Genetic Syndromes and Mental Retardation
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Continuum of Care
Health Science Center University of New Mexico
Learning Objectives

1. Increase awareness of genetic basis in mental retardation
2. Increase knowledge of typical physical and learning characteristics of 4 MR syndromes.
3. Increase knowledge of ongoing medical management of these chronic conditions.
Genetic Syndromes

Have specific associations including behavioral and learning phenotypes
<table>
<thead>
<tr>
<th>Genetic Syndrome</th>
<th>Behavior(s) possibly unique to particular syndrome</th>
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<tbody>
<tr>
<td>Prader-Willi Syndrome</td>
<td>Hyperphagia, food ideation</td>
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<tr>
<td>Lesch-Nyahn Syndrome</td>
<td>Extreme self-injury</td>
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<td>Down Syndrome</td>
<td>Better visual versus auditory receptive abilities</td>
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<td>Smith-Magenis Syndrome</td>
<td>Putting objects into body orifices; bodily self-hugging</td>
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<tr>
<td>Genetic Etiologies with Possibly Unique Associated Behaviors</td>
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<td><strong>Williams Syndrome</strong></td>
<td>High level language abilities in face of lower overall mental age</td>
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<tr>
<td><strong>Rett Syndrome</strong></td>
<td>Stereotypic hand movements</td>
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<tr>
<td><strong>Angelman Syndrome</strong></td>
<td>Ataxic gait</td>
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<tr>
<td><strong>Cri-du-chat Syndrome</strong></td>
<td>“cat cry”</td>
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</table>
Fragile X Syndrome
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Fragile X Syndrome

• Most common known inherited cause of mental retardation
• Occurs 1 in 4,000 males and at least half as many females
• In all racial & ethnic groups
• 14% of unexplained MR
• 1/3 of all x-linked mental retardation is due to fragile X syndrome
Fragile X Syndrome

• Is the first known human disease attributed to a trinucleotide repeat CGG
• In full mutation there are >200 repeats (gene becomes inactive or methylated)
• Results in a wide range of cognitive involvement
• Results in problems relating to others, which ranges from shyness to autism
Fragile X: Clinical Features

- Head is usually large
- Face: prominent ears, long face, prominent jaw, high arched palate, flattened nasal bridge, coarse features
- Genitalia: large testes
- CNS: hypotonia, poor coordination
Fragile X: Physical features

- Flat feet 65%
- Hyper extensible finger joints 64%
- Mitral valve prolapse 55%
- Seizures 58% (EEG similar to BRS)
Fragile X: Medical Issues

• Most are physically healthy
• Chronic Otitis media
• High frequency of mitral valve prolapse
• Seizures in 20%
• Strabismus & scoliosis
• Normal life span
Fragile X: Learning Profile

- Almost all have MR: moderate/severe
- Boys experience drop in IQ
- Speech-language: “cluttered” (rapid erratic rhythm, disorganized, repetitious; dysfluency, dyspraxia)
- 2/3 hyperactive or inattentive
- Poor social skills (16-17% autism)
- Higher incidence of mental illness (affective or schizoid)

Adesman, AR, M.D.
Cognitive Profile

Strengths:
• Verbal skills.
• Expressive and receptive vocab.
• Adaptive ADLs.
• Long term memory

Weaknesses:
• Auditory-verbal short-term memory
• Adaptive socialization skills
• Sustaining attention
• Sequential processing

Dykens, EM. Hodapp, RM.
Finucane, BM, Brookes Ed. 2000
Behavior Phenotype

- Hyperactivity + ADD in >75%
- Autistic type features:
  - perseverative speech
  - hand biting
  - hand flapping
  - tactile defensiveness
- Tourette’s syndrome like stereotypic movements
- Anxiety: “approach-widrawal”
- Mental retardation
Fragile X: Management

• Stimulant and neuroleptics helpful
• Folate supplementation
• Early intervention/Special Ed.
• Behavior supports/modifications
• Associated morbidities: OM., Sz
Educational-Vocational Considerations

• Teaching approaches that emphasize simultaneous processing and verbal long-term memory, embedded in a familiar context.
• Performance improves when integrative tasks stress the overall meaning of the concept to be learned.
• Cubicles: to reduce visual & auditory stimulation.
• Social skills training.
Down Syndrome

One of the first symptom complexes associated with mental retardation to be identified as a syndrome.
Down Syndrome

• Most prevalent chromosomal cause of mental retardation
• Most common congenital disorder associated with mental retardation
• Most function in the moderate range
• Life span (60’s in the 1990’s)
Down Syndrome:

- The most common pattern of human malformation
- Prevalence: 1:660-1,000 newborns (decreasing)
- 1% recurrence after child with trisomy 21
- 10-95% risk if parental translocation
Down Syndrome: Description

• Trisomy 21 (usually duplication from the distal long arm of chromosome 21): 96%
• Mosaicism: 1-2.4%
• Translocation: 3-3.3% (D/G or G/G)
Down Syndrome

- Children with translocation do not differ cognitively or medically
- With mosaic pattern, typically score 10-30 points higher and have fewer medical complications
Down Syndrome: Etiology

• Defect may be related to a group of 50 genes: Contiguous Gene Syndrome

  (Korenmberg, Chen, Schipper, 1994)

• The “critical region” is located on the long arm (q11.1-q22.3)

  (Epstein, C.E., 1991 Morphogenesis and Down Syndrome)
Down Syndrome: Prevalence by maternal age

15 – 29 yrs  1:1500 – 2000
30 – 34 yrs  1:800
35 – 39 yrs  1:270
40 – 44 yrs  1:100
>45 yrs     1:20 – 50

(Trimble & Baird, 1978)
Down Syndrome: Translocation

• There is no age effect in translocation.
• 1/3 inherit translocation from carrier parents.
• Translocation occurs more often (74%) in females.
Down Syndrome: Physical Features

- Slanted palpebral fissures (80%)
- Anomalous auricles (60%)
- Flat facial profile (90%)
- Hypotonia (80%)
- Poor Moro (85%)
- Hyperflexible joints (80%)
- Small stature
Down Syndrome: Features

- Dysplasia of pelvis (70%)
- Dysplasia of midphalanx of fifth finger (60%)
- Single transverse crease (45%)
- Extra skin fold back of neck (80%)
- Tendency to keep mouth open and protrude tongue
Down Syndrome: CNS abnormalities

• delayed myelination
• fewer neurons
• decreased synaptic density and
• decreased acetylcholine neurotransmitter receptors
• Amyloid gene located on chromosome 21 ? Relation to >Alzheimer’s
Medical Concerns

- Congenital heart defects 50%
- Hearing loss 66-89%
- Eye conditions 60%
- Endocrine 50-90%
- GI 5%
- Dental 60-100%
- Orthopedic 15%
- Obesity 5-60%
- Skin conditions 50%
- Seizures 6-13%
- Leukemia 0.6%
Down Syndrome: Ophthalmic features

- strabismus 23-44%
- keratoconus 5-8%
- blepharitis 50% (over lifetime)
- cataracts
- nystagmus
- Brushfield’s spots (speckling of iris)
- fine lens opacities 59%
- myopia 35-40%
- hyperopia 20-25%
- astigmatism 70%
- cataracts
- nystagmus
Down Syndrome: Audiological Features

• Small ear canals 53%
• Overfolding of angulated upper helix
• Small or absent earlobes
• Small ears

• Middle ear problems fluid and recurrent otitis media 40-60%
• Sensorineural hearing loss
Down Syndrome: Learning Issues

- Delayed visual-perceptual and prelinguistic language milestones
- Delayed cognition: worse with CHD or hypotonia
- Greater deficits in verbal-linguistic skills with increasing age
- Language comprehension and production develop at significantly different rates
- Maladaptive behaviors
Cognitive Profiles

Strengths:
• Visual-spatial tasks

Weaknesses:
• Auditory tasks
• Grammatical abilities
• Expressive language
• Impaired pronunciation
Down Syndrome: Behavioral Issues

In one study 13% of children have psychiatric disorders:

- Depression
- Schizophrenia
- Anorexia nervosa
Down Syndrome: Management

- Periodic thyroid screening
- Periodic vision and hearing screening
- Annual physical and neurological examinations
Down Syndrome: Management

- Sign language during early years (total communication support)
- Reading instruction during school-age period
Williams Syndrome
Williams Syndrome

- Contiguous gene deletion syndrome on chromosome 7 (as many as 13)
- Insufficiency of Elastin
- 1:20,000; No gender difference
- SVAS, infantile hypercalcemia & developmental delays
Williams Syndrome: Features

- Facial features not apparent < 6 months
- “Elfin-faces”: short upturned nose; long philtrum; broad forehead with bi-temporal narrowing; full cheeks; prominent ear lobes
Potential Areas of Vulnerability for Adults

• ENT / Audiologic
• Endocrine
• Dental
• Gastrointestinal
• Anxiety & other emotional problems
• Accelerated aging - "appears" to be a characteristic (possibly related to elastin deletion)
Williams Syndrome:
Medical Features

- **Cardiac:** supra valvular aortic stenosis 60%; hypertension 40%
- **Musculoskeletal:** hyper extensible joints; hypotonic initially; joint contractures; clumsiness 50-85%
- **GI/GU:** colic 70%; feeding difficulties, reflux, FTT; constipation. Bladder diverticula, renal hypoplasia; enuresis and urinary frequency 50%
Williams Syndrome: Medical Features

• Visual problems: strabismus 54%; farsightedness in 25-50%; stellate iris pattern 75%

• Auditory: hyperacusis 95%; chronic OM 60%
Williams Syndrome:
Cognitive Profile

• Mild to moderate MR (50-60)
• Striking dissociation between language and cognition
Williams Syndrome

Strengths:
• Vocabulary
• Auditory short-term memory
• Facial recognition
• Theory of mind
• Musicality
• Adaptive communication

Weaknesses:
• Visual-spatial construction
• Perceptual planning
• Fine motor control (copying, drawing)
• Activities of daily living
Williams Syndrome: Behavioral Profile

Adaptive:

• “Friendly, charming & lovable”
• Kind-spirited, caring and forgiving
• Vulnerable to abuse!

Maladaptive:

• hyperactive
• impulsive
• inattentive and
• temper tantrums
Williams Syndrome: Management

**Medical: monitor**
- cardiac,
- GI,
- GU,
- visual,
- auditory and
- musculoskeletal

**Educational-vocational:**
- >use of computers, calculators, audiotapes
- Encouraged to use verbal mediation to solve problems
- Phonetic approach to reading
- People-oriented jobs with supervision
Rett Syndrome
Rett Syndrome

- Rare neurodevelopmental disorder
- Gene located on the x chromosome
- Onset of symptoms start after a period of typical development
- Regression of skills typically after 2 years old
Diagnostic Criteria

• Period of apparent normal development until 6-18 months (some girls have an earlier onset of RTT symptoms and therefore have no normal period of development)

• Normal head circumference at birth followed by slowing of the rate of head growth (there is a subset of girls whose rate of head growth does not decelerate)

• Loss of verbal language
Diagnostic Criteria

• Purposeful hand use is replaced by stereotypical hand movements (these can include a multitude of hand movements, some girls have movements unique to them or none at all)

• If able to walk the gait is usually wide-based and stiff legged

• Shakiness of torso and/or limbs, especially when upset
Supportive Criteria

- Breathing pattern irregularities which include hyperventilation, breath holding, apnea, air swallowing
- EEG abnormalities
- Seizures
- Scoliosis
- Teeth grinding
Supportive Criteria

- Decreased mobility with age
- Muscle rigidity/spasticity/joint contractures
- Small feet
- Abnormal sleep patterns
- Irritability and agitation

- Gastrointestinal issues which may include reflux, constipation, poor nutrient absorption
- Growth retardation and decreased body fat and muscle mass
- Biting / Chewing / Swallowing difficulties
- Poor circulation to legs and feet