What's So Special About Genetics?

Practical Implications of Genetic Diagnoses for Children with Special Developmental Needs

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Etiology

- Etiology: Underlying cause
- Intellectual and developmental disabilities: symptom diagnoses for which there are numerous different etiologies
- Genetic and / or medical factors play a role in the etiology of most intellectual disabilities

Why is Etiology Important?

- Genetic counseling for families
- Alleviates guilt, misconceptions
- Anticipation of medical needs
- Insight into behavior, learning styles
- Syndrome-specific support groups

Etiological Diagnoses

In the school setting:
- Etiological diagnoses often considered irrelevant
- Educational / psychiatric diagnoses determine services and treatment approaches

Psychiatric Diagnoses

- based on observed, recognizable patterns of human behavior
- diagnosed using criteria found in the DSM (Diagnostic & Statistical Manual)
- symptom diagnoses - do not emphasize etiology
- never diagnosed using laboratory tests

Psychiatric Diagnoses

- OCD
- ADD
- ANXIETY DISORDER
- OPPOSITIONAL DEFIANT DISORDER
- BIPOLAR DISORDER
- AUTISTIC SPECTRUM DISORDER
- IMPULSE CONTROL DISORDER
- ID DISORDER
5 different psychiatric diagnoses
1 etiological diagnosis: fragile X

Genetic Syndromes

>1200 genetic conditions associated with intellectual disability (OMIM, 2012)
- Down syndrome: described in 1866
- Cornelia de Lange syndrome: 1933
- Prader-Willi syndrome: 1956
- Williams syndrome: 1961
- Angelman syndrome: 1965
- Smith-Magenis syndrome: 1986
- Phelan-McDermid syndrome: 1998
- Potocki-Lupski syndrome: 2000

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 3,600 males
1 in 4 – 6,000 females

Premutation carriers:
1 in 259 females
1 in 750 males

Fragile X Syndrome

General Population: 1 in 3,600 males
Intellectual disability: 1 in 100

Among males with ID: 1 in 36

Physical Findings

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

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

Behavioral Characteristics

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

Fragile X and Autism

• ~ 20% of young boys with fragile X syndrome meet former strict diagnostic criteria for Autistic Disorder
• Majority of males and many females with fragile X syndrome have symptoms consistent with an autism spectrum disorder

Finucane et al., Fragile Syndrome: A Handbook for Families and Professionals, NFXF, 2004
Hagerman & Hagerman, Fragile X Syndrome. Diagnosis, Treatment, and Research, 2002
Hager et al., American Journal of Medical Genetics, 2006
Gilford 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

**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

**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

References:
- Garrett et al., Archives of General Psychiatry, 2004
- Scharfenaker and Stackhouse, Natl Fragile X Fdtn Quarterly, 2006
Age of Molecular Mechanisms

- Human Genome Project
- Advances in laboratory technologies
- Gene sequencing, protein expression
- Elucidation of gene function and biochemical pathways
- Fragile X: the model for how a gene becomes a syndrome!
- Animal models of genetic disease

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

FMRP and mGluR

- Group I metabotropic glutamate receptors (mGluR) stimulate protein synthesis at neuronal synapses
- FMRP inhibits synaptic protein synthesis
- Two systems act in tandem to regulate translation of neuronal proteins
- Without FMRP, mGluR activity is unchecked: abnormal synaptic signaling and dendritic structure; learning / behavioral differences

Targeted Pharmaceuticals

- Targeted approach addresses underlying pathophysiology, not just symptoms
- Fragile X: single gene disorder with known molecular mechanism, robust animal models
- Well-organized support organization, successfully lobbies for research funding
- Human clinical trials well underway for pharmaceutical treatments that target biochemical underpinnings of FXS

Pharmaceutical Research

- Rett Syndrome (MeCP2): www.rettsyndrome.org
- Angelman Syndrome (UBE3A): www.cureangelman.org
- Phelan-McDermid Syndrome (SHANK3) http://22q13.org
- Tuberous Sclerosis (TSC) www.tsalliance.org

Of Mice and Flies

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

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

Bear et al., Trends in Neurosci, 2004
Reviews


Fragile Syndrome

- Geisinger Fragile X Clinic
- Autism and Developmental Medicine Institute
  www.GeisingerADMI.org
- National Fragile X Foundation
  www.fragileX.org
- FRAXA Research Foundation
  www.fraxa.org