Fragile X Syndrome: New Advances

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Fragile X: A Family Affair, all generations may be involved with fragile X mutations

Fragile X Syndrome: leading inherited of ID and leading single gene associated with autism: 1 in 4,000 to 1 in 6000 with FXS. 60% with ASD; 2-6% with autism have FXS.
Pockets of Fragile X throughout the world including Ricaurte Columbia
Colombia Project of Hope
Two different mutations in the same *FMR1* gene

1/130-250 females
1/250-810 males
1/4000-6000

Typical (CGG) < 45

Premutation (CGG) 55 - 200

Full mutation (CGG) > 200

Fragile X syndrome (FXS)
Primary Ovarian Insufficiency (FXPOI)
Fragile X-associated Tremor Ataxia Syndrome (FXTAS)
Depression and anxiety
ADHD and ASD
Expression of the *FMR1* gene

![Diagram showing the expression of the FMR1 gene across different CGG repeat numbers.

- **Normal**
- **Gray**
- **Premutation**
- **Full Mutation**

- **Relative FMR1 mRNA level**
- **FMRP level**

- **Unmethylated**
- **Partially methylated**
- **Hyper-methylated**

- **FXTAS and FXPOI**
- **FXS**
The more FMRP you have the smarter you are. 85% of males with the full mutation have ID or IQ< 70. 25% of females have ID but 70% have an IQ<85.

Loesch et al 2004

Low FMRP in Schizophrenia
Kelemen et al 2013

Kovacs et al 2013  IQ and age of onset of schizophrenia correlates with FMRP level.
Lowered Brain FMRP levels in Psychiatric Disorders
Fatemi et al Schizophrenia Research 2010

FMRP lower in adult autism brains
Often many members in a family affected by FXS or premutation involvement
Different phenotype in young vs old
13 yo boy with XXY and FXS
Behavioral Features in FXS

- Poor eye contact: 90%
- Handbiting: 60%
- Handflapping: 80%
- Tactile defensiveness: 80%
- Unusual sensory responses to stimuli
- Perseverative speech or behavior in almost all-routines

Images of children demonstrating these features.
Emotional & Neurocognitive Features

- Hyperactivity, impulsivity and/or short attention span
- Executive function deficits: problems with organization, shifting set, planning, inhibition, tangential speech, perseveration
- Over reactivity to stimuli: enhanced electrodermal response to stimuli; enhanced cortisol release after stressors
- Anxiety
- Autism or ASD
- Mood instability: excessive outbursts, tantrums
Information transmission is no longer discriminative. Noise that is usually filtered out is being transmitted indiscriminately in absence of FMRP

Deng et al 2013 Neuron
Anxiety Disorders Interview Scale (ADIS) for DSM IV

Cordiero et al 2011 JND
Communication and Social Deficits are continuous in boys with FXS: 60% with ASD. Significant heterogeneity in the FXS-autism phenotype.

DSM5: 60% of boys with FXS have ASD.
Communication and Social Deficits in boys with FXS: 60% with ASD, significant heterogeneity in the FXS-autism phenotype.

DSM5: 60% of boys with FXS have ASD
Sensory Modulation or Processing Problems in FXS

Enhanced electrodermal responses and lack of habituation to sensory stimuli correlate inversely with FMRP levels

(Miller et al 1999)
Lack of habituation in fMRI studies

- Bruno et al 2014 AJP: 30 FXS and 24 controls IQ and ASD matched; habituation defined as less activation in 2nd run to faces with direct or indirect eye contact
- FXS with deficits in habituation in regions important for visual and emotional processing including fusiform gyrus, occipital region, anterior cingulate and frontal regions.
- Sensitization or enhanced activation seen with 2nd run
Lack of habituation in fMRI brain activation to gaze in FXS vs IQ and ASD matched controls (15 to 25yo)

FIGURE 2. Habituation of Dorsal Anterior Cingulate Activation by Group and Condition

Bruno et al 2014 AJP
Habituation correlated with FMRP levels in females with FXS

Bruno et al 2014 AJP
Lack of habituation correlated with ADOS score in females

(Bruno et al 2014 AJP)
Vineland Adaptive Behavior over time in boys

Klaiman et al 2014 Pediatrics
The Prader-Willi Phenotype (PWP) of Fragile X Syndrome

Those with the PWP have a higher rate of autism (70%) than those with FXS alone and lower CYFIP levels (Nowicki et al 2007). GH is a treatment for PWS and maybe for PWP.
FXS and ASD had a higher rate of seizures + med problems

<table>
<thead>
<tr>
<th></th>
<th>FXS Alone (n = 33)</th>
<th>FXS+ ASD (n = 57)</th>
<th>Chi-Square Test (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full mutation</td>
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<td>Mosaic</td>
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<td>Seizures</td>
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<td>MRI Abnormalities</td>
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<tr>
<td>Genetic Abnormalities</td>
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<td>Total Medical Problems</td>
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</tr>
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<td>n</td>
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<td>61.4</td>
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<tr>
<td>percentage</td>
<td>18.2</td>
<td>38.6</td>
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</table>

Garcia Nonell et al 2007
Early life seizures displaces FMRP from dendritic puncta to perinuclear location

A: control with FMRP (green color and white arrows) in puncta of dendrites in rat hippocampus at 60d

B: After early life seizures FMRP shifts to perinuclear location (yellow arrow) and enhanced LTP With focal deficits of FMRP

Bernard, Costanos, Benke 2012 SFN
Bernard et al 2013
### TABLE III. Frequency of Reported Developmental Delay and Other Conditions for Premutation Males Compared With a Sample of Normal Males Matched on Age and Family Income

<table>
<thead>
<tr>
<th>Condition</th>
<th>Premutation males (n = 57)</th>
<th>Non-FX males (n = 57)</th>
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<tbody>
<tr>
<td>Developmental delay</td>
<td>33.0***</td>
<td>1.8</td>
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<tr>
<td>Attention problems</td>
<td>41.1*</td>
<td>21.4</td>
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<td>Hyperactivity</td>
<td>28.1</td>
<td>14.0</td>
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<td>Aggressiveness</td>
<td>19.3*</td>
<td>5.3</td>
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<tr>
<td>Self-injury</td>
<td>8.9</td>
<td>1.8</td>
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<tr>
<td>Autism</td>
<td>19.3*</td>
<td>5.3</td>
</tr>
<tr>
<td>Seizures</td>
<td>11.3**</td>
<td>1.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>33.3**</td>
<td>8.8</td>
</tr>
<tr>
<td>Depression</td>
<td>10.7</td>
<td>10.7</td>
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</table>

*P < 0.05  
**P < 0.01  
***P < 0.001
In premutation boys with seizures there is a strong association with autism and ID.

Percentage

20% of premutation carriers with autism or ID had an additional CNV associated with clinical involvement.

Lozano et al 2014 JND
The Fragile X Mutation
A family affair

Four generations

The Fragile X Mutation
A family affair

Four generations
Spectrum of Premutation Involvement

**FMR1** CGG-repeat toxic RNA "trigger"

- Upregulation of heatshock proteins
- ASFMR1 splice isoforms in FXTAS
- Kinase activation
- Sequestration of DROSHA, DGCR8, Sam68
- Mitochondrial dysfunction
- RAN translation
- Inclusion formation
- Neuropathology

**Background gene effects**

**Environmental effects**

**Neurodevelopmental problems**
- Social anxiety → ASD
- ADHD
- Cognitive deficits

**Psychiatric involvement**
- Anxiety
- Stress
- Depression

**Endocrine dysfunction**
- FXPOI
- Immune dysregulation
  - Hypothyroidism
  - Fibromyalgia, central pain syndrome
  - Lupus - MS features

**Neurological problems**
- Neuropathy
- Migraine, sleep apnea, RLS
- Memory problems, foggy thinking
- Hypertension, chronic fatigue

**FXTAS**
- tremor, ataxia, Parkinsonism
- autonomic dysfunction, EF deficits, memory and cognitive decline
Collaborators

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