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An Investigation on The History and Current Research of Fragile X Syndrome

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1943

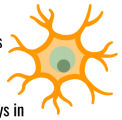
First documentation of a sex-linked mental retardation, which was firmly known as Martin-Bell syndrome. [§]


1991

In 1991, after identification of the fragile X mental retardation (FMR1) gene, the cytogenetic marker (a fragile site at Xq27.3) became replaced by molecular diagnosis. [2]

2002

The "mGluR Theory of FXS" was established as one of the main mechanisms to explain the cognitive and intellectual delays in FXS patients. [10]



2004

Although the exact modifier genes are not known, based on several tests conducted, the results were compatible with an effect of modifier genes on the Fragile X phenotype due to the differences between the knockout and control participants [4]

2020

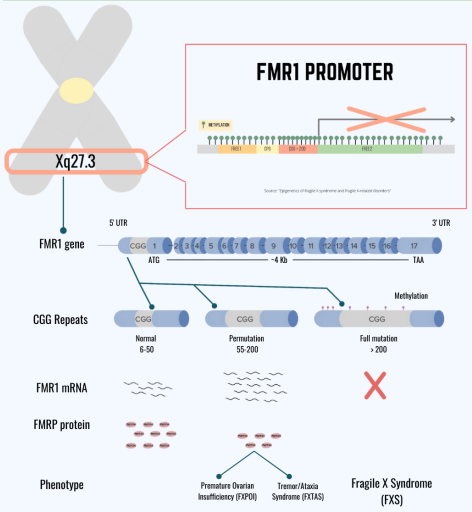
The University of Buffalo and Tetra Therapeutics discovered a new drug, BPN14770 . This drug has the potential to promote the regeneration of impaired neurons present in patients with Fragile X Syndrome. [9]

2021

"Screening Combinatorial Pharmacological Therapies for Fragile X Syndrome" by Philippe Jacques Mourrain, PhD, and Gordon Wang, PhD

Ongoing research on pharmaceutical interventions that hopes to find suitable drug therapies for FXS patients. [3]

Molecular and Cellular Mechanism FXS

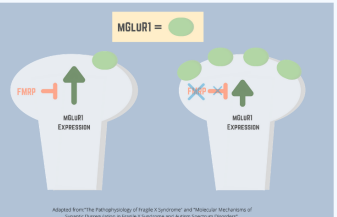


Adapted from Lecturio: https://www.lecturio.com/concepts/fragile-x-syndrome/

Hypermenthylation of the FMR1 Promoter brought out by >200 CGG repeats. Repeats are possible caused by DNA Polymerase slippage during the synthesis of the lagging strand. A LOF of the FMR1 causes a lack of FMRP production.
FMRP's primary role is regulation of translation. FRMP regulates by binding to RNA, which may trigger stalling of ribosomes, coordination with RNA-induced silencing complexes, or binding directly to ribosomes to initiate the stall. [2]

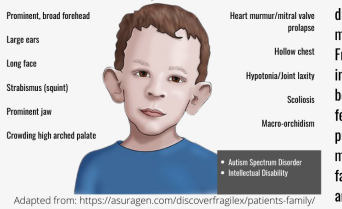
mGluR Theory of Fragile X Syndrome

Increased mGluR1/5 production leads to Long Term Depression (LTD). LTD is attributed to lower rates of synaptic maturation, which can result to the formation of long dendrites and the eventual loss of the synapse. [1,10]



Phenotypic Presentation

Common Physical Features



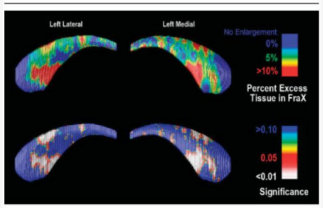
Adapted from: https://asuragen.com/discoverfragilex/patients-family/

Affected males typically have an average IQ ranging from less than 50 to normal range (100).

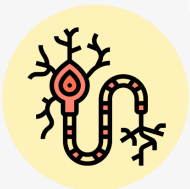
Females have less intellectual disability, with a borderline to normal IQ (100). [§]

Mild to moderate intellectual disabilites and deficitis are the most prominent phenotype in Fragile X Syndrome. Many individuals will also have behavioral abnormalities. Physical features vary in relation to puberty, including a facial morphology with a long narrow face with prominent forehead, jaw, and ears. [8, §]
However, these clinical findings are not unique to Fragile X Syndrome. Therefore diagnosis is determined by molecular detection of mutations.

FXS patients have an increase in grey-matter volume in the Caudate Nucleus (CN). This increase is brought out by the decrease in FMRP production.
Abnormal CN is attributed to abnormal learning abilities and daily functioning, which is seen in FXS patients. [§]



Source: "Neuroanatomy of fragile X syndrome is associated with aberrant behavior and the fragile X mental retardation protein (FMRP)

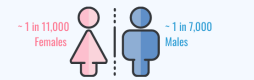


FXS patients have characteristically larger amounts of thin, long dendritic spines brought out by the alterations in mRNA translation due to the absence of FMRP. The formation of this types of dendrites is consistent with having weakened synaptic plasticity. [§]

Social Impact

Individuals with FXS have co-morbidities and associated symptoms coinciding with various neuropsychiatric disorders including Autism Spectrum Disorder. Patients are faced with poor communication skills, learning disabilities, cognitive, and behavioral problems that may lead to low quality of life, developmental delay, and economic instability. [7]

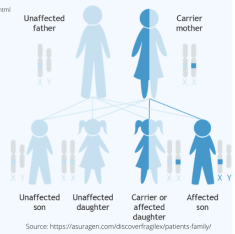
Penetrance and Expressivity



Source: "Data and Statistics on Fragile X Syndrome" https://www.cdc.gov/ncbddd/fxs/data.html

A meta-analysis conducted in 2014 estimated the prevalence of FXS in about every 1 in 11,000 females and about 1 in every 7,000 males. If a full mutation is inherited, nearly all males and 40-50% of females will have Fragile X Syndrome. [§]

The severity of phenotype is dependent on the degree of methylation in the FMR1 promoter and CGG repeat sequence length in the 5' untranslated region of the FMR1 gene.

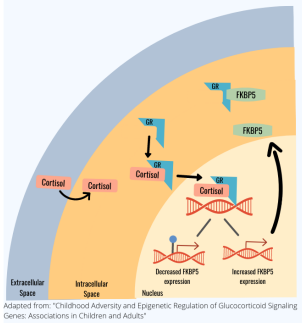


Source: https://asuragen.com/discoverfragilex/patients-family/

FXS is not more prominent in any particular ethnic group or population. In regards to Hardy-Weinberg Law, affected population matings are random and FXS allele frequencies are constant throughout all populations.

Environmental Influences

The behavior of male FXS patients improved upon exposure to educational and therapeutic services.
The quality of the home environment contributes to intellectual amplitude. Parents of the FXS patient have been seen to affect the behavior of the patient, especially when the parent exhibits psychological issues. This may foster negative behavior patterns and result in poor verbal development and dysregulated stress responses in the patient. Such findings strengthen the need to foster a positive atmosphere around FXS patients in order to alleviate neurobehavioral symptoms and manifestations. [5, 6]

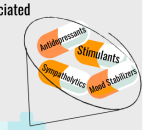


Adapted from: "Childhood Adversity and Epigenetic Regulation of Glucocorticoid Signaling Genes: Associations in Children and Adults"

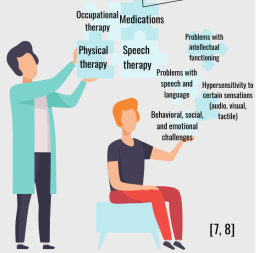
Numerous studies indicate that poor maternal care and childhood adversity induce epigenetic changes including increased methylation to cortisol (stress hormone) response regulating genes. [§]
This poses a potential epigenetic change in FXS patients when they experience stressors, especially when associated with their condition.

Treatment

There is no curative treatment for Fragile X Syndrome. Past and current treatment regimens have been focused on psychiatric intervention and pharmacological management of associated symptoms. [7]

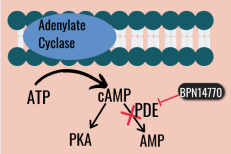


An emphasis on collaborative care from the fields of "internal medicine, psychiatry, psychology, and social work" is the most conducive and sustainable treatment for FXS. Patients should regularly receive wellness check ups to see if current behavioral therapies, medication, and resources are helping FXS patients. [§]



[7, 8]

The Future for FXS Treatment



Diminished production of cAMP is a molecular feature of FXS. BPN14770 aims to treat and eliminate this issue by blocking the activity of phosphodiesterase 4D (PDE), an enzyme that degrades cAMP, consequently increasing cAMP production thus cell responses. [9]

Resources

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5. Dyer - Friedman, J et al. PubMed, 41(3), 2002
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