Fragile X syndrome (FXS) and Fragile X-associated tremor/ataxia syndrome (FXTAS)

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Objectives:

- Understand the clinical presentation of patients with FXS and FXTAS.
- Understand the molecular and phenotype difference between the full FXS mutation and the premutation, and the variability of presentation of individuals.
- Understand the molecular effects of FMRP deficiency on other parts of the genome.

The fragile X mental retardation gene (FMR1) mutation involves a CGG trinucleotide repeat. Although fragile X is a single gene disorder, there is a broad impact on the genome. Different CGG repeat lengths in the gene result in two disorders through separate mechanisms:

- **Fragile X syndrome (FXS),** the leading heritable form of mental impairment, occurs in individuals with the full mutation (over 200 CGG repeats). FXS results from the transcriptional silencing of FMR1 with consequent **deficiency/absence of the FMR1 protein (FMRP).** Because FMRP is an RNA-binding protein, deficiency leads to dysregulation of many genes.

- **Fragile X-associated tremor/ataxia syndrome (FXTAS),** a neurodegenerative disease**,** occurs in some older individuals (usually male) with the premutation (55-200 CGG repeats). FXTAS is caused by the **elevation of FMR1-mRNA**. This causes an **RNA gain-of-function toxicity** which does not cause symptoms until after middle age.

Basic concepts about the FMR1 gene and protein

There is a repetitive CGG triplet repeat on the front end of the FMR1 gene. Normal individuals have between 5 and 44 CGG repeats. The premutation is defined as 55-200 repeats. All individuals with the premutation have elevated FMR1 mRNA (2-8 times normal). The full mutation (>200 CGG repeats) is associated with features of FXS (see below). Usually the full mutation expansion is methylated and transcription of the gene is significantly reduced or eliminated, so very little FMR1 mRNA is transcribed. Thus there is a severe deficiency of FMR1 protein. and the mRNAs that FMRP binds to become dysregulated.

The FMR1 protein (FMRP) in neurons is an RNA-binding protein that is involved with the regulation of translation (typically a translation suppressor) of many other messages. FMRP regulates local protein synthesis of specific mRNAs in response to synaptic stimulation. FMRP may bind to mRNA at the synapse, or bind to mRNA in the nucleus with subsequent transport of these messages to the synapse. With stimulation of the metabotropic glutamate system, FMRP organizes the translation of messages important for **synaptic plasticity**.

Fragile X (FXS) phenotype

Features of FXS include prominent ears, long face, hyperextensible finger joints and cognitive deficits including learning disabilities and/or mental retardation. There may also be ADHD, anxiety and autism in these patients.

In the absence of FMRP, functions involving **changes in synaptic connections** are altered. E.g. involvement of the metabotropic glutamate receptor 5 (mGluR5) leads to enhanced long term depression (LTD) resulting in weakened synaptic connections, enhanced synaptic elimination, and structural changes including immature and elongated synaptic connections. The enhanced mGluR5 pathway in FXS also leads to internalization and subsequent reduction at the synapse of AMPA receptors, particularly in the hippocampus.

A number of messages that which are regulated by FMRP have been identified to help explain the involvement of anxiety and mental retardation (common features), and epilepsy (in 20% of FXS individuals) in FXS. Anxiety may be related to the dysregulation of the glucocorticoid receptor whose

message binds to FRMP. Mental retardation is probably related to dysregulation of several mRNAs, including those of the cahedrins and MAP1B, that are important for synaptic plasticity and synaptic structure. Epilepsy may be related to the dysregulation of the GABA-A receptor, whose message binds to FMRP.

There is substantial **variability** in the phenotypic expression. The most severely involved patients with FXS often have autism and are nonverbal. Mild involvement without mental retardation occurs when FMRP is only mildly deficient. The extent of FMRP deficiency depends in part on the extent of methylation of the gene.

Overlap between FXS and autism: About one-third of patients with FXS have autism. Research has compared patients with FXS and autism with those with FXS alone to get clues to pathogenesis. The level of FRMP correlates with IQ, but not with the presence/absence of autism. Those with FXS and autism are an important subgroup of patients with autism because they may provide insight into the biological mechanisms that underlie other forms of autism.

The **treatment** of patients with FXS involves a multi-modality intervention that includes speech and language therapy, occupational therapy, behavioral interventions, special education support and psychopharmacological interventions. Genetic counseling is important.

Premutation carriers and FXTAS

Most individuals with the premutation have a normal IQ, but premature ovarian failure occurs in about 21% of female carriers and FXTAS occurs in about 38% of older male carriers. Approximately 30% of female premutation carriers have emotional problems including anxiety, social phobia and depression. Although most premutation carriers have relatively normal levels of FMRP, some do not. Some individuals with the premutation may present with ADHD, learning disabilities, mental retardation, or autism spectrum disorder, since these individuals may have a decreased FMRP level due to a relative block in translation. This is important for clinicians to understand because children with the premutation who present with mental retardation and features of FXS are sometimes ignored and told that their problems cannot be due to the premutation.

FXTAS: In older individuals (usually male), the RNA toxicity leads to ataxia, intention tremor, peripheral neuropathy and cognitive decline. About 4% of adults presenting with cerebellar ataxia have the premutation. Often individuals with FXTAS are misdiagnosed with Parkinson Disease or essential tremor or cerebellar ataxias because they were not initially tested for the FMR1 mutation. The correct diagnosis of FXTAS in grandfathers (eg, older men originally diagnosed with PD or cerebellar ataxia) may occur following the birth of a grandchild with FXS. Pathological changes in FXTAS include brain atrophy, white matter disease, Purkinje cell loss, and the presence of eosinophilic intranuclear inclusions in neurons and astrocytes throughout the cortex. The inclusions are most dense in the hippocampus (they do not contain specific proteins like tau or alpha-synuclein). The excess FMR1-mRNA in premutation carriers is hypothesized to exert a toxic gain of function effect leading to excessive binding of cellular proteins to the expanded CGG sequence and subsequent sequestration of these proteins and the mRNA in the inclusions. The inclusions themselves may not be toxic but the sequestration of important proteins may lead to neuronal toxicity and cell death. It is important for pediatricians to understand the RNA toxicity mechanism of involvement in FXTAS because young males with the premutation who have social deficits and/or cognitive deficits may have a similar mechanism of involvement at an earlier state in development.

References

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