Smith-Magenis Syndrome

Putting the Genetic Diagnosis into Context

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Developmental Disabilities

Also known as:

- Intellectual and developmental disabilities
- Neurodevelopmental disorders

*Developmental disabilities are a group of conditions due to an impairment in **physical, learning, language**, or **behavior** areas. These conditions begin during the **developmental** period, may impact day-to-day functioning, and usually last throughout a person's lifetime.*

Centers for Disease Control and Prevention, 2017

Prevalence: 1 in 6 children has a developmental disability

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Developmental Disabilities

- Autism spectrum Disorder (ASD)
- Intellectual disability (ID)
- Cerebral Palsy
- Specific language impairment
- Attention deficit disorder
- Dyslexia
- Etc., etc.

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Autism Spectrum Disorder (ASD)

……complex disorder of brain development characterized, in varying degrees, by difficulties in social interaction, verbal and nonverbal communication and repetitive behaviors

Autism Speaks, 2015

Prevalence: 1 in 68 children has ASD *(CDC, 2016)*

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Intellectual Disability (ID)

*Intellectual disability: characterized by significant limitations in both **intellectual functioning** and in **adaptive behavior**, which covers many everyday social and practical skills. This disability originates **before the age of 18**.*

American Association on Intellectual and Developmental Disabilities, 2015

Prevalence: 1 in 91 children has ID *(CDC, 2006)*

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Developmental Disabilities

- ASD, ID, CP, etc.: symptom constellations with numerous underlying causes
- Often co-occur:
  - ~50% with ASD have ID / learning difficulties
  - ~40% with ID diagnosed with psychiatric disorder
  - ~40% with CP have ID

Clinically-defined "symptom" diagnoses for which there are numerous underlying causes

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Psychiatric Diagnoses

- childhood and adult-onset
- based on observed, recognizable patterns of human behavior described in the DSM (Diagnostic & Statistical Manual)
- clinical, symptom-based diagnoses: do not emphasize etiology
- not diagnosed using laboratory tests or imaging

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Psychiatric Diagnoses

Symptoms versus Causes

- Etiology: Underlying cause
- Autism, ID, and other brain disorders: symptom-based clinical diagnoses for which there are *numerous* different etiologies
- Genetic and / or medical factors play a major role in the etiology of developmental brain dysfunction
- Advances in genetic testing have revealed shared underpinnings for distinct developmental and psychiatric clinical disorders

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Etiology Matters

- Genetic counseling for families
  - to address reproductive concerns
  - to alleviate guilt, misconceptions
- Anticipation of medical needs
- Insight into behavior, learning styles
- Syndrome-specific support organizations
- Targeted research and intervention

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The Human Genome

- Genome: the entire set of genetic instructions found in a cell; the entirety of a person's genetic make-up
- Human genome ~20,000 genes

National Human Genome Research Initiative (NHGRI)

www.genome.gov

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Genetics Vocabulary

- DNA (deoxyribonucleic acid)
  - contains the genetic information in a body's cells
  - made up of 4 similar chemicals (A,G,C,T) that come in pairs and make up the DNA code
- Gene: specific section of DNA code that contains instructions for making body chemicals (proteins)
- Chromosome: a cell structure that contains numerous genes

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Genetics Vocabulary

- Genomic variants (formerly 'mutations'): significant differences in the expected DNA code that can be inherited or occur for the first time in an individual
  - Copy number variants (CNVs)
    - Deletions, duplications: differences in the amount of chromosomal material
    - Usually involve multiple genes
  - Sequence variants
    - Changes in the letters of the DNA code
    - Single gene disorders

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Genetics Vocabulary

- Syndrome ("running together"): recognizable pattern of features that repeatedly occurs
- Congenital: present at birth
- Dysmorphology: the study of structural differences, particularly birth defects
- Phenotype: observable characteristic(s) (physical, behavioral) related to the expression of a gene(s)

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Medical Genetics

- a.k.a. Clinical Genetics
- Recognized medical specialty
- Healthcare teams include
  - Clinical / Medical Geneticist
  - Genetic Counselor

AboutGeneticCounselors.com

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RESOURCES

Websites

- www.genome.gov/Education
- www.genome.gov/Glossary
- http://unlockinglifescode.org
- www.ashg.org/education/k12_geon.shtml
- www.dnaftb.org
- www.dnai.org
- www.nchpeg.org

Courses

- https://www.coursera.org/course/usefulgenetics
- https://www.coursera.org/course/usefulgenetics2
- Amer College of Med Genetics genetics course: www.acmg.net
- Nat'l Society of Genetic Counselors online course on genomics: www.nsgc.org

Different types of genetic testing

- Diagnostic testing
  - Clinical testing (not research)
  - Examples: microarray, fragile X analysis
  - Identifies *rare* causative genomic variants (differences) with large effects on brain function
- Pharmacogenomics for medication response
  - Tests for genomic variants affecting drug metabolism
  - Primarily looking at genes expressed in the liver
  - Limited clinical utility for psychotropic medications
  - Lots of marketing, little evidence

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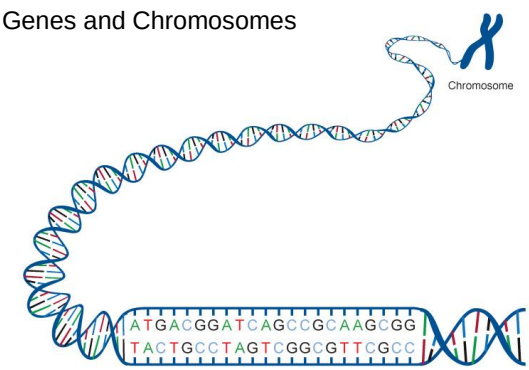
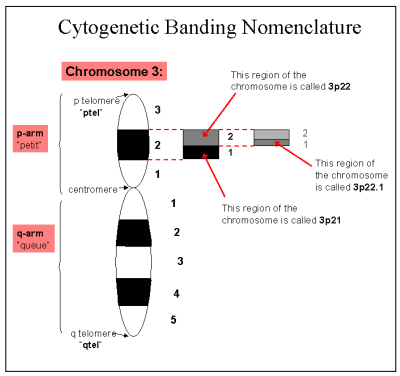
Genes and Chromosomes



adenine (A), cytosine (C), guanine (G), thymine (T).

ISCN: An International System for Human Cytogenetic Nomenclature (2009)

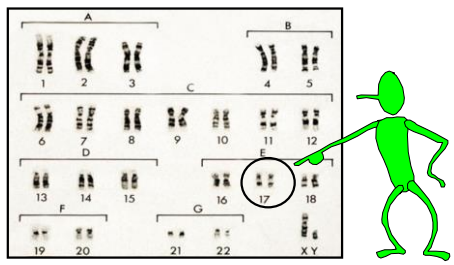


Diagnostic Genetic Testing

- First line recommendations* for individuals with global developmental delay / ID / ASD of unknown cause:
  - Fragile X *(FMR1)* DNA analysis
  - Chromosomal microarray analysis
- Whole exome sequencing (WES) increasingly ordered in the evaluation of those with uninformative fragile X and microarray results (25 – 30% diagnostic yield)

**American College of Medical Genetics and Genomics*
**American Academy of Pediatrics*

Smith-Magenis Syndrome



Smith-Magenis Syndrome

SELF-INJURIOUS BEHAVIORS

- Hand biting
- Head banging
- Picking at finger / toenails
- Skin picking
- Inserting objects into nose, ears, etc.

Smith-Magenis Syndrome

SLEEP DISTURBANCE

- Frequent awakenings at night
- Early wake-up
- "Sleep attacks" during the day
- Inversion of melatonin cycle

Smith-Magenis Syndrome

CHALLENGING BEHAVIORS

- Attention-seeking: Crave one-to-one interactions with adults
- Often in competition with peers or siblings for staff or parent attention
- Perseveration - repeatedly asking the same question

Smith-Magenis Syndrome

CHALLENGING BEHAVIORS

- Poor impulse control
- Aggressive hugging of others
- Prolonged tantrums, outbursts
- Difficulty adjusting to changes in routine
- Poor sense of time - can't be rushed!

Smith-Magenis Syndrome

POSITIVE ASPECTS

- Engaging, endearing, and full of personality!
- Appreciative of attention
- Eager to please
- Sense of humor
- Communicative

Smith-Magenis Syndrome

POSITIVE ASPECTS

- Responsive to structure, routine
- Motivated by variety of reinforcers, activities
- Causes of aggression, outbursts often identifiable
- Outbursts, aggression can often be redirected if caught early

"Emotional Toddler" IN SMS

- Emotionally volatile
- Low frustration tolerance
- Prone to tantrums / outbursts
- Attention-seeking
- Distractible
- Excitable
- Reactive

"Emotional Toddler" IN SMS

- Inconsistent ("Yes / no" game)
- Upset by seeing people out of context
- Live in the moment
- Possessive attachments to caregivers
- Difficulty awaiting turn (me first!)
- Adult vs. peer-oriented
- Relentless question-asking
- Need ongoing reassurance

Resources

Parents and Researchers Interested in
Smith-Magenis Syndrome
(PRISMS)
www.prisms.org

SMS Specialty Clinic
Autism & Developmental Medicine Institute (ADMI)
www.geisingerADMI.org