



Fragile X Syndrome and Fragile X-associated Disorders

First described

Martin & Bell (1943): families with sex-linked inheritance for learning difficulties & characteristic physical features. Lubs (1969) identified the chromosome fragile site just above the tip of the X chromosome's long arm. Sutherland (1977) confirmed the importance of a folate-deficient culture in revealing the site. Verkerk et al. (1991) described the multiple CGG repeat sequence at Xq27.3 producing local hyper-methylation and impaired protein synthesis of FMRP. This protein is an RNA binding protein that transports mRNAs to the synapse and typically inhibits translation. The lack or deficiency of FMRP in fragile X syndrome causes enhanced translation of many proteins important for synaptic plasticity and other functions in the CNS. FMRP regulates the translation of hundreds of proteins many of which are important for synaptic plasticity and are associated with autism spectrum disorder (ASD). Fragile X syndrome is the most common inherited cause of intellectual disability and the most common single gene cause of ASD. Therefore, all individuals with intellectual disability or ASD should have fragile X DNA testing if the etiology is unknown. In fragile X syndrome there is enhanced metabotropic glutamate receptor 5 (mGluR5) activity leading to enhanced long term depression (LTD). There is also down-regulation of the GABA system and dysregulation of the dopamine system. Levels of cAMP are low in those with fragile X syndrome. Targeted treatments have been developed to reverse some of the neurobiological abnormalities of fragile X syndrome and are currently being studied in patients with fragile X syndrome.

Genetic aspects

There is sex-linked transmission because the *FMR1* gene is on the bottom end of the X chromosome (Xq27.3), so males are affected more severely than females. There is an expansion of the CGG repeat in the promotor region of the *FMR1* gene through the generations but progression to a full mutation (>200 CGG repeats) only occurs when it passes through a woman to the next generation. Ninety percent of males with a full mutation (>200 CGG repeats) have intellectual disability and the rest have learning and/or emotional problems. When the CGG repeat in the promotor region of *FMR1* is greater than 200 there is typically methylation of the *FMR1* gene. However, those males with fragile X syndrome who are high functioning (IQ>70) are mosaic (some cells with the premutation (55 to 200 repeats) or partially/ completely unmethylated so that some FMRP is produced. In females with fragile X syndrome there is one X chromosome that is normal and the second X chromosome with the full mutation. In these females approximately 25% have intellectual disability and an additional 60% have learning difficulties particularly in math, attention and impulsivity. Some females with the full mutation have no intellectual disability and very few clinical problems and these individuals usually have a favorable activation ratio, meaning the majority of their cells have the normal X as the active X as measured in blood. The diagnosis of fragile X syndrome is made by *FMR1* DNA testing. Cytogenetic studies may also show the fragile site in folate deficient media, but DNA studies are essential for diagnosis and to identify the CGG repeat expansion number. More recent whole genome and whole exome studies have documented point mutations and deletions in *FMR1* that can lead to a fragile X syndrome phenotype without the CGG expansion because the FMRP is abnormal or partially deleted.

Carriers have a premutation and are typically unaffected cognitively, although in approximately 10 to 20% intellectual disability or ASD can occur, particularly in males. Carriers have an elevation of their *FMR1* mRNA level of 2 to 8 times the normal range. This elevation of mRNA leads to a gain-of-function toxicity that can be associated with medical or emotional problems. Primary ovarian insufficiency (menopause before age 40) occurs in 16 to 20% and it is termed fragile X-associated primary ovarian insufficiency (FXPOI). The neuropsychiatric problems occur in approximately 50% and they can include anxiety, depression, insomnia, chronic fatigue, fibromyalgia or chronic pain disorder and these problems are covered by the umbrella term fragile X-associated neuropsychiatric disorders (FXAND). Additional medical problems that can occur in carriers to a greater extent than age matched controls includes hypertension, migraine headaches, insomnia, sleep apnea, hypothyroidism, gastroesophageal reflux, immune mediated problems, chronic fatigue, fibromyalgia and neuropathy. These problems can be characterized as fragile X-associated conditions (FXPAC) and the psychiatric problems in FXAND that do not meet the DSM5 criteria for a disorder can be labeled as FXPAC.

The most severe neurological problem in a subgroup of aging male and female carriers is called the fragile X-associated tremor/ataxia syndrome (FXTAS). FXTAS is defined as intention tremor, cerebellar ataxia, neuropathy combined with memory and executive function deficits. FXTAS is associated with global brain atrophy and white matter disease, often in the middle cerebellar peduncles, splenium, insula, pons and/or periventricular areas. FXTAS occurs in approximately 40% of older male carriers and 8% to 16% of older female carriers. FXTAS only occurs in premutation carriers because they have elevated *FMR1* mRNA levels which lead to toxicity in the neurons and glial cells; intranuclear inclusions form in the neurons and astrocytes and also in the peripheral nervous system and even in some organs. The FXTAS inclusions have the *FMR1* mRNA combined with proteins that are sequestered by the elevated mRNA. An abnormal protein FMRPolyG is also thought to be formed in those with FXTAS because of RAN translation meaning abnormal translation that does not start at the normal AUG start site but instead upstream, therefore causing the production of the FMRP that has a polyglutamine tail. There are other pathological mechanisms that can lead to neurodegeneration in those with FXTAS including mitochondrial dysfunction and calcium dysregulation in neurons.

Incidence/Prevalence

The allele frequency of the full mutation is 1 in 4000 to 6000 in the general population, however some individuals with the full mutation especially females do not have intellectual disability, although their learning difficulties and emotional problems still constitute fragile X syndrome. The premutation is more common and 1 in 130-250 females and 1 in 250-800 males in the general population have the premutation. Some parts of the world including Colombia, Israel and Mallorca have a much higher prevalence of the premutation and the full mutation likely related to founder effects.

Institutionalized individuals with intellectual impairment of unknown origin have rates of fragile X syndrome ranging from 2.5% to 5.9%. Fragile X syndrome is the most common inherited cause of learning disability or intellectual impairment and many families have multiple individuals affected by the fragile X mutation. Approximately 2 to 6% of those with autism have fragile X syndrome and it is the most common single gene associated with autism. For males with fragile X syndrome about 60% have ASD but in females only 20% have ASD,

Physical Features in Fragile X Syndrome

Prominent ears are seen in 60% of children and adults usually have a long face and sometimes a prominent jaw. A high arched palate is seen in the majority and strabismus is present in up to

30%. Macroorchidism or large testicles are a feature in adolescence in over 90% of males. A connective tissue dysplasia produces joint laxity particularly hyperextensible finger joints, soft velvety skin and flat feet with pronation. This connective tissue problem can also cause aortic dilatation and/ or mitral valve prolapse, sometimes in adults. Seizures occur in approximately 16 to 20% and recurrent otitis media occurs in the majority in early childhood.

Life expectancy/Natural history

Those with fragile X syndrome have a normal life expectancy except for those who have seizures since death can occur during a seizure rarely. Rare cases of sudden death have been reported in childhood or adulthood. Aging studies in individuals with fragile X syndrome have documented a high rate of Parkinsonian symptoms in the 50s and older which can be exacerbated by the use of antipsychotics in older adults with fragile X syndrome.

Behavioural characteristics

Intellectual impairment is variable and correlates with the molecular findings. Those with higher levels of FMRP, such as females and those with an unmethylated full mutation or mosaic status (some cells with the premutation and some with the full mutation), will have a higher IQ because they are producing more FMRP. Verbal intelligence usually exceeds performance abilities in both affected males and non-learning disabled female carriers, although about 10% of patients will be non-verbal or will have very low verbal abilities. Particular difficulties with numeracy, visuospatial skills and visual motor abilities are common. The rate of intellectual development diminishes with age, particularly after puberty. This will lead to a lower IQ overtime, although there is no regression of abilities but instead a lack of abstract reasoning development which holds the IQ lower with age.

Speech & language development is almost always delayed with dysfluent conversation, incomplete sentences, echolalia, palilalia and verbal perseverations. There is often a jocular quality to speech with narrative, compulsive utterances and swings of pitch ("litany-like"). "Cluttering" refers to the fast and fluctuating rate of talking with marked and frequent repetitions, garbled and disorganized speech, poor topic maintenance, and tangential comments. Social impairments, ASD, ADHD and social anxiety with aversion to eye contact are present in the majority of children and adults with fragile X syndrome. Approximately 60% of men will have an autism spectrum disorder (ASD). The rest are socially responsive and affectionate individuals with good understanding of emotions, although autistic like features such as perseverations, hand flapping and poor eye contact with shyness are seen in the majority. Self-injury, notably hand biting and aggression provoked by frustration, anxiety and excitement are common. Hand flapping is seen in the majority both with and without autism. Obsessive and compulsive features are common and often lead to rituals and picky eating habits. Mouth stuffing, tactile defensiveness and overreaction to sensory stimuli leading to hyperarousal and tantrum behavior are seen in the majority. Approximately 30% of males have aggression; and anxiety associated with hyperarousal is a component of this aggression. Individuals with fragile X syndrome have a GABA (inhibitory) deficit and this leads to a lack of habituation to sensory stimuli both in electrodermal studies and also in fMRI studies. The lack of habituation to sensory stimuli in the CNS is correlated to the severity of ASD in females. Hyperactivity is seen in about 80% of boys although attention problems and impulsivity without hyperactivity can be seen in 40% of girls with the full mutation.

Treatment

Individuals with fragile X syndrome typically respond well to a stimulant medication after 5 years of age. Clonidine or guanfacine have been helpful for hyperarousal and hyperactivity in children

under 5yo or older. Selective serotonin reuptake inhibitors (SSRIs) help anxiety and can be used even in those under 5, although activation can be seen in about 20%, requiring a lowering of the dose or discontinuation. Atypical antipsychotics, most notably aripiprazole, when used in low dose helps to stabilize mood, decrease aggression, improve attention, and decrease anxiety. Minocycline is a targeted treatment for fragile X because it lowers matrix metalloproteinase 9 (MMP9) levels and a controlled trial demonstrated efficacy in young children with fragile X syndrome, however this can cause darkening of the teeth when started before age 8 so it is rarely used currently. Metformin, a type 2 diabetes drug also lowers MMP9 and it also down regulates the mTOR pathway that is too high in those with Fragile X syndrome so it is also considered a targeted treatment. Metformin has rescued the fragile X phenotype in animal models and it is now undergoing a controlled trial in children ages 6 to 45yo at three centers. Anecdotal cases have demonstrated a benefit from metformin treatment in language skills and behavior and when started before puberty it can decrease the macroorchidism that typically develops.

Arbaclofen, a GABA_B agonist has also been shown to benefit patients with fragile X syndrome particularly those with ASD or social deficits although a controlled trial in adolescents and adults did not show efficacy. However, limited efficacy is seen in younger children ages 5 to 11 treated with arbaclofen. The metabotropic glutamate receptor 5 (mGluR5) antagonists have not demonstrated efficacy in adolescents or adults with fragile X syndrome in controlled trials and a more recent FXLEARN trial involving AFQ056 plus parent implemented language intervention (PILI) in children ages 3 to 6 did not demonstrate efficacy. A controlled trial of low dose sertraline (2.5 to 5.0 mg) in children ages 2 to 6yo with fragile X syndrome demonstrated efficacy in developmental profiles and is often used clinically. A multicenter trial of a topical ointment with cannabidiol (CBD) underwent a controlled trial at multiple centers to target anxiety in 3 to 18 yo children and it demonstrated efficacy compared to placebo in the social avoidance subtest of the Aberrant Behavior Checklist_{FX}. However, the efficacy was significant only in those with a full mutation that was at least 90% methylated so a second trial is being carried out in multiple centers currently in an effort to gain FXA approval.

An exciting new study has shown that an inhibitor of phosphodiesterase 4D (PDE4D) which inhibits the enzyme that metabolizes cAMP, thus allowing cAMP to rise to normal levels, can improve several aspects of cognition in 30 adult males with fragile X syndrome. This controlled trial excited the interest of families and researchers worldwide so currently further phase 3 controlled trials in adolescent and adult males with fragile X syndrome are taking place. These studies will likely lead to many more treatment options for those with fragile X syndrome and some of the targeted treatments may improve language and cognition in this disorder. The future also looks bright for gene therapy for fragile X syndrome and FXTAS and hopefully clinical trials will begin in the next few years.

Resources

- **The Fragile X Society**, The Chestnuts, 4 Stortford Rd, Great Dunmow Essex. CM61DA, UK. info@fragileX.org.uk. Phone 01371875100
- **The National Fragile X Foundation**, 1012 14th st NW suite 500, Washington DC, 20005, USA. 800-688-8765
- **FRAXA Research Foundation**, 45 Pleasant St., Newburyport, MA 01950, USA. 978-462-1866

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The SSBP strongly recommends patients to follow the advice and direction of their clinical team, who will be most able to assess their individual situation