

# **Genetic Disorders and Associated Behavioral Phenotypes**

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## Commonalities

- Regardless of etiology of IDD, there is a core set of deficits in executive functioning shared by all people with IDD
- Executive Function is a set of mental processes that help us with planning, organization and task management.
- Deficits in executive functions affect:
  - attention
  - organization
  - time management
  - impulse control
  - memory
  - self-monitoring

## Differences

- When we know the etiology of IDD, specifically if there is a genetic syndrome, we are much better prepared to understand and support the person effectively
- Genetic Syndromes are associated with behavioral phenotypes, or characteristic patterns of behavior and psychological symptoms

*Knowing that a person with Down syndrome who is hallucinating is more likely to have major depressive disorder with psychotic features than schizophrenia, and that the cause may be hypothyroidism, is important to treatment*

## **Behavioral Phenotypes Associated with Most Common IDD Syndromes**

- Klinefelter's Syndrome
  - Down Syndrome
  - Williams Syndrome
  - Angelman Syndrome
  - Prader-Willi
  - Fragile X Syndrome
- Smith Magenis
  - Velocardialfacial Syndrome/DiGeorge

## Klinefelter Syndrome

- *Much of the medical literature defines Klinefelter syndrome as a person with an XXY (or other extra X) chromosomal arrangement, and considers every XXY individual to have Klinefelter syndrome. However, many (including some XXY individuals themselves) consider Klinefelter syndrome to be a set of physical characteristics that are present in just some XXY individuals.*

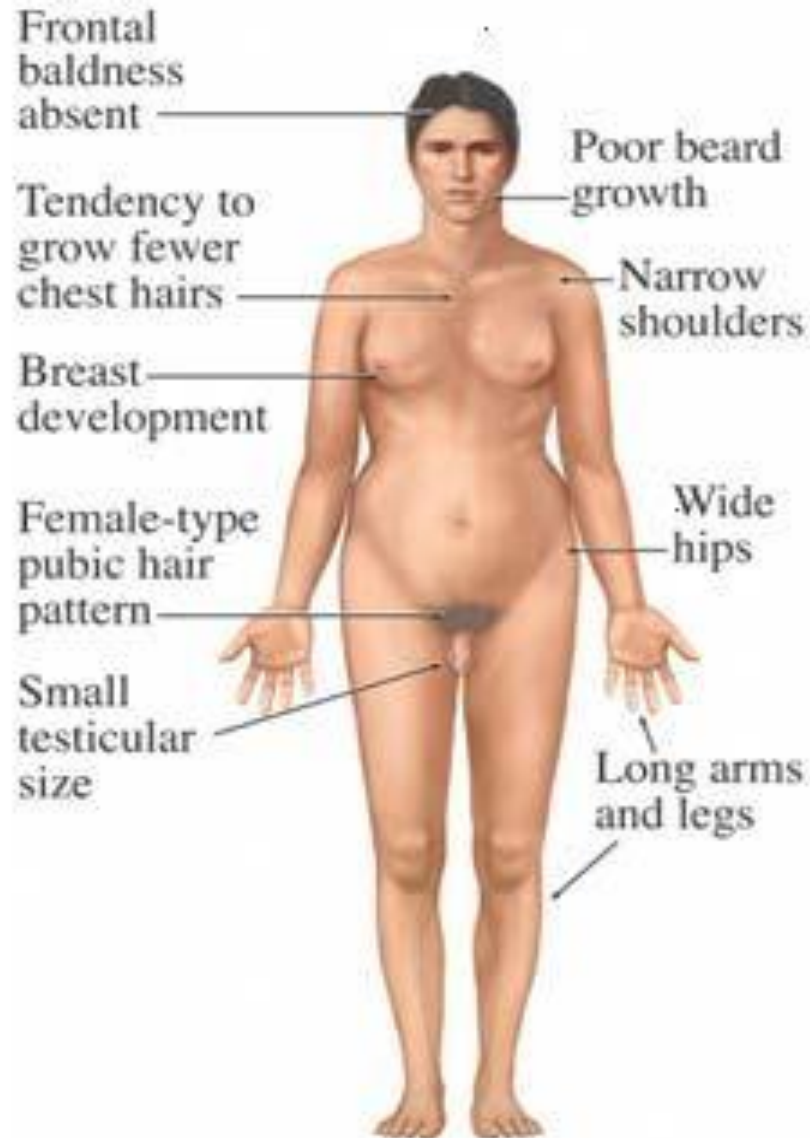
## Klinefelter Syndrome

- Incidence: 1 in 660 males – one of the most common genetic conditions. Probably underdiagnosed.
- Genetics: 47 XXY (80%)  
48, XXXY; 48, XXYY; 49, XXXXY (stronger physical, health and other characteristics – including ID)  
47, XXY/46,XY (mosaic)
- Cause: failure of cells to divide evenly (can be egg, sperm, or zygote). Origin does not seem to affect the clinical features. Some studies have shown increased maternal or paternal age to be associated with extra X chromosome.

# Klinefelter Syndrome

## Cognitive Characteristics

- Many people with KS have normal IQ although may be 10 – 15 points lower than average.
  - Verbal IQ less than Performance IQ
  - Speech and language delays
  - Dyslexia
  - Learning disabilities
  - Reduced problem-solving abilities
  - Attention and memory problems





# Klinefelter Syndrome

## Behavioral Phenotypes

- In a study by Bruining, et al. (2009), children with Klinefelter are at higher risk of:
  - language disorder (65%)
  - attention-deficit disorders (63%)
  - autism spectrum disorder (27%)

- **CONCLUSION:**

*Children with Klinefelter syndrome seem to be at risk for problems in social and language development, as well as for problems in regulation of emotion and behavior.*

# **Klinefelter Syndrome**

## **Behavioral Phenotypes**

- Higher incidence of depression, anxiety, schizophrenia, and psychosis than general population
- In adolescence, often described as sensitive and introverted
- Feelings of insecurity about physique and language difficulties
- Difficulty interpreting social cues
- Impulsivity

# Klinefelter Syndrome

## Medical Issues

- Testosterone replacement therapy can assist in normal pubertal development (muscle mass, distribution of body tissue, body and facial hair).
- Testosterone replacement therapy may also improve mood, concentration, energy, and social interactions with peers.
- Infertility usually persists
- Ten-fold risk of varicose veins and venous ulcers; increased risk of deep vein thrombosis and pulmonary embolism
- Taurodontism (dental issue that can lead to tooth decay) is present in 40 – 75% of people with KS
- Increased risk of diabetes and metabolic syndrome

## Down syndrome

- Incidence: 1 in 700 births
- Cause: Trisomy 21 (3 copies of 21<sup>st</sup> chromosome). Most are full trisomy (95%), small % are partial/mosaic with only some cells with extra chromosome. Mosaic often milder presentation
- Cognition: most people with Down syndrome have mild to moderate ID, with some in borderline range and some with severe/profound ID

## DS Physical Characteristics

- small stature
- small head with flat face
- small ears and mouth
- upward slant to eyes
- Simian crease in palm of hand
- low muscle tone



## **DS Behavioral Phenotypes**

- As children, less likely than other children with DD to show behavioral difficulties
- Temperamental features show a global positive mood
- Hyperactivity and oppositional behaviors may be present
- Significant delay in cognitive development with specific deficits in speech and language production
- Adaptation level is globally higher than cognitive and learning levels, and increases with age

## DS Behavioral Phenotypes

- As adults, increased risk for (associated with hypothyroidism):
  - Depressive Disorder (with psychotic features)
  - Obsessive-Compulsive Disorder
  - Anxiety Disorders
- Later, increased risk for Alzheimer's, new onset: increased aggression, fearfulness, sadness, sleep problems, social inadequacy, stealing, and general regressive behavior

## DS Medical Concerns

- Congenital heart disease
- Hearing problems
- Intestinal problems (Celiac disease)
- Eye problems
- Thyroid dysfunction
- Sleep apnea
- Skeletal problems
- Dementia – *protein that is product of gene on 21 contributes to degeneration of specific neural circuits – same degeneration seen in Alzheimer's.*



# Williams Syndrome

- Incidence: 1 in 7500
- Cause: microdeletion on chromosome 7 (7q11)
- Cognition: most people function in mild to moderate range ID (average IQ is 50-60); strengths in language ability, facial recognition, and short-term memory; deficits in visual-spatial ability, perceptual planning, and eye-hand coordination

# Williams Syndrome

## Physical Characteristics



- Full lips
- Puffy cheeks
- Puffiness around eyes
- Wide mouth
- Long upper lip
- Small jaw
- Short stature
- Slumped posture

# **Williams Syndrome**

## **Behavioral Phenotypes**

- Outgoing demeanor (overly friendly; may decline with age)
- High verbal communication abilities and empathy
- Exaggerated linguistic affect
- Socially uninhibited (at risk for sexual exploitation)
- Strength in interpersonal and socialization skills
- Interest in faces
- Weakness in daily living and motor skill

# Williams Syndrome

## Behavioral Phenotypes

- Musical ability (perfect pitch)
- Emotionally labile
- Attention problems (ADHD)
- Increased anxiety and fears
- Phobias (often related to noise, natural disasters, fears about future)
- Increased sensitivity to sound

# Williams Syndrome

## Medical Concerns

- Heart defects
- Immune deficiencies
- Vascular abnormalities
- Abnormality of calcium and Vitamin D metabolism
- Hernias are common
- Low muscle tone and joint stiffness

# Angelman Syndrome

Incidence: 1 in 12,000 – 20,000

Cause: loss of active genes on chromosome 15q11-13 (maternal); most caused by deletion, small percentage by Uniparental Disomy (UPD). UPD associated with increased parental age

Cognition: most have severe ID; non-focused actions and limited communication, but interest in others

## Angelman Syndrome

- Signs of AS can be seen as early as 6-12 months of age and is most often diagnosed between 2-5 years old.
- The number of individuals with AS who are undiagnosed or diagnosed with other conditions is unknown.
  - Other conditions that are often diagnosed include Prader-Willi Syndrome, Autism Spectrum Disorders and Cerebral Palsy

# Angelman Syndrome

## Physical Characteristics

- Microcephaly
  - Ataxic movements
  - Hand-flapping
  - Some have unusually light skin and light hair
  - Protruding tongues
- \* *Deletion results in more severe characteristics – higher incidence of seizure, microcephaly, and hypopigmentation. Dysmorphic features more subtle in UPD*





# Angelman Syndrome

## Behavioral Phenotypes

- Smiling/laughter unrelated to context
- Strong drive for adult attention
- Sociability may decrease with age
- Very low linguistic abilities
- Unsteady gait
- Sleep issues (falling and staying asleep at night) - can persist beyond the age of puberty

# Angelman Syndrome

## Behavioral Phenotypes

- Motoric hyperactivity and inattention
- Hand-flapping, twirling, stereotyped movements (e.g., puppet-like movements)
- Sensory processing abnormalities
- Attraction to water and shiny objects
- Tendency to catch hold of persons and objects: grabbing and pulling people and their hair
- Tantrums occasionally

# Angelman Syndrome

## Medical Concerns

- Seizure disorder (waxes and wanes in severity); more prominent in deletion subtype, low incidence in UPD
- Risk of scoliosis
- Increased sensitivity to heat
- Abnormal sleep/wake cycles; diminished need for sleep
- Obesity
- Constipation
- Decreased mobility in later years

## Prader-Willi Syndrome

- Incidence: 1 in 10,000 – 25,000
- Cause: loss of active genes on chromosome 15 (paternal); 70% due to deletion, smaller percentage due to UPD (uniparental disomy). UPD associated with increased parental age.
- Cognition: mild to moderate ID (adaptive behavior often lower than cognitive level); relative strengths in reading, long-term memory, visual spatial skills.

# Prader-Willi

## Physical Characteristics

- Small stature
- Small hands and feet
- Low muscle tone/ FTT at birth
- Temperature control problems
- Dysmorphic facial features: narrow nasal bridge, narrow diameter of face, down-turned mouth, almond-shaped eyes, full cheeks
- Fair skin coloring

*\* Deletion results in more prominent facial features and fair skin. . PW due to UPD more likely to resemble their parents.*



## **Prader-Willi**

### **Behavioral Phenotypes**

- Food seeking and overeating (lying to get it)
- Tantrums, stubbornness, argumentative
- Emotional lability
- Compulsive behaviors – hoarding, arranging, concerns with symmetry
- Anxiety
- Repetitive skin picking

# Prader-Willi

## Behavioral Phenotypes

- Perseverating speech
- Impulsiveness
- Social withdrawal/ difficulty recognizing nonverbal cues
- Elevated risk of developing a mood disorder
- Mood disorder with psychotic symptomatology is more common in people with UPD PWS

*\* Larger deletions associated with more severe behavior issues. PW due to UPD with higher IQ, less behavioral issues – but higher incidence of psychiatric disorders including psychoses*

# Prader-Willi

## Medical Concerns

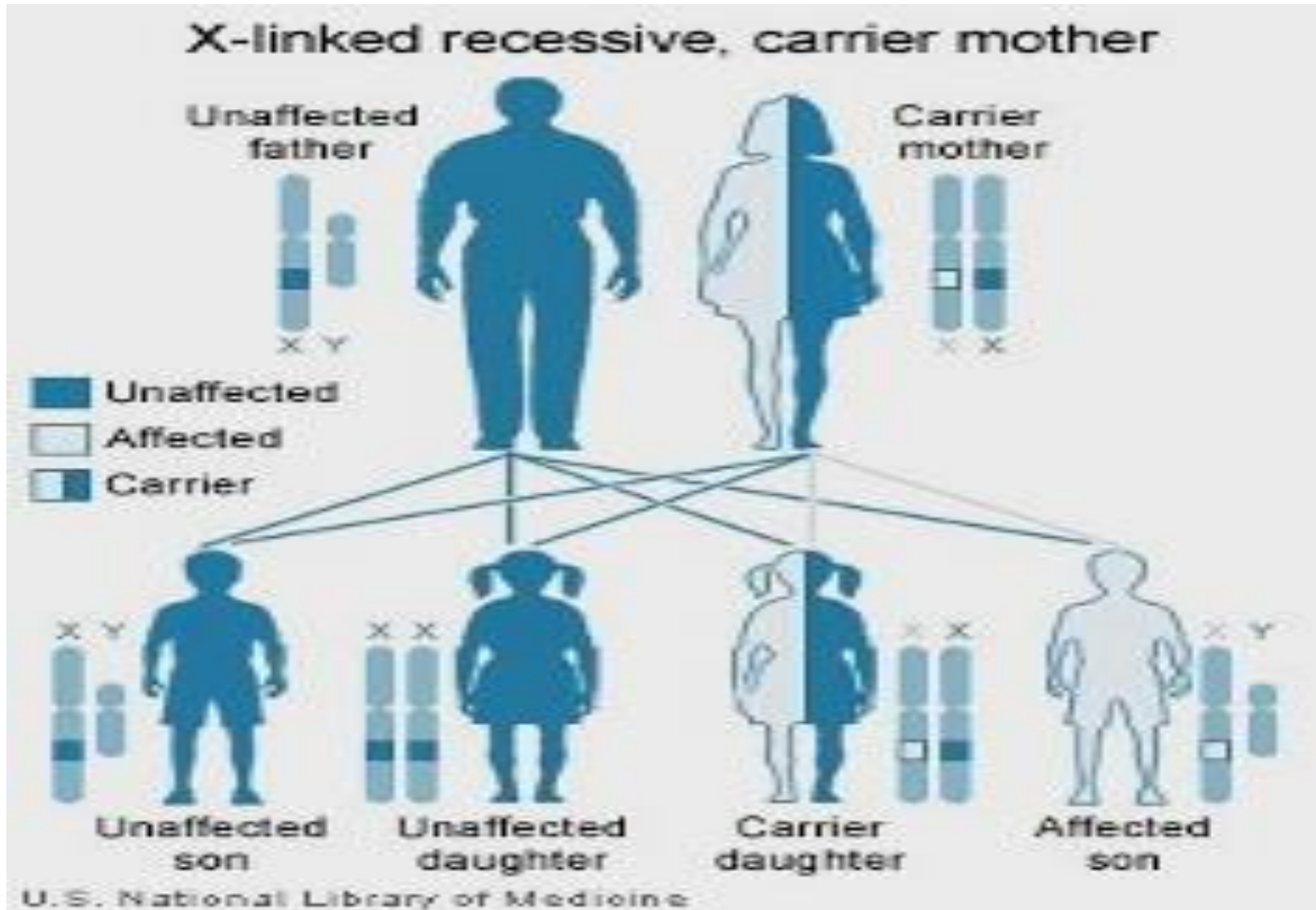
- Sleep disturbances and excessive daytime sleepiness
- Complications of obesity
- Diabetes
- Heart failure
- Skin picking
- Deficit in oxytocin-producing neurons
- High pain threshold



## Fragile X

- Incidence: 1 in 4000 males (most common cause of *inherited* IDD); 1 of 259 females have premutation
- Cause: mutation of FMR1 gene (A small part of the gene code is repeated on a fragile area of the X chromosome. The more repeats, the more likely there is to be a problem)
- Cognition: ranges from mild learning disabilities to severe ID; females with full mutation function in borderline to mild range of ID, males are more severely affected; 1/3 of individuals with Fragile X have some degree of autism

# Genetic Links



## Fragile X Physical Characteristics

- Long face
- Large or prominent ears
- Hyperextensible joints
- Large testicles
- High arched palate
- Connective tissue anomalies
- Family history of ID



# Fragile X

## Behavioral Phenotypes

- Hyperactivity
- Short attention span
- Impulsivity
- Tactilely defensive
- Poor eye contact; gaze avoidance
- Perseverative speech; self-talk
- Hand-flapping, hand-biting
- Social Anxiety (but not lack of interest)

# Fragile X

## Behavioral Phenotypes

- Emotional and behavioral problems are common in both sexes.
- About 30% of boys meet full criteria for autism
- Both cognitive and adaptive levels decline with increasing age in fully-mutated Fragile-X males.
- A moderate and significant negative correlation between maladaptive behavior levels and age; adaptive and maladaptive behaviors did not correlate with each other

# Fragile X

## Behavioral Phenotypes

Klaiman, et al. (2014) investigated changes in adaptive behavior in children and adolescents with Fragile X

- Standard scores of adaptive behavior significantly decline over time in:
  - all domains for males
  - communication for females
- Socialization skills are a relative strength as compared with the other domains for males with fragile X syndrome.
- Females with fragile X syndrome did not show a discernible pattern of developmental strengths and weaknesses.

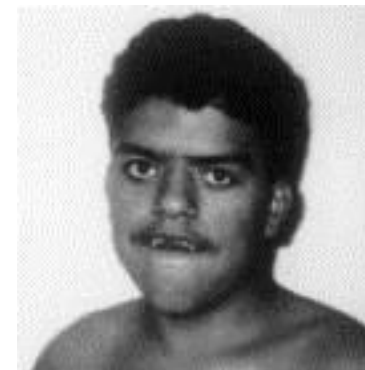
# Smith-Magenis Syndrome

- Incidence: 1 in 15,000 to 25,000
- Cause: deletion on chromosome 17 or mutation on chromosome 17 (less severe)
- Cognition: mild to moderate ID; relative strengths in long-term memory and visual–spatial; weaknesses in short-term memory and sequential processing

# Smith Magenis Physical Characteristics

- Short stature
  - Broad square shaped face
  - Deep set eyes
  - Under-developed cheekbones
  - Prominent jaw
  - Prominent forehead
- (facial characteristics are subtle early in life but become more distinctive in adulthood)
- Short fingers and toes
  - Skin on hands and feet dry and leathery
  - Congenital heart defects and cleft palates are common

\* Significant clinical overlap with Down syndrome; infants are often initially thought to have DS





# Smith Magenis

## Behavioral Phenotypes

- Rarely cry as infants, lethargic
- Speech more delayed than motor skills
- Expressive language < receptive language
- By age 4, sleep problems begin
- Disturbed sleep patterns present life-long challenge
- Crave constant attention (especially from adults)
- Prolonged outbursts and temper tantrums; aggression
- Impulsivity
- Look through magazines, lick fingers, flipping pages over and over

# Smith Magenis

## Behavioral Phenotypes

- Adherence to routine
- Body rocking; twirling
- Self-injurious behavior (includes pulling out fingernails and toenails, and inserting foreign objects into body orifices – these are unique to SMS; prevalence of SIB increases with age, as does repertoire)
- “Self-hugging” when excited also is key element of SMS
- Reduced sensitivity to pain

## Smith Magenis Medical Concerns

- Congenital heart defects
- Kidney defects
- Hearing loss (65%), chronic ear infections (87% tube placement)
- Otolaryngologic problems : vocal polyps/hoarse voice, hyperacusis (78%)
- Poor vision (myopia, strabismus)
- Dental anomalies (missing teeth, malformed roots, increased cavities), palate abnormalities
- Infant feeding problems (poor sucking reflex, GERD, hypotonia, lingual weakness)

## Smith Magenis Medical Concerns

- Sleep problems (75-100%): develop in early childhood and last throughout life. Shortened sleep cycles, frequent awakenings, early rising, daytime sleepiness. Inverted circadian rhythm of melatonin (diurnal secretion)



- Obesity: up to 90% are overweight or obese by age 14. Not more prone to Type II diabetes, but to high cholesterol (50%)
- Appear to have normal life expectancy

# Velocardiofacial Syndrome

## (VCFS/ also known as DiGeorge Syndrome)

- Incidence: 1 in 4000
- Cause: microdeletion on chromosome 22.
- Cognition: average is borderline ID; yet can range from average to moderate. Verbal IQ often higher than Performance IQ. Deficits seen (even in those with borderline ID) in language comprehension, mathematics, visual-perceptual integration, memory, and executive function.

## VCFS Physical Characteristics

- Long face
- Long pear-shaped nose
- Small ears
- Almond shaped eyes
- Reduced facial animation
- Cleft palate



# VCFS Behavioral Phenotypes

## Children

- Impulsivity/ADHD (25%)
- Inattention
- Temper outbursts
- Perseveration/OCD
- Social withdrawal

# VCFS Behavioral Phenotypes

## Adults

- Severe mood swings (Bipolar Disorder?)
- Thought disorders: Up to 30% will develop schizophrenia during adolescence/adulthood
- GAD (cardiac defects)
- Depression (cardiac defects)
- ODC (hypocalcemia)

*\*current research is trying to distinguish the behavioral phenotype in this disorder from Schizophrenia and Bipolar Disorder in the general population*



## VCFS Medical Concerns

- Cardiac anomaly
- Developmental Delay
- Palatal anomaly
- Immunodeficiency
- Hypocalcemia
- Renal anomaly
- Skeletal anomaly
- Growth hormone deficiency
- Seizure dx

## Physical Signs to Notice

- Height – small stature in Down Syndrome, Williams, Prader Willi
- Head size – small in DS and Angelman
- Shape of face – elongated in Fragile X; small jaw in Williams; broad square face in Smith Magenis

# Physical Signs to Notice

- Eyes:
  - Puffiness around eyes in WS
  - Upward slant to eyes in DS
  - Almond shaped eyes in VCFS/DiGeorge

# Physical Signs to Notice

- Ears:
  - Large size in Fragile X
  - Small ears – Down Syndrome
- Hands
  - Simian crease – Down Syndrome

## Physical Signs to Notice

- Pale skin - Angelman, Prader-Willi
- Low Muscle Tone – Down Syndrome and Prader Willi

## **Behavioral Signs to Notice**

- Specific/Unusual Phobias – Williams Syndrome
- Unusual self injury – Smith Magenis
- Overly social – Williams Syndrome
- Hyperactivity – Fragile X, Cri du Chat, Angelman
- Impulsivity – Fragile X, Smith Magenis, DiGeorge

# Remember

- There is a core set of characteristics shared by all people with IDD, regardless of cause.
- There are also more specific patterns of abilities, deficits, and other characteristics associated with known genetic syndromes.

## Therefore...

- Professionals working with people with IDD need to be aware of the contribution of behavioral characteristics of genetic syndromes to diagnosis and treatment.