, intellectual or teachissues (iii) a fragile X genetics and inheritance. A general intelligence phenotype was discovered. It was associated with weak to strong brain impairment. Attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, enuresis, and encopresis were the most common psychiatric comorbidities (Oostra, 2008). There was no evidence of a link between certain phenotypic characteristics and genotype (Kidd, 2014). Some of the characteristics included cortical atrophy, dolichocephaly, short stature, cleft palate, micrognathia, prominent upper central incisors, bilateral Sidney line, minor foot deformities, instability in walking, early hypotonia, hyperreflexia, hyperactivity, psychomotor retardation, and severe delay in language development (Berry-Kravis, 2014). The patients all had deafness, significant mental disability, facial dysmorphism, and genital abnormalities such as a small penis, hypospadias, and cryptorchidism.

# CONCLUSION

The goal of this study was to see if FMR1 premutation alleles had any influence on success in neuropsychology in young adult males and females. Treatments for FXS and FMR1 expansions are clinically essential to families with fragile-X spectrum diseases. This study is clinically significant for families affected by the fragile X syndrome and Treatments for FXS and FMR1 expansionsFemales with the premutation are more likely to have severe ADHD symptoms, although this does not always mean they have clinical ADHD. The higher mean score for self-concept issues among female premutation allele carriers is consistent with findings from a recent study of this cohort, which found that premutation allele carriers had higher scores for overall negative affect.

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