Dawn of a New Age: Targeted Treatments for Fragile X Syndrome

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Fragile X Syndrome
Fragile X Syndrome

- Most common hereditary cause of developmental disabilities in all populations
- Occurs in both males and females, although males are more commonly affected
- Diagnosed through DNA blood testing
- Physical features often subtle
- Majority of those affected are undiagnosed

Prevalence

- Fragile X syndrome:
  - 1 in 4,000 males
  - 1 in 8,000 females
- Premutation carriers:
  - 1 in 259 females
  - 1 in 750 males
Fragile X Syndrome

- General Population: 1 in 4,000 males
- Intellectual disability: 1 in 100

Among males with ID: 1 in 40

Physical Findings

- Macrocephaly (large head)
- Large ears
- Hyperextensible joints
- Long, narrow face
- Macroorchidism (enlarged testicles)
- Low muscle tone
- Mitral valve prolapse

Finucane et al., Fragile Syndrome: A Handbook for Families and Professionals, NFXF, 2004
**Intellectual Functioning**

- Majority of males function in the moderate range of intellectual disability
- <5% of males have IQs above 70
- Much more variability among females, ranging from severe intellectual disability to above average IQ

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**Behavioral Characteristics**

- Hyperactivity
- Hand-flapping
- Hand-biting
- Tactile defensiveness
- Perseverative speech
- Sensory hyperarousal
- Gaze aversion

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Just One Gene

- 1991: scientists discover the cause of fragile X syndrome
- A single gene called FMR1 shuts down and fails to produce its normal protein (called FMRP)
- FMRP is expressed in the brain and essential for normal brain functioning
- Fragile X inheritance is complicated; gene changes cause a wide range of effects from one generation to the next

McConkie Rosell et al., Journal of Genetic Counseling, 2005

5 DIFFERENT PSYCHIATRIC DIAGNOSES
1 ETIOLOGICAL DIAGNOSIS: FRAGILE X SYNDROME
Fragile X and Autism

- Up to 21% of young boys with fragile X syndrome meet diagnostic criteria for Autistic Disorder
- A majority of males and many females with fragile X syndrome have symptoms consistent with an autism spectrum disorder

Hatton et al., American Journal of Medical Genetics, 2006
Clifford et al., Journal of Autism and Developmental Disorders, 2007

Autism and Fragile X

- Autism: recognizable pattern of behavioral symptoms
- Numerous known and unknown causes
- Fragile X: most common known single gene cause of autism
- Prevalence of fragile X among children with autism estimated to be around 1 in 20

Belmonte and Bourgeron, Nature Neuroscience, 2006
Hyperarousal in Fragile X Syndrome

- Over-reaction to sensory stimuli
- Enhanced electrodermal response to sensory stimuli which correlates inversely with FMRP levels
- Enhanced cortisol release after stressors
- Delayed physiological recovery after hyperarousal

Hessl et al., Journal of Child Psychology and Psychiatry, 2006
Scharfenaker and Stackhouse, Natl Fragile X Fdtn Quarterly, 2006
Boccia and Roberts, Behavior Research Methods, Instruments, and Computers, 2000

Gaze Aversion

- Gaze aversion: distinctive form of poor eye contact (active turning away versus “looking through you”)
- Majority of males with fragile X syndrome exhibit gaze aversion, starting in early childhood
- Forced eye contact in males with fragile X syndrome triggers abnormal cortisol response
- Gaze aversion may serve as an avoidance behavior

Hessl et al., Journal of Child Psychology and Psychiatry, 2006
Garrett et al., Archives of General Psychiatry, 2004
Cohen et al., Journal of Child Psychology and Psychiatry, 1989
Gaze Aversion

- Verbal prompting and forced eye contact often exacerbate gaze aversion in males with fragile X
- When eye contact goals are de-emphasized, eye contact often improves

Practical Implications

- Majority of boys with fragile X syndrome meet criteria for an autism spectrum disorder, therefore most are potential candidates for ABA therapy
- ABA therapy for boys with fragile X syndrome needs to take into account gaze aversion, hyperarousal, and anxiety issues
- Forced eye contact, intensive teaching, discrete trial teaching, and desensitization techniques may be counterproductive for many students with fragile X syndrome

Scharfenaker and Stackhouse, Natl Fragile X Fdtn Quarterly, 2006
Survey of Autism Professionals

- Questionnaire format
- Study group: professionals working with children who have autism spectrum disorders
- Designed to assess:
  - knowledge of fragile X syndrome
  - utilization of syndrome-specific resources
  - knowledge and attitudes about genetic testing

Finucane, Haas-Givler, and Simon, work in progress, 2009

Study Cohort

- Total surveys returned: 439
- Gender:
  - 368 female (83.8%)
  - 54 male (12.3%)
- Mean age: 38.54 ± 11.14 years
- Work experience: 11.51 ± 9.15 years
- Work setting:
  - regular education school: 40.3%
  - special education school or center: 37.8%
  - home-based services: 21%

Finucane, Haas-Givler, and Simon, work in progress, 2009
Self-reported Position or Title (N=439)

Utilization of Resources

- 48.5% reported having worked with students diagnosed with fragile X syndrome
- Self-rated knowledge about fragile X syndrome
  - not at all knowledgeable: 44.2%
  - somewhat knowledgeable: 53.5%
  - very knowledgeable: 1.8%
- 16% had contacted a fragile X-specific organization for information
- 6.4% had attended a conference or seminar about fragile X syndrome

Finucane, Haas-Givler, and Simon, work in progress, 2009
Conclusions

- Almost half of autism professionals surveyed have provided services for children with fragile X syndrome.
- Despite this, a majority lacked basic knowledge about the physical and behavioral features of fragile X, as well as its role in causing autism.
- Only a quarter routinely asked parents about the cause of their child’s disability.
- ABA therapists and related professionals under-utilize available resources on fragile X and rarely attend syndrome-specific conferences and seminars.

Practical Implications

- Fragile X is a family affair – diagnosis in a child has important implications for extended family.
- Majority of people with fragile X syndrome have not been genetically diagnosed.
- Special educators, ABA therapists, and related professionals are a key point of contact for families of children with autism.
- Potentially play an important role in referring families for genetic evaluation.

References:
- Finucane, Haas-Givler, and Simon, work in progress, 2009
- McConkie Rosell et al., Journal of Genetic Counseling, 2005
- Finucane, Haas-Givler, and Simon, American Journal of Medical Genetics, 2003
Just One Gene

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- A single gene called FMR1 shuts down and fails to produce its normal protein (called FMRP)
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McConkie Rosell et al., Journal of Genetic Counseling, 2005

Molecular Basis

Three FMR-1 states:
- Normal allele: 6 - <55 CGG repeats
- Premutation: >55 - <200 CGG repeats
- Full mutation: >200 CGG repeats
Trinucleotide Repeats in FMR1

...CGG CGG CGG CGG CGG CGG CGG CGG CGG CGG...

- **NORMAL RANGE**
  - FMR1 protein produced
  - No apparent cognitive effects
  - Psychiatric symptoms in females
  - Premature ovarian failure (POF)
  - Fragile X Associated Tremor / Ataxia Syndrome (FXTAS): Parkinsonian symptoms in males, some females

- **PREMUTATION RANGE**
  - No FMR1 protein produced
  - Premature ovarian failure (POF)
  - FXTAS:
    - Parkinsonian symptoms in males, some females

- **FULL MUTATION RANGE**
  - No FMR1 protein produced
  - Fragile X Syndrome in males, some females

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<table>
<thead>
<tr>
<th>Normal</th>
<th>Premutation</th>
<th>Full mutation</th>
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<tr>
<td>(CGG) n &lt; 45</td>
<td>(CGG) 55 ≥ n ≤ 200</td>
<td>(CGG) n ≥ 200</td>
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<tr>
<td>gene</td>
<td>mRNA</td>
<td>FMRP</td>
</tr>
<tr>
<td>transcription</td>
<td>translation</td>
<td>Clinical phenotype</td>
</tr>
</tbody>
</table>

- **Unaffected**
- Premature ovarian failure
- FXTAS
- Psychiatric issues
- Fragile X syndrome

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15
Fragile X Premutations

- No cognitive impairment in males or females
- Associated with symptoms of mRNA toxicity
- Females:
  - Increased risk for psychiatric symptoms – depression, social anxiety, shyness
  - Premature ovarian failure (POF): menopause < 40
    - 13 – 24% of premutation carriers have POF
    - Conversely, fraX premutations found in:
      - 2% of women with idiopathic POF
      - 14% of women with a family history of POF

McConkie Rosell et al., Journal of Genetic Counseling, 2005

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

- Neurodegenerative condition in otherwise unaffected premutation males, some females
- First reported in 2001
- At least 1/3 premutation males develop FXTAS
  - Intention tremor, ataxia, parkinsonism, peripheral neuropathy, dysautonomia
  - Distinctive MRI findings
    - Increased T2 signal in the middle cerebellar peduncles (MCP sign)
- Prevalence
  - Affects up to 1/3000 adult males over 50 years of age
  - Less frequent and milder in females
- Reproductive implications

Hagerman and Hagerman, Ment Retard Dev Disabil Res Rev. 2004
5 DIFFERENT PSYCHIATRIC DIAGNOSES
1 ETIOLOGICAL DIAGNOSIS: FRAGILE X SYNDROME

The Many Faces of Fragile X
The Many Faces of Fragile X

A Cure for Fragile X?

- Targeted pharmaceutical treatments are currently undergoing human clinical trials and are expected to be available within the next 5 years
- New treatments target underlying biochemical pathway affected by the fragile X gene mutation
- Only those families diagnosed with fragile X syndrome will be able to benefit from these medical breakthroughs!

Penagarikano et al., Annual Review of Genomics and Human Genetics, 2007
mGluR Theory of Fragile X

- Group I metabotropic glutamate receptors (mGluR1/5) stimulate synthesis of proteins at neuronal synapses
- FMRP normally acts to inhibit this protein synthesis
- Two systems act in tandem to regulate synaptic connections
- Without FMRP, mGluR1/5 activity is unchecked
- Synapses are weak, abnormal structure – impaired synaptic signaling, learning / behavioral abnormalities

Bear et al., Trends in Neurosciences, 2004
**Of Mice and Flies**

**Drosophila (fruit flies):**
Well-characterized genetically, behaviorally
FraX fruit fly shows structural abnormalities, measurable differences in behavior (courtship)

**Mice:**
Well-characterized genetically, behaviorally
FraX mouse shows physical differences, audiogenic seizures, hyperactivity, anxiety issues

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**Drosophila Love**

A. Innate Courtship:
- WT males court receptive females
- KO males court less vigorously

B. Courtship Suppression: Learning
- When placed with an unreceptive trainer female, the male initially courts vigorously, but over time courtship activity declines (training suppression).
- KO males show normal suppression (learning)

C. Courtship Suppression: Memory
- WT males will not court receptive tester female
- KO males court tester female at naive levels

D. Courtship Suppression: Memory Recovery
- Drug treatment has no effect on WT courtship memory.
- Drug treated KO males now exhibit courtship memory after training

Dolen and Bear, *Neuron*, 2005
Transgenic mice

- Fragile X mice: structural neuronal abnormalities (long, thin dendritic spines with weak signaling, excessive spine formation)
- p21-activated kinase (PAK): one of many enzymes activated by mGluR, involved in dendritic spine formation, synaptic signaling; PAK mice show reduced spine formation, excessive signaling
- Genetically-crossed mice strain “rescues” fragile X phenotype

Hayashi et al., Proc Natl Acad Sci USA, 2007

Lithium

- Well-studied in treatment of mood disorders
- mGluR antagonist: reduces unregulated mGluR-mediated protein synthesis
- Reverses memory problems in fraX fruit fly
- Reduces audiogenic seizures, hyperactivity in fraX mouse

MPEP

- Older drug, not for use in humans
- mGluR5 antagonist: reduces unregulated mGluR5-mediated protein synthesis
- In fraX fruit fly, corrects memory problems and structural abnormalities
- In fraX mouse, corrects audiogenic seizures, hyperactivity, structural abnormalities and multiple behavioral issues


Fenobam

- In clinical trials as an anxiolytic in 1970s; recently found to be an mGluR5 antagonist
- Granted orphan drug status for fragile X syndrome by FDA – fast track for approval
- Preliminary human trials in adults with fragile X recently completed, awaiting analysis
- Several other similar drugs in pipeline

Research Review

Fragile X Research: A Status Report
Elizabeth Berry-Kravis, MD, PhD
July 2008 issue of Fragile X Quarterly
Nat'l Fragile X Foundation
www.fragileX.org

Population Screening

• Pregnant women
• Special populations
  • Children / adults with intellectual disability
  • Psychiatric patients
  • Women with infertility
  • Males or females with early onset Parkinsonian symptoms / ataxia / dementia
• Newborn screening
• Everybody ??
Resources

National Fragile X Foundation
www.fragileX.org

FRAXA Research Foundation
www.fraxa.org