Outline

• Overview of Fragile X Syndrome
• Overlap of Fragile X Syndrome and Autism

What is Fragile X Syndrome?

FXS was first known example of a trinucleotide repeat disorder.

History of Fragile X Syndrome

• In 1943, Leo Kanner described the condition.
  - James Purdon Martin and Julia Bell

### Fragile X Syndrome

#### Phenotype

- **Males**
  - Varying degrees of symptoms ranging from mild to severe

- **Females**
  - 1/3 have intellectual disability
  - More common – learning difficulties and emotional problems

- **Physical Features**
  - Large ears, long face, soft skin, macroorchidism in post-pubertal males, connective tissue problems

- **Behavioral Features**
  - ADHD, autism and autistic behaviors, social anxiety, hand-biting and/or flapping, poor eye-contact, sensory disorders, increased risk for aggression

### Checklists

#### Phenotypic Screening Checklist (Maes et al, 2000)

<table>
<thead>
<tr>
<th>1. Narrow and elongated face</th>
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<tbody>
<tr>
<td>2. High forehead</td>
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<tr>
<td>3. Prominent lower jaw</td>
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<tr>
<td>4. Large, protruding ears</td>
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<tr>
<td>5. Macroorchidism</td>
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<tr>
<td>6. Hyperextensible finger joints</td>
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<tr>
<td>7. Hyperextensible joints (other)</td>
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<td>8. Hyperactivity</td>
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<tr>
<td>9. Sensory oversensitivity</td>
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<tr>
<td>10. Impulsivity</td>
</tr>
<tr>
<td>11. Being chaotic</td>
</tr>
<tr>
<td>12. Shyness</td>
</tr>
<tr>
<td>13. Being too helpful</td>
</tr>
<tr>
<td>14. Approach-avoidance conflict</td>
</tr>
<tr>
<td>15. Fearfulness</td>
</tr>
<tr>
<td>16. Gaiety, cheerfulness</td>
</tr>
<tr>
<td>17. Hypersensitivity for changes</td>
</tr>
<tr>
<td>18. Hand biting</td>
</tr>
<tr>
<td>19. Stereotypic hand movements</td>
</tr>
<tr>
<td>20. Flapping hands and arms</td>
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<tr>
<td>21. Avoiding eye contact</td>
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<tr>
<td>22. Turning away the face</td>
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<tr>
<td>23. Tactile defensiveness</td>
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<tr>
<td>24. Rapid speed of language</td>
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<tr>
<td>25. Being talkative</td>
</tr>
<tr>
<td>26. Perseveration</td>
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<td>27. Echolalia</td>
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<td>28. Imitation of own language</td>
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### Fragile X and Autism

- Many behavioral features similar to ASD
- FXS increasingly considered a subtype of ASD or even commonly seen in ASD
- Excess of repetitive behaviors may account for many of the ASD symptoms associated with FXS

### More on Fragile X Syndrome

- **Fragile X Syndrome**
  - X-linked dominant condition
  - Leading inherited cause of developmental disability in males
  - Affects 1:4000 males and 1:8000 females
  - Phenotype

#### More on Autism

- Autism spectrum disorder (ASD)
  - Communication difficulties
  - Social interaction difficulties
  - Repetitive behaviors

#### Molecular Testing

- To identify individuals with undiagnosed developmental disability
- In all children with developmental delay/intellectual disability, FXS is best practice to recommend testing for FXS
- Despite 3% of children do not have apparent physical features
- How many disabilities can be applied if the FXS is not diagnosed?

#### PhenoType

- Risk for regression
- and/or failure to reach cognitive, social, or adaptive milestones
- Inability to under autism, social anxiety, hand-flapping
- Social-communication issues
- Language delays and delays in social and communication skills
- Physical features
- More common—learning difficulties and emotional disabilities
- Females
  - Females
  - Phenotypic features

#### More on Fragile X Syndrome

- Less frequent
- Less severe
- X-linked dominant condition
- Leading inherited cause of developmental disability in males
- Affects 1:4000 males and 1:8000 females

#### Marcus Autism Center

- More on Fragile X Syndrome
  - X-linked dominant condition
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Children with FXS initiation deficits may reflect social anxiety common to FXS+ASD social achievement, similar to that seen in ASD social skills. The result of an inability to social cues, they may be more attuned to social cues than those with ASD.

Is hyperepression of the FXS behavioral phenotype.

Summary of Wolff et al., 2012 findings:

- **Repititive behaviors**
  - Greatest degree of symptom overlap in repetitive motor behaviors (stereotypy, self-injury).
  - Significantly less compulsive or ritual behaviors in boys with FXS+ASD.
  - Repititive motor behaviors are linked to developmental disability in general and not specific to ASD.

- **Social behaviors**
  - Boys with FXS+ASD significantly less impairment on measurements of social response.
  - Significantly less impairment on social response outcome measures.
  - Boys with FXS+ASD significantly less impairment on social behaviors.

- **RRB Symptom Overlap**
  - Difference could be due to minimal degrees of difference in social performance from those without ASD.
  - FXS+ASD likely not reliably distinguish those with ASD.
  - Social evidence and anxiety are common to children with the core ASD symptom.
  - However, improvements on a continuum in FXS regardless of AsD.

Empirical data on ASD symptoms:

- Overall patterns most similar for social initiation items.
- Mixed evidence of social response.

Fragile X and Autism Overlap:

- Is hyperepression of the FXS behavioral phenotype.

Continuum of Autism Impairments:

- Children with FXS+ASD may be more attuned to social cues than those with ASD.
- Repititive behaviors.
- Social behaviors.

Study by Wolff et al., 2012, JACAP.
Neuroanatomical Differences

• Neuroanatomy backs up FXS+ASD being different from ASD
  – FXS+ASD show highly enlarged caudate and small amygdala
  – ASD show modest caudate and amygdala enlargement

• In FXS, social avoidance been associated with neuroendocrine dysfunction; in ASD social indifference or inattention associated with amygdala overgrowth and dysfunction

• THUS, neurodevelopmental pathways leading to seemingly similar but qualitatively different social deficits between ASD and FXS+ASD may also differ with respect to the brain.

Overview – Williams Syndrome

• De novo deletion of ~26-28 genes on chromosome 7
• Incidence: 1 in ~10,000 live births (under diagnosed)
• “De novo” deletion of ~26-28 genes on chromosome 7
• First identified in 1961

Physical Characteristics

• Facial features
  – Periorbital fullness, long philtrum, full lips, short nose
• Cardiovascular disease
  – Supravalvular aortic stenosis (SVAS; ~70%)
  – High blood pressure (50%)
• Endocrine
  – Early puberty, glucose intolerance, subclinical hyperthyroidism
  – Hypertension, weight issues
• Gastrointestinal, weight issues
  – Short stature, short people, short children (SAS; ~50%)
  – Young blood pressure (SBP) levels
• Cardiovacular disease

Genetics of WS

• Typically deletion of 1.5 to 1.8 million base pairs
• 2-3% of patients have atypical deletions

Williams Syndrome

Physical Characteristics

• Cognitive-behavioral profile of Williams Syndrome
• Genes of Williams Syndrome
• Physical Features of Williams Syndrome

Overview – Williams Syndrome

ASD and FXS+ASD may also differ with respect to the brain, similar but qualitatively different social deficits between ASD and FXS+ASD may also differ with respect to the brain. Thus, neurodevelopmental pathways leading to seemingly different dysfunction associated with amygdala overgrowth and neurodevelopmental dysfunction in ASD social indifference or from ASD

ASD show modest amygdala and amygdala enlargement

FXS+ASD show highly enlarged amygdala and small

Neuroanatomical Differences
Genotype-Phenotype Relations

(Pober, 2010; Schubert, 2010)

- **ELN**: hypertension, arteriopathy with vascular stenoses, vascular smooth-muscle-cell overgrowth; soft skin with premature aging, hoarse voice, hernias, facial features
- **STX1A**: impaired glucose tolerance
- **LIMK1**: visuospatial impairments?
- **GTF21 family**: craniofacial features, social behavior, intellectual disability, neurocognitive profile, impaired visual responses?
- **Dup7 cases**: expressive language difficulties, social anxiety

**Cognitive Profile**

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**Language**

- Strengths and Weaknesses
  - Socially-expressive language
  - Linguistic affect

- Delayed language development

**Spatial**

- Early phonologic delays (SW vs WS)

- Visuospatial Processing

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**Sociability**

- Everyone in the world is my friend

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**Visual Processing**

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**Genotype-Phenotype Relations**

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Dyadic vs. Triadic Interactions (Laing et al., 2002)

- Parents rate their child with WS as more willing to approach strangers than controls
- "Rate happy faces as more approachable than controls"

Social Impairment on ADOS

- 10-50% of individuals with WS meet criteria for ASD on ADOS Mod I

- Majority fall in PDD-NOS/ASD range rather than Autism
- Common difficulties in WS: declarative pointing, language, Attention

Psychopathology

- Specific phobia (35% DX)
- Social Impairments (Elison et al., 2010):
  - 1/3 of adults have problems making friends
  - ~50% have poor concept of friendship
  - 40% never had romantic relationship

Social Approach/Vulnerability

- Rate "happy faces" as more approachable than controls

ADHD, Overactivity, Hyperactivity

Attention Deficit Hyperactivity Disorder (ADHD, ODD, CD)

Attention/Seeking

- Attention Deficit Hyperactivity Disorder (ADHD)
- Overactivity
- No rows (22%)
- GD (12%)
- CD (4%)
- DS symptoms (18-35%)