prisms 2022
Envisioning the Possibilities

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.

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Autism Spectrum Disorder (ASD)

- Developmental disability often characterized by differences in communication, interests, sensory processing, motor coordination, and socialization. (Autistic Self Advocacy Network, 2022)
- Prevalence: 1 in 44 children has ASD (CDC, 2021)

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Intellectual Disability

- 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

- ADHD
- Anxiety Disorder
- OCD
- Oppositional Defiant Disorder
- Bipolar disorder
- Autism Spectrum Disorder
- Schizophrenia
- Depression
- Impulse Control Disorder

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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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A behavioral diagnosis tells you "WHAT"

An etiological diagnosis tells you "WHY"

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image from hrvoice.org

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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 call; the entirety of a person's genetic makeup
- Human genome contains ~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, aka bases, (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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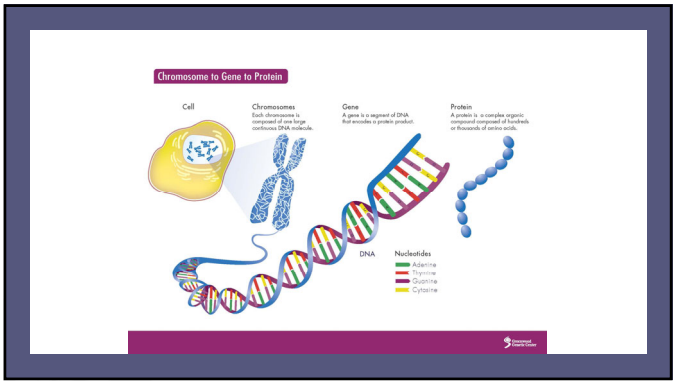

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Genetics Vocabulary

- 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

- Aka 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 course: www.acmg.net
  - Nat'l Society of Genetic Counselors online course on genomics: www.nsgc.org

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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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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 and now strongly recommended (ACMG, 2021) as a first- or second-tier test for patients with CAs or DD/ID (25-30% diagnostic yield)

*American College of Medical Genetics and Genomics

*American Academy of Pediatrics

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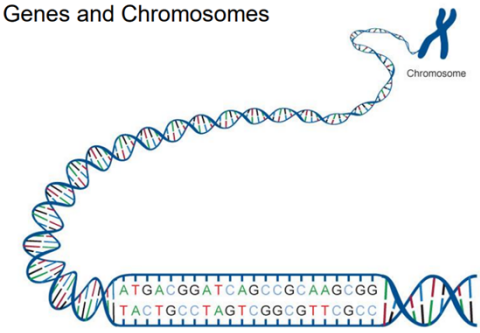
Genes and Chromosomes



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

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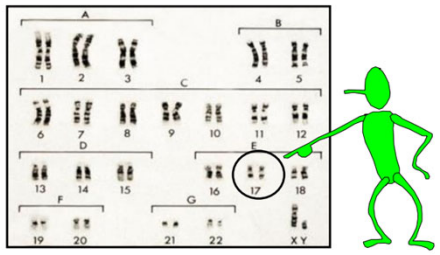
Smith-Magenis Syndrome



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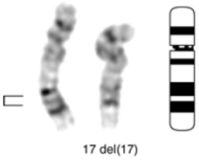

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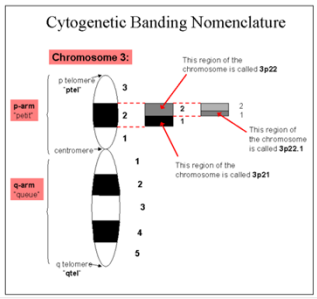
ISCN: An International System for Human Cytogenetic Nomenclature (2009)



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Smith-Magenis Syndrome

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

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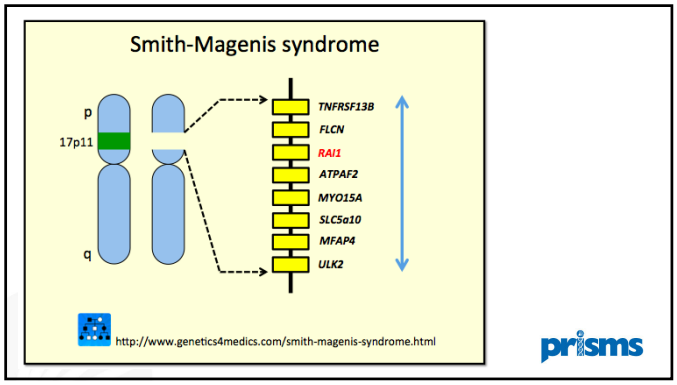

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Smith-Magenis Syndrome

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

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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 interaction
  - Perseveration – repeatedly asking the same question

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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

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Smith-Magenis Syndrome

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

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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

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"Emotional Toddler" in SMS

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

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"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

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Resources

Parents and Researchers Interested in Smith-Magenis Syndrome

(PRISMS)

www.prisms.org

SMS Specialty Clinic

Autism & Developmental Medicine Institute (ADMI)

www.geisingerADMI.org

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Conclusions

- Diagnostic confusion abounds!
- Psychiatric/behavioral symptoms: Found in association with many genetic disorders, including Smith-Magenis Syndrome
- Causes vs. Symptoms: Important for parents and professionals to understand distinction

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Conclusions

- Educational and behavioral diagnoses, not genetic diagnoses, determine eligibility and services within the school setting
- Individuals with Smith Magenis Syndrome often meet criteria for one or more behavioral/ educational diagnoses
- Use these diagnoses for obtaining services, realizing that the genetic variant is the underlying cause of the learning/ behavioral symptoms

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Conclusions

- Schools and teachers unlikely to be familiar with Smith-Magenis Syndrome
- This does not necessarily mean they are unable to provide excellent services
- An open mind, willingness to learn about the genetic diagnosis, and a creative approach to meeting a child's needs are just as important as experience with the specific genetic condition

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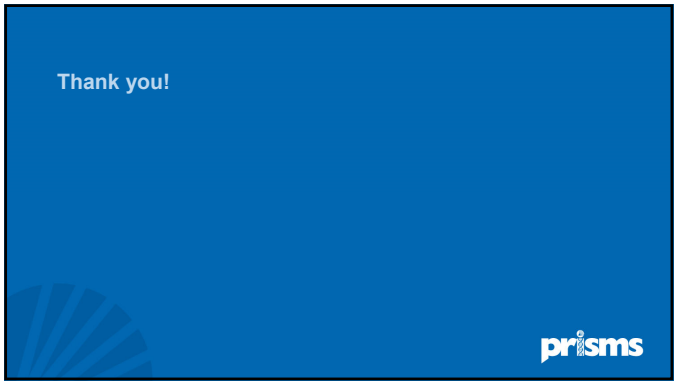

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