ABSTRACT

Fragile X syndrome is the most common inherited cause of cognitive disability and autism that is known. The behavioral phenotype includes anxiety, sensory hyperarousal, hyperactivity and mood instability. The physical phenotype is associated with connective tissue problems leading to prominent ear pinnae, hyperextensible finger joints and flat feet. Fragile X syndrome is caused by a full mutation in the FMR1 gene on the bottom end of the X chromosome and the CGG trinucleotide repeat on the front end of the gene expands to >200 repeats leading to gene silencing and a dramatic reduction in transcription and translation.

The molecular clinical correlations have been studied and many of the features of the fragile X syndrome including cognitive deficits, and physical features are associated with FMRP deficits. The association between fragile X and autism was first reported in 1982 and there has been a plethora of studies confirming this association. There are a number of neurobiological commonalities between fragile X and autism including dysregulation of GABA and glutamate systems, enhanced brain growth in early childhood, a decrease in AMPA receptors, and white matter abnormalities in the brain. We have also seen an association between autism spectrum disorders and the fragile X premutation (55-200 CGG repeats).

The premutation is associated with a toxic RNA gain of function related to elevated message. The clinical consequences of this is the fragile X-associated tremor/ataxia syndrome (FXTAS) in older individuals but there is emerging research suggesting that a subgroup of carriers, particularly boys have problems with anxiety, social deficits, and ADHD.