R.C.P.U. NEWSLETTER

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R.C. Philips Research and Education Unit
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Fragile X syndrome & the link to autism.

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Fragile X syndrome (aka Martin Bell syndrome, Escalante syndrome) is the most common form of inherited mental retardation and intellectual disabilities with a frequency that is estimated to be as high as 1 in 2000 males and 1 in 4000-6000 females worldwide. It is also a frequent cause of autism, and it is estimated that 6% of males with the diagnosis of autism have Fragile X syndrome as the root cause.

Physical findings of Fragile X are subtle in infants and young boys. However, there are physical findings that can be present from a young age:

- Relative macrocephaly (head > 50%ile for age/sex
- Strabismus
- Light colored irides (colored part of eye)
- Midface hypoplasia
- Mitral valve prolapse
- Joint hyperlaxity (particularly of thumbs & fingers
- Flat feet
- Hypotonia
- Soft skin
- Large, soft & flexible ears
- Tall forehead
- High arched palate

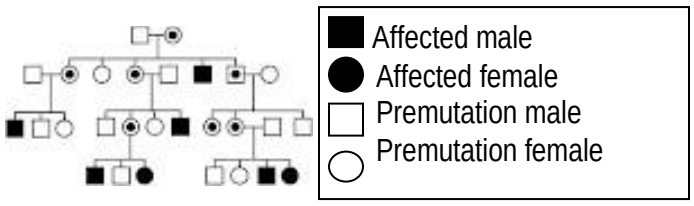
The major physical finding in boys with Fragile X syndrome is macro-orchidism (enlarged testicles) is often not identifiable until after puberty. Macro-orchidism can be accompanied by elongated phallus, but this is not always the case.

Cognitive function - Developmental delay (including delayed attainment of motor and language milestones), intellectual disability (previously termed mental retardation), and learning disabilities are the most consistent and significant clinical features of fragile X syndrome. Boys with Fragile X typically sit alone at 10 months, walk at 20.6 months, and say their first clear words at 20 months (compared with approximately 7 months, 13 months, and 11 months, respectively, in typically developing children).

Intelligence quotient [IQ] is typically between 35-70, and children are noted to have mathematical learning disabilities, deficiencies in abstract thinking that become more notable as children with this condition get older. IQ testing is often noted to be lower at older ages than when children are younger, but developmental regression is not typical of this condition.

Behavioral functioning - Problems include mild-to-moderate autistic-like behaviors including: hand flapping & avoidance of eye contact as well as shyness, sensory integration difficulties, attention deficits, hyperactivity, impulsivity, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), depressed affect, anxiety and aggression. The range of behavioral difficulties is quite large, even within families.

Inheritance pattern:



Fragile X syndrome is inherited in an X-linked dominant pattern with reduced expression in females (although you may also see it listed as an X-linked recessive pattern). A condition is considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes. (The Y chromosome is the other sex chromosome.) The inheritance is dominant if one copy of the altered gene in each cell is sufficient to cause the condition. X-linked dominant means that in females (who have two X chromosomes), a mutation in one of the two copies of a gene in each cell is sufficient to cause the disorder. In males (who have only one X

chromosome), a mutation in the only copy of a gene in each cell causes the disorder. In most cases, males experience more severe symptoms of the disorder than females.

In women, the *FMR1* gene premutation on the X chromosome can expand to more than 200 CGG repeats in cells that develop into eggs. This means that women with the premutation have an increased risk of having a child with fragile X syndrome. By contrast, the premutation in men does not expand to more than 200 repeats as it is passed to the next generation. Men pass the premutation only to their daughters. Their sons receive a Y chromosome, which does not include the *FMR1* gene.

Table 1: Effects of FMR1 repeat by size and methylation status:

Mutation Type	Number of CGG Trinucleotide Repeats	Methylation Status of *FMR1*	Clinical Status	
			Male	Female
Premutation	~55-200	Unmethylated	At risk for FXTAS [1]	At risk for POF and FXTAS [1]
Full mutation	>200	Completely methylated	100% with MR	~50% with ID, ~50% normal intellect
Repeat size mosaicism	Varies between premutation and full mutation in different cell lines	Partial: unmethylated in the premutation cell line; methylated in the full-mutation cell line	Nearly 100% affected with ID; may be higher functioning [2] than males with full mutation	Highly variable: ranges from normal intellect to affected
Methylation mosaicism	>200	Partial: mixture of methylated and unmethylated cell lines		
Unmethylated full mutation	>200	Unmethylated	Nearly all have ID but often have high-functioning MR to low-normal intellect	

ID=intellectual disability Ref: www.genereviews.org

Diagnostic testing - In 1943, Martin and Bell investigated a family with multiple male members who had mental retardation. These investigators were able to link the cognitive disorders in this family to an unidentified mode of X-linked inheritance. In 1969, Lubs discovered excessive genetic material that extended beyond the long arm of the X chromosome in affected males and in their unaffected female relatives. Initially, these results were not reproducible. However this became the first clinically available test for Fragile X syndrome once the importance of the folate-deficient thymidine-deficient medium, which was used in the initial studies to culture lymphocytes, was realized.

Since the 1960s and early 1970s, progress toward mapping the gene has been steady and rewarding, and the precise genetic defect that causes fragile X syndrome has been characterized. Advances in molecular genetics have provided reliable diagnostic testing, and this test is available from large commercial laboratories such as Quest and Labcorp now as well as through specialty genetics laboratories.

Fragile X Tremor Ataxia Syndrome in *FMR1* Premutations

While in the past, individuals who were carriers of premutation changes in the FMR1 gene were informed that they may be at risk to have a child/grandchild with Fragile X syndrome, they were not informed that they might be at risk to have health problems of their own. In more recent years, it has been noted that individuals who carry a premutation are at risk to develop a Parkinsons-like condition known as the Fragile X Tremor Ataxia Syndrome (FXTAS). This condition results in development of an intention tremor, gait ataxia, Parkinsonism and working memory defects. FXTAS occurs more frequently in males than females with premutation Fragile X alleles, but can occur in individuals of either sex. FXTAS results in white matter lesions on MRI in the middle cerebellar peduncles and/or brainstem.

RISK of FXTAS in males by age:

50-59 years	17% risk
60-69 years	38% risk
70-79 years	47% risk
>80 years	75% risk

Adapted from Greco et al [2005]

Premature Ovarian Failure POF in *FMR1* Premutations

One of the other medical concerns associated with premutation Fragile X status is premature ovarian failure (POF). This is defined as the onset of menopause before age 40 years. Although there are many causes of POF, premutation Fragile X status is expected to be the cause in 2% of women who have a negative family history of POF and 14% of women who have a positive family history of POF. Onset has been as early as 11 years of age, but does not absolutely preclude conception. It is anticipated that perhaps 5-10% of women with POF may conceive a child after POF is diagnosed.

RISK of POF in females by repeat size:

59-79 repeats	6.9 Odds Ratio
80-99 repeats	25.1 Odds Ratio
>100 repeats	16.4 Odds Ratio

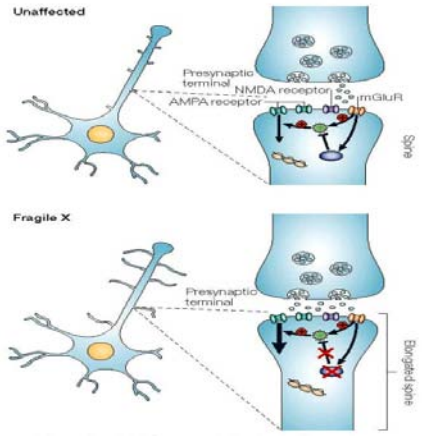
Adapted from Greco et al [2005]

Functioning of FMRP- The FMRP gene appears to be important in the production of mature synapses (see figures 1 and 2). Brain morphology studies of the brains of individuals with Fragile X have noted that the dendritic spines of these individuals are longer and thinner than are seen in normal brains. This is indicative of immaturity of the dendritic spines. This immaturity is felt to have a detrimental effect on synaptic plasticity (the ability of neurons to strengthen and weaken synaptic connections in response to activity

patterns). This synaptic plasticity is felt to be the basis of cognition and memory. Thus, the immaturity of dendritic spines in Fragile X has a negative effect on both cognition and memory.

Studies have also noted that absence of FMRP protein expression leads to excessive activity of the neurotransmitter, glutamate, in the glutamate receptor pathway within the synapse. It is believed that excessive glutamate activity is the root cause of Fragile X behaviors. Trials in animal models have shown that drugs that inhibit glutamate activity alleviate behavioral symptoms in both young and adult study animals.

Figure 1. Synaptic regions of dendritic spines in Fragile X and normal Neurons



Ref: Gratcher & Zoghbi, 2005

Drug Treatment Trials

Treatment trials are underway for several medications that either: inhibit glutamate expression, or glutamate receptor activity, and have shown some promising results.
Arbaclofen (by Novartis) is currently in treatment trials for adults and adolescents with Fragile X syndrome who have social withdrawal. The mechanism of action is to reduce the available glutamate in the synapse. Early trials have suggested the reduction of hyperactivity and inappropriate speech.

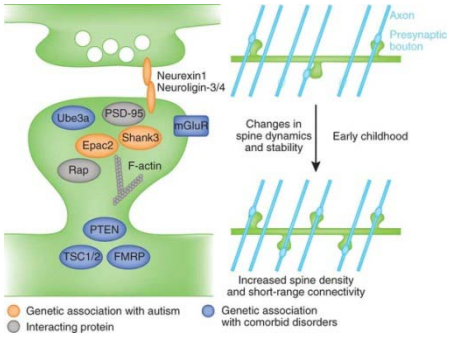
Roche also has a similar drug in treatment trials.

Memantine is a drug which blocks the glutamate receptors. Mouse model treatment trials have shown that treatment results in maturation of the dendritic spines.

Implications for Autism & Related Disorders:

While the initial success of these drugs in reducing or ameliorating the behavioral effects of Fragile X syndrome is very promising and holds tremendous hope for families struggling with some of the behavioral difficulties associated with this condition, the promising early trial results hold out hope for a much greater population of individuals. The complex in the synaptic region holds many proteins that interact with the FMRP protein. Many neurologic conditions are associated with mutations within these related proteins.

Figure 2. Associated proteins in the synaptic region



Protein name and associated condition:
UBE3a – Angelman sx
Neurexin1 – autism
Neuroligin 3 & 4 - autism
PTEN – Ruvalcaba Myhre sx
SHANK3 – Phelan McDermid sx
Epac2 – learning & social delays Ref: Penzes et al, 2011

Treatment trials of some of these medications have been started in individuals with autism. Families and physicians are currently optimistic that results of these trials will soon provide assistance to children with developmental delays

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  Web: http://www.fragilex.org/

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About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.
Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large.

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