Fragile X Syndrome

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 transcription of many proteins important for synaptic plasticity. FMRP regulates the translation of hundreds of proteins many of which are important for synaptic plasticity and are associated with autism. Fragile X syndrome is the most common inherited cause of intellectual disability and the most common single gene cause of autism. Therefore all individuals with intellectual disability or autism 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. Targeted treatments have been developed to reverse 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 in addition to emotional problems. 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.

Carriers have a premutation and are typically unaffected cognitively, although in approximately 10 to 20% intellectual disability or autism can occur. 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 developmental delay at times but more commonly causes emotional difficulties, such as anxiety or depression in about 30 to 40%, primary ovarian insufficiency in 20% and neurological problems in a subgroup of aging male and female carriers. Additional medical problems that can occur in carriers includes hypertension, migraine

headaches, insomnia, sleep apnea, hypothyroidism, gastroesophageal reflux, immune mediated problems, chronic fatigue, fibromyalgia and neuropathy. Additional neurological problems include autonomic dysfunction, intention tremor and ataxia, and the combination of these problems is called the fragile X-associated tremor ataxia syndrome (FXTAS). FXTAS occurs in approximately 40% of older male carriers and 8% to 16% of older female carriers. Brain atrophy and white matter disease are seen on MRI in those with FXTAS. The premutation disorders including FXTAS and the fragile X-associated primary ovarian insufficiency (FXPOI) typically do not occur in those with a full mutation because they usually do not have elevated *FMR1* mRNA levels. However, a rare individual with fragile X syndrome who is partially or completely unmethylated who has elevated *FMR1* mRNA has been reported with FXTAS. FXTAS has also been reported in a rare individual with a gray zone allele, specifically a CGG repeat in the 45 to 54 range.

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.

Institutionalized individuals with intellectual impairment of unknown origin have rates of fragile X syndrome ranging from 2.5% to 5.9%. The syndrome is the most common inherited cause of learning disability or intellectual impairment. Approximately 2 to 6% of those with autism have fragile X syndrome and it is the most common single gene associated with autism.

Physical

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, 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 20% and recurrent otitis media occurs in the majority in early childhood.

Life expectancy/Natural history

Probably normal except for those who have seizures. 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 beyond 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 unnmethylated full mutation or mosaic status (some cells with the premutation and some with the full mutation), will have a higher IQ. Verbal intelligence 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 and visuospatial skills are common. The rate of intellectual development diminishes with age, particularly after puberty.

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, autism and ADHD and social anxiety with aversion to eye contact is present in the majority of children and adults with fragile X syndrome. Approximately 60% 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 mannerisms 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 in the CNS is correlated to the severity of autism in females. Hyperactivity is seen in about 80% of boys although attention problems and impulsivity without hyperactivity can be seen especially in 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. Arbaclofen, a $GABA_B$ agonist has also been shown to benefit patients with fragile X syndrome particularly those with autism or social deficits although a controlled trial in adolescents 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. Newer targeted treatments including metadoxine, lovastatin and an IGF1 analogue are currently undergoing trials in adolescents and adults with fragile X syndrome.

Resources

- **The Fragile X Society**, 53 Winchelsea Lane, Hastings, East Sussex, TN35 4LG. 01424 813 147
- **The National Fragile X Foundation**, P.O. Box 37, Walnut Creek, California, 94597, USA. 800-688-8765
- **FRAXA Research Foundation**, 45 Pleasant St., Newburyport, MA 01950, USA. 978-462-1866

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