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Fragile X Disease and Its Overview

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Tushar Katariya[1*], Avinash Dhobale[2], Borkar Shubham[3], Vishal Shelke[4]

Loknete Shri Dada Patil Pharate College of Pharmacy Mandavgan Pharata, Pune. Maharashtra, India 412211.

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ABSTRACT

Fragile X disease is the genetic disorder. The disease is caused due to the intellectual disability. In 1943 Martin and Bell showed that particular form of mental retardation. In 1969 Herber Lubs developed the chromosomal test for fragile X disease. This disease is transformed by genetically i.e. human to human transmission occur. FMRP is an RNA-binding protein that shuttles between the nucleus and cytoplasm. This protein has been implicated in protein translation as it is found associated with polyribosomes and the rough endoplasmic reticulum. We discuss here the recent progress made towards understanding the molecular mechanism of CGG repeat expansion and physiological function(s) of FMRP. These studies will not only help to illuminate the molecular basis of the general class of human diseases with trinucleotide repeat expansion but also provide an avenue to understand aspects of human cognition and intelligence.

INTRODUCTION

The Fragile-X-Syndrome (FXS) is a genetic syndrome, which causes inherited mental retardation. The disease was identified in 1991. It is the second leading syndrome causing mental retardation, after the Down syndrome. It concerns 1/4000 male and 1/8000 female. Besides mental retardation, it causes learning disabilities and almost half of the children, suffering from this disease, are also diagnosed autistic. FXS patients also present physical dysmorphia. The mutation is a monogenic dynamic mutation. In the 5' UTR part of FMR1 gene, the repeats of the CGG sequence is normally quantitatively stable. An increase of this number can lead to 2 state of the mutation: the premutation and the full mutation. Fragile X syndrome (FXS) is the most common inherited cause of mental retardation with approximately 1 in 4000 males affected.[1] Fragile X syndrome is the most common form of inherited intellectual disability worldwide. In addition to intellectual issues, there are many more possible symptoms with males being more affected than females. In fact, females may not be classed as having an intellectual disability at all but may just have some learning difficulties and other challenges.[5] Individuals with FXS may present anywhere on a continuum from learning disabilities in the context of a normal intelligence quotient (IQ) to severe intellectual disability, with an average IQ of 40 in males who have complete silencing of the FMR1 (fragile X mental retardation 1) gene.[9] Females have two X chromosomes and males have one X and one Y. Normally the X chromosome contains between 6 and 50 repeats of a gene (FMR1 gene) responsible for producing a protein vital for normal brain an development.[10] There is no cure This condition causes a range of developmental problems including learning disabilities and cognitive impairment.[22]

Fragile X syndrome is caused by a change (mutation) in the FMR1 gene and is inherited in an X-linked dominant manner.[22]

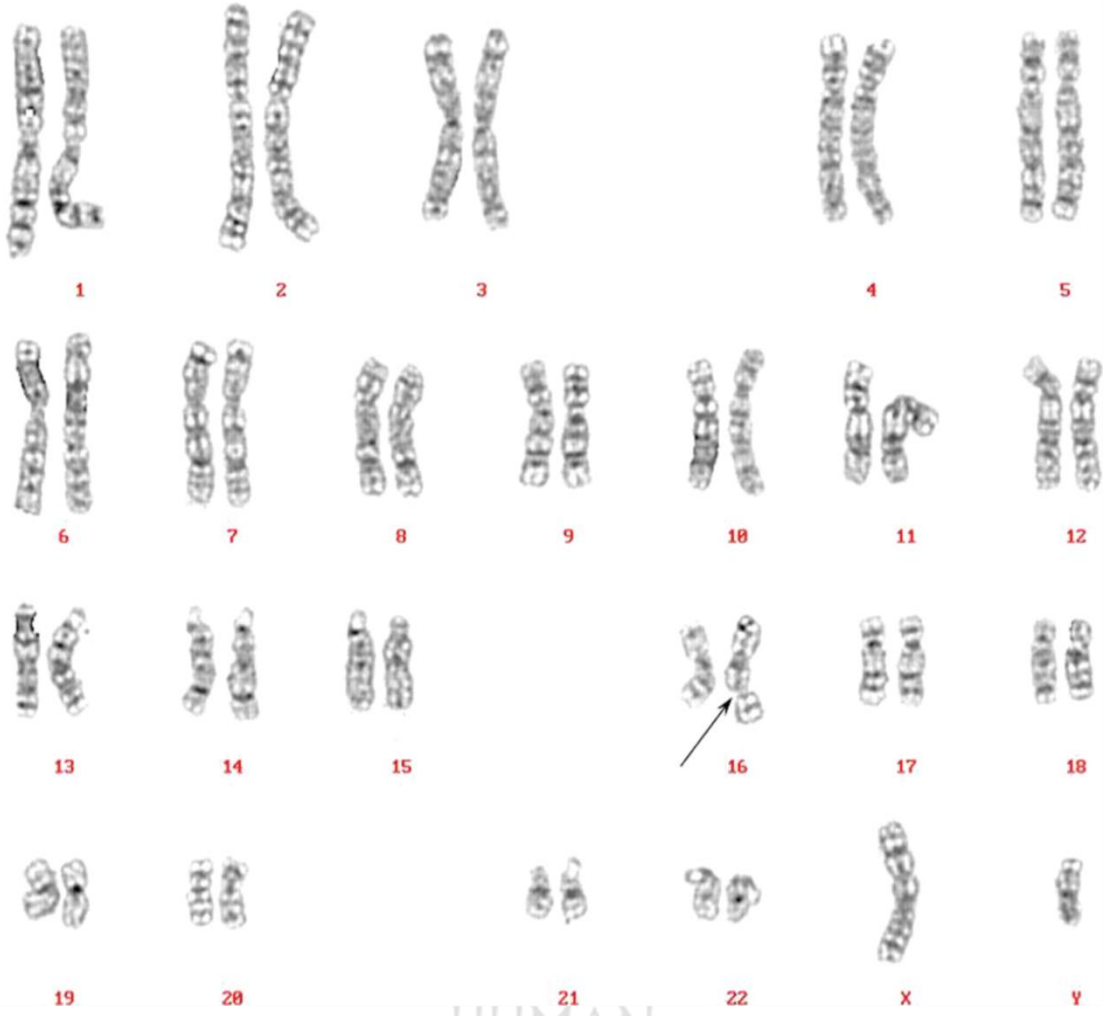

Fig1: Fragile Disease

SIGN AND SYMPTOMS

Fragile X syndrome is characterized by developmental problems including intellectual disability and delayed speech and language development. Males are usually more severely affected than females.[10] The way that Fragile X syndrome affects people will vary. Girls and women are usually less affected than boys and men.[11] Children who are born with this genetic condition can get special education and therapy to help them learn and develop like other kids.[12]

TRANSMISSION

Fragile X syndrome is a genetic disorder which occurs as a result of a mutation of the fragile X mental retardation 1 (FMR1) gene on the X chromosome most commonly an increase in

the number of CGG trinucleotide repeats in the 5' untranslated region of FMR1 (fragile X mental retardation 1).[3]

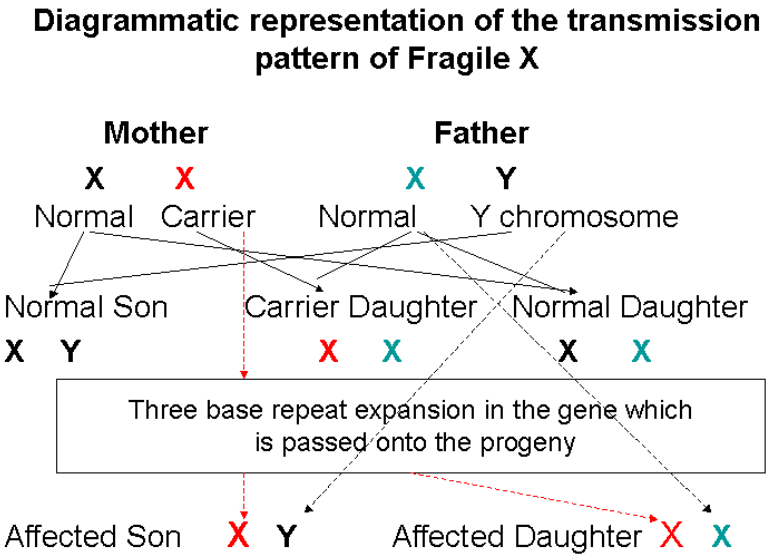

Fig 2: Transmission of Disease

This methylation of FMR1 (fragile X mental retardation 1) in chromosome band Xq27.3 is believed to result in constriction of the X chromosome which appears 'fragile' under the microscope at that point a phenomenon that gave the syndrome its name. One study found that FMR1 silencing is mediated by the FMR1 mRNA. The FMR1 mRNA contains the transcribed CGG - repeat tract as part of the 5' untranslated region which hybridizes to the complementary CGG-repeat portion of the FMR1 gene to form an RNA, DNA duplex.[4]

RISK FACTOR

The main risk factor for FXS is having a parent with an FMR1 mutation. These mutations vary in degree. Most people who inherit a minor mutation which is sometimes called a premutation do not develop the symptoms and signs of FXS.[6] A risk factor is something that increases your chances of getting a disease or condition.[8] The children of mother with FMR1 premutation are risk of inheriting a fully mutated FMR1 gene severe enough to causes symptomatic fragile x symptoms.[8]

TREATMENT

- **Neurobiological Features And Targeted Treatments**

FMRP is a RNA-binding protein that modulates dendritic maturation and synaptic plasticity through a mechanism involving particularly the inhibition of group 1 mGluR-mediated dendritic protein synthesis.[7] This concept is based in part on the finding that hippocampal and cerebellar long-term depression (weakening of synaptic connections).[6]

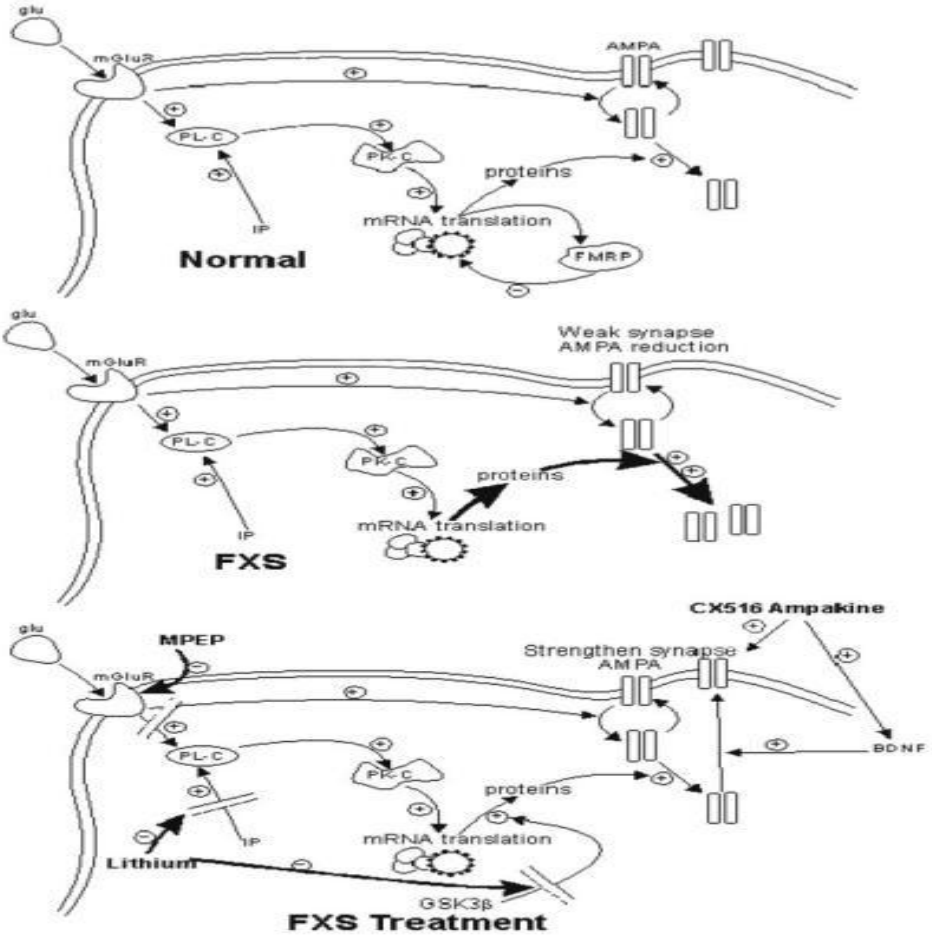

Fig 3: Fragile X disease treatment

Behavioral Features and Treatment

Behavioral Phenotype

The behavioral phenotype of FXS involves poor eye contact, excessive shyness, anxiety, hand flapping, hand biting, aggression, tactile defensiveness, attention deficits, hyperactivity, impulsivity, hyperarousal to sensory stimuli.[13,14]

Treatment of Anxiety

Selective serotonin reuptake inhibitors (SSRIs) at typical doses were helpful >50% of the time in relieving anxiety and related problems in surveys of patients with FXS (fragile x disease).[15] Selective mutism is a form of anxiety in some female individuals with FXS it is rare among male individuals with FXS. Fluoxetine can be beneficial for this problem as reported for 1 family with FXS.[16]

Treatment of Aggression and Mood Instability

Antipsychotic drugs generally are helpful in clinical settings to target irritability, aggression, mood instability and perseverative behaviors in both male individuals and female individuals with FXS. In a study of a large FXS clinic population, ~80% of individuals with FXS responded to ≥1 antipsychotic drug without adverse effects requiring withdrawal.[17]

Seizures and Treatment

Individuals with FXS have increased risk for seizures, with rates of 13% to 18% for boys and ~5% for girls.[18] In general, the risk of epilepsy onset seems to be highest in childhood one study suggested that the peak incidence was between the ages of 6 months and 4 years with a mean age of onset of 2 years.[19]

GENETIC COUNSELING

When an individual is identified as being at risk for FXS it is imperative that the clinician explains to the family the indications for testing. If the testing results are positive, then referral to a geneticist and genetic counselor is recommended so that the appropriate clinician can interpret the results for the family according to the guidelines for FXS established by the National Society of Genetic Counselors and the American Society of Human Genetics.[2,20,21] This may involve personal contact between family members or an informational letter or the family may choose to have the genetic counselor, geneticist or pediatrician meet with members of the extended family to discuss the diagnosis of FXS and FX-associated conditions and to facilitate testing for family members who are at risk.

DRUG USED FOR FXS

STIMULANTS

The psychostimulants as a class have been around for a long time. These were some of the first drugs to be used in psychiatry and so physicians feel fairly comfortable with these medications some would say too comfortable. In children, stimulants are by far the most commonly prescribed psychoactive medications, primarily for the treatment of attention deficit/hyperactivity disorder.[22]

ANTIDEPRESSANT

The term itself is a misnomer since antidepressant medications are effective for treating much more than just clinical depression. It has long been recognized that most antidepressant medications are effective treatments for certain anxiety disorders such as panic disorder and generalized anxiety disorder.[22]

SYMPATHOLYTICS

These medications are designed to counteract the effects of the sympathetic nervous system (lyric means "that which dissolves or severs") by various neurochemical means. While they are all marketed as treatments for high blood pressure this effect is of benefit to many individuals with Fragile X who suffer from troublesome hyperarousal or "overstimulation" which may result in hyperactivity, anxiety or even aggression.[22]

MOOD STABILIZERS

This class of medications varies widely from a biochemical perspective. These medications work in very different ways. However, they all have one thing in common. They tend to stabilize moods and decrease effective liability.[22]

CONCLUSION

Fragile X syndrome is result of triple nucleotide repeat mutation of nucleotide sequence. Mutation is hereditary. It causes a variety of intellectual disabilities that mainly affect males. Diagnosis occurs by southern blotting. Psychologically it is important to diagnose fragile X No FDA (Food and drug administration) approved medication to treat fragile X syndrome. Syndrome to assist the individual and the parents.

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