Harvard University Conte Center and Life Sciences Outreach

Fragile X Syndrome: A Window into Neurodevelopmental Disorders

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Fragile X Syndrome: A Window into Neurodevelopmental Disorders

• Fragile X syndrome is the most common inherited cause of intellectual disability.
• Fragile X syndrome is the most common genetic cause of autism.
• Fragile X syndrome is associated with other common neurodevelopmental disorders (e.g., ADHD).
• Fragile X syndrome has a distinctive cognitive profile with greater nonverbal impairment, in particular math disability.
• Fragile X syndrome is strongly associated with anxiety, in particular social anxiety.
• Male carriers of the Fragile X mutation are at (high) risk of developing a neurodegenerative disorder: Fragile X Tremor Ataxia Syndrome (FXTAS).
• Female carriers of the Fragile X mutation present a range of behavioral-emotional and neurologic problems.
One Gene (FMR1): Three (or More) Disorders

Typical (CGG) < 45
- mRNA
- FMRP
- Clinical: Normal

Premutation (CGG) 55-200
- mRNA
- FMRP
- Clinical: Primary ovarian insufficiency (POI), fragile X-associated tremor ataxia syndrome (FXTAS) due to excess mRNA

Full mutation (CGG) > 200
- mRNA
- FMRP
- Clinical: Fragile X syndrome due to lack of FMRP

M: 1:800, F: 1:250
M: 1:4000, F: 1:6000
ID, ASD, LD?

One Gene (*FMR1*): Multiple disorders in the same family

Three Generations: The young man and woman on the right both carry the full mutation for fragile X syndrome. Their grandfather is now affected by FXTAS and is the fragile X syndrome carrier who passed on the carrier status to his daughter, their mother.

Fragile X Syndrome: One gene, Three Major Disorders

Fragile X syndrome: in males and females with full mutation (200-2,000 repeats) or mosaicism (full mutation+premutation). Life-long disorder: intellectual disability, ADHD, anxiety, autism, other behavioral problems (aggressive behavior, stereotypies, etc.).

Fragile X tremor ataxia syndrome (FXTAS): predominantly older (>50 years) males with premutation (61-199 repeats). Manifestations: gait ataxia, intention tremor, cognitive impairment (frontal lobe dementia).

Premutation-related disorders: POI, females with emotional problems and perseverative thinking, children (mainly boys) with ADHD, intellectual disability and/or autism.

Intermediate or gray zone (41-60 repeats) : ??
**Fragile X Syndrome**

**FMR1 Mutation**

**Diagnosis by** *FMR1* **Southern blot and PCR**

FMRP quantifications provide complementary information

**FMRP Patterns**


**Cytogenetics**


**FMRP quantifications provide complementary information**

**FMRP Patterns**


**X-linked: Males more Affected than Females**

Fragile X Phenotype

- Affects about 1:4000 males, 1:6000 females

- **Neuro Phenotype (VARIABLE)**
  - Mild/Moderate ID
  - ADHD
  - Autism
  - Social Withdrawal/Anxiety (incl. GAD)
  - Aggressive Behavior
  - Hyperarousal
  - Seizures

- **Non-Neuro Phenotype**
  - Facial characteristics (**non-diagnostic**)
  - Connective tissue abnormalities (joint laxity, mitral valve prolapse)
  - Strabismus
  - Recurrent OM
  - GER

From Fragile X Research Foundation website

Fragile X is a Major Cause of Intellectual Disability (ID) & Autism (ASD)

Mild to Moderate ID in Fragile X vs. Moderate to Severe in Other Genetic Disorders

**Down Syndrome**

**Fragile X Syndrome**


Fragile X syndrome is a Major Cause of Autism

- High-resolution chromosome studies (5%)
- aCGH—beyond what would be detected by chromosomal analysis (10%)
- Fragile X (5%)
- MECP2 (5%—women only)
- PTEN (3%—if head circumference >2.5 SDs)
- Other (10%)


Typical Fragile X  Fragile X + Autism
Autism in Fragile X and Down Syndromes

Low IQ *per se* has a minimal influence upon ASD status in ID. In contrast, autism-related behaviors predict ASD diagnosis.

**DS+ASD vs. DS Typical**
- **IQ/DQ** $\rightarrow$ ASD, $p=0.99$
- **ABCstereo** $\rightarrow$ ASD, $p=0.001$
- **AutBehav rel** $\rightarrow$ ASD, $p<0.0001$

**% Variance**
- IQ/DQ: 0%
- ABCstereo: 13%
- AutBehav rel: 27%

**FXS+ASD vs. FXS Typical**
- **IQ/DQ** $\rightarrow$ ASD, $p=0.54$
- **ABCleth** $\rightarrow$ ASD, $p=0.79$
- **ADIrecs** $\rightarrow$ ASD, $p<0.0001$

**% Variance**
- IQ/DQ: 0.5%
- ABCleth: 0.1%
- ADIrecs: 53%
Autism in Fragile X

16-50% prevalence of Autism/ASD in Fragile X Syndrome

Example of Research in Autism in Fragile X: Determining Behavioral Profiles

1. Delayed/impaired adaptive socialization is the primary determinant of FXS+ASD. CORTEX

<table>
<thead>
<tr>
<th>Adaptive Socialization Measures</th>
<th>YES ASD</th>
<th>NO ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td>VABSSoc total score</td>
<td>79.2%</td>
<td>93.8%</td>
</tr>
<tr>
<td>VABSSoc items (24, 30, 31, 32, 36, 38)</td>
<td>83.3%</td>
<td>90.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SB-IV Composites</th>
<th>t-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Reasoning</td>
<td>4.23</td>
<td>0.0002</td>
</tr>
<tr>
<td>Abstract/Visual Reasoning</td>
<td>1.49</td>
<td>0.15</td>
</tr>
<tr>
<td>Quantitative Reasoning</td>
<td>2.12</td>
<td>0.04</td>
</tr>
<tr>
<td>Short-Term Memory</td>
<td>1.67</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Autism in Fragile X

16-50% prevalence of Autism/ASD in Fragile X Syndrome

Example of Research in Autism in Fragile X: Determining Behavioral Profiles

2. Severe social withdrawal (avoidance+indifference) is an important secondary contributor. **LIMBIC SYSTEM**

<table>
<thead>
<tr>
<th>T1 ABCsw Items</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SW5</td>
<td>YES ASD= 87.5%</td>
<td>YES ASD= 75.0%</td>
<td>YES ASD= 77.8%</td>
</tr>
<tr>
<td>SW16</td>
<td>YES ASD= 87.5%</td>
<td>YES ASD= 75.0%</td>
<td>YES ASD= 77.8%</td>
</tr>
<tr>
<td>SW30</td>
<td>YES ASD= 87.5%</td>
<td>YES ASD= 75.0%</td>
<td>YES ASD= 77.8%</td>
</tr>
<tr>
<td>SW40</td>
<td>YES ASD= 87.5%</td>
<td>YES ASD= 75.0%</td>
<td>YES ASD= 77.8%</td>
</tr>
<tr>
<td>SW42</td>
<td>YES ASD= 87.5%</td>
<td>YES ASD= 75.0%</td>
<td>YES ASD= 77.8%</td>
</tr>
</tbody>
</table>


Social Avoidance Factor: Sansone et al. JADD 42:1377-1392
Data and cluster analyses of social withdrawal behaviors identify boys with ASD only or a ASD+Social Anxiety co-morbidity

Model 6: Social Withdrawal Clusters and DSM-IV Diagnoses

<table>
<thead>
<tr>
<th>SW Cluster</th>
<th>Distribution of Social Withdrawal in FXS Using ULS</th>
<th>Total # of Subjects Per Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Groups</td>
<td>None</td>
</tr>
<tr>
<td>Cluster 1</td>
<td>% Within Cluster</td>
<td>19</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>% Within Cluster</td>
<td>54</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>% Within Cluster</td>
<td>14</td>
</tr>
<tr>
<td>Cluster 4</td>
<td>% Within Cluster</td>
<td>0</td>
</tr>
</tbody>
</table>

Statistically significant data appear in italics and bold.

Note: Cross-tabulation of forced four-clusters, which is a final solution, distributed among the four DSM groups. Forced four-factor solution, which is also a final solution, generated from selected ABC and CBCL social withdrawal items (8+4). Sampling adequacy coefficient was 0.78 (KMO > .70 is considered strong). Unweighted Least Squared Factoring extraction method (correlation matrix) was applied.

Statistical significance revealed Pearson Chi-Square value 36.674, df = 15, P= .001 (2-tailed), number of valid cases 62.
Behavioral Features in FXS: Diagnostic Challenges
Shy temperament: misdiagnosis
Social Anxiety: missing diagnosis (Social Anxiety is the most common psychiatric co-morbidity in “Idiopathic” Autism)

Example of Research in Autism in Fragile X: Studying Social Withdrawal

Fragile X Greeting
Autism in Fragile X

The Social Approach Scale paradigm identifies dynamics of social avoidance and indifference that can distinguish Autism from Social Anxiety in Fragile X.

High baseline and post-stimulus cortisol levels are seen in FXS+ASD

Cognitive trajectory distinguishes FXS+ASD


2. Abnormalities in the cytoplasmic $FMR1$ interacting protein 1 ($CYFIP1$) pathway in lymphoblasts from boys with FXS+ASD (vs. controls and dup15q): $GPR155$ in FXS, $CYFP1$ & $JAKMIP1/MARLIN-1$ in dup15q (Nishimura et al. Hum Mol Genet 16:1682-1698, 2007)