

## Practical Implications of Genetic Diagnoses for People with Intellectual Disabilities

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www.elwyngenetics.org

## Why Diagnose?

- Reimbursement
- Eligibility for services
- Treatment
- Research

## What is Etiology?

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

## Why is Etiology Important?

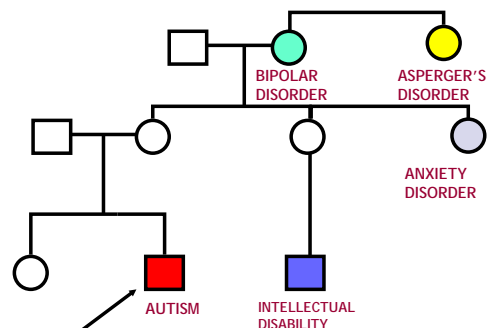
- **Genetic counseling for families**
- **Alleviates guilt, misconceptions**
- **Anticipation of medical needs**
- **Insight into behavior, learning styles**
- **Support groups**

## Psychiatric Diagnoses

ADD ANXIETY DISORDER OPPOSITIONAL DEFIANT DISORDER OCD  
ADHD BIPOLAR DISORDER  
AUTISTIC DISORDER MR IMPULSE CONTROL DISORDER  
INTERMITTENT EXPLOSIVE DISORDER

5 DIFFERENT PSYCHIATRIC DIAGNOSES

1 ETIOLOGICAL DIAGNOSIS: FRAGILE X SYNDROME



## Diagnostic Alphabet Soup



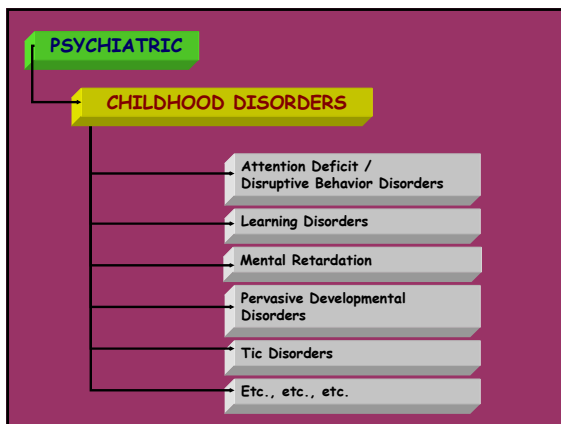
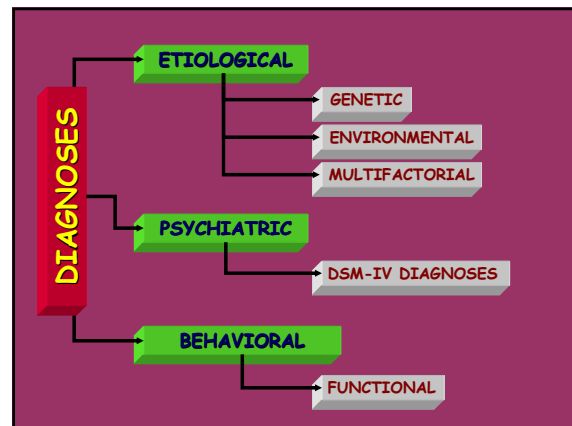
## Etiological Diagnoses

### In the school setting:

- Etiological diagnoses often considered irrelevant
- Educational / psychiatric diagnoses determine services and treatment approaches

## Psychiatric Diagnoses

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



## Attention Deficit / Disruptive Behavior Disorders

- HD, ADD
- ADHD, ADHD-NOS,
- Conduct Disorder
- ODD (Oppositional Defiant Disorder)
- Disruptive Behavior - NOS



## HA / ADD / ADHD

- Characterized by a majority of the following symptoms being present in either category (inattention or hyperactivity).
- Symptoms are inconsistent with the child's developmental level.



## Symptoms of Inattention

- Fails to give close attention to details / makes careless mistakes
- Difficulty sustaining attention on tasks
- Does not seem to listen when spoken to directly
- Does not follow through on instructions / fails to finish schoolwork, chores, etc.



## Symptoms of Inattention

- Avoids, dislikes tasks requiring sustained mental effort
- Loses things necessary for tasks, activities
- Easily distracted by extraneous stimuli
- Forgetful in daily activities
- Fidgets with hands / feet, squirms in seat



## Symptoms of Hyperactivity

- Leaves seat in class / other situations when required to remain seated
- Runs about or climbs excessively in inappropriate situations
- "On the go", acts as if "driven by a motor"
- Talks excessively



## Symptoms of Impulsivity

- Blurts out answers before questions have been completed
- Has difficulty awaiting turn
- Interrupts or intrudes on others



## HA / ADD / ADHD

- Symptoms have been present  $\geq$  6 months
- Some symptoms present by age 7 years
- Symptoms must exist in at least 2 separate settings
- Symptoms create significant impairment in social, academic or occupational functioning or relationships

## THE PDD UMBRELLA

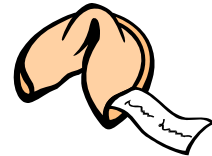
- Pervasive Developmental Disorders (PDD):  
Formal DSM-IV Designation
- Autism Spectrum Disorders (ASD)
- In practice: ASD = PDD
- Subtypes under ASD, PDD umbrella:
  - Autistic Disorder (a.k.a. autism)
  - Asperger's Disorder
  - Childhood Disintegrative Disorder
  - Rett's Disorder
  - PDD-NOS



## Autistic Disorder (Autism)

(I) Need 6 or more items from section A, B, and C with at least 2 from A and 1 each from B and C.

(Chinese menu approach)



## Autistic Disorder

- A) Qualitative impairment in social interaction as manifested by at least 2 of the following:
- Impairment in use of nonverbal behaviors
  - Failure to develop peer relationships
  - Lack of spontaneous seeking to share enjoyment, interests, etc. with others
  - Lack of social or emotional reciprocity

## Autistic Disorder

- B) Qualitative impairment in communication as manifested by at least 1 of the following:
- Delay in, or total lack of, spoken language
  - Impairment in ability to initiate or sustain a conversation with others
  - Stereotyped, repetitive, or idiosyncratic language
  - Lack of make-believe or imitative play

## Autistic Disorder

- C) Restricted, repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least 2 of the following:
- Preoccupation with one or more stereotyped / restricted patterns of interest
  - Adherence to routine, rituals
  - Stereotyped / repetitive motor mannerisms
  - Preoccupation with parts of objects

## Autistic Disorder

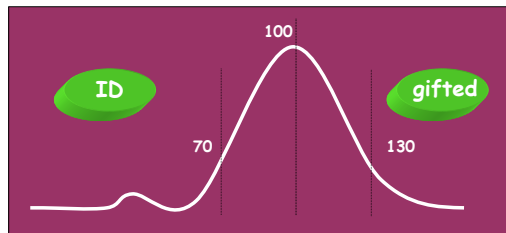
- (II) Delays or abnormal functioning in at least 1 of the following areas, with onset prior to age 3 years:
- A. social interaction
  - B. language as used in social communication
  - C. symbolic or imaginative play
- (III) Not better accounted for by Rett's or Childhood Disintegrative Disorder



### INTELLECTUAL DISABILITY (formerly MR)

- Significantly subaverage intellectual functioning (IQ of 70 or below)
- Deficits in adaptive functioning
- Onset prior to age 18

### Distribution of IQ scores



### Degree of Intellectual Disability

DEGREE	RANGE
mild	55- 70
moderate	40 - 55
severe	25 - 40
profound	below 25



### Genetic Evaluation: Indications for Referral

- Disability of unknown cause
- Congenital structural anomalies
- Unusual appearance
- Abnormal genitalia
- Abnormal growth pattern
- Skeletal abnormalities
- Unusual skin or hair features
- Unusual behaviors
- Regression in developmental progress



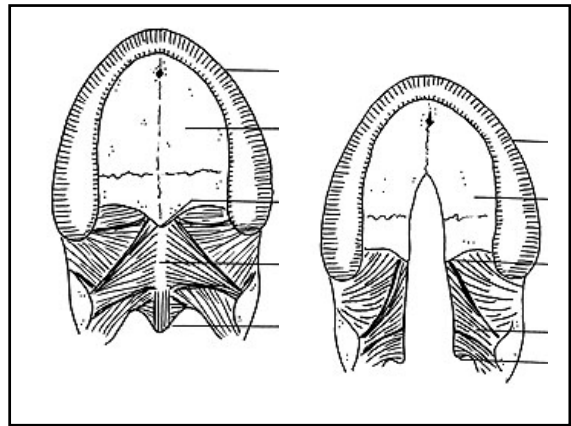
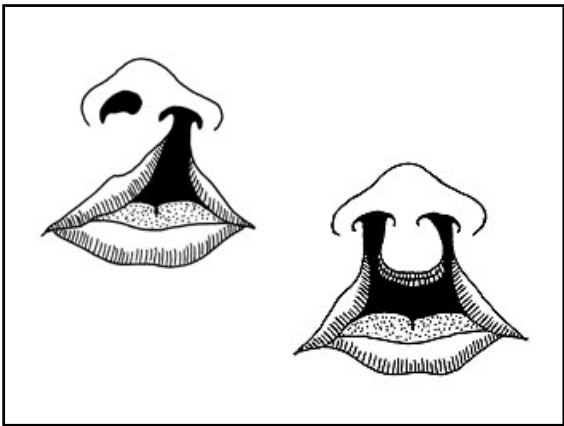
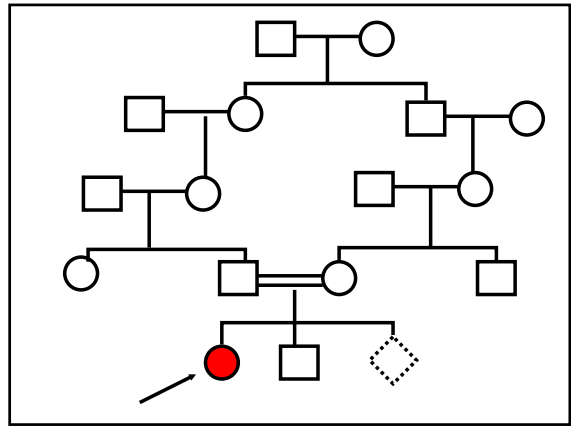
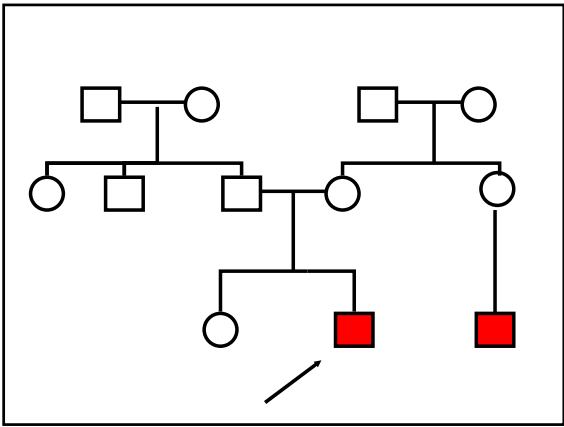
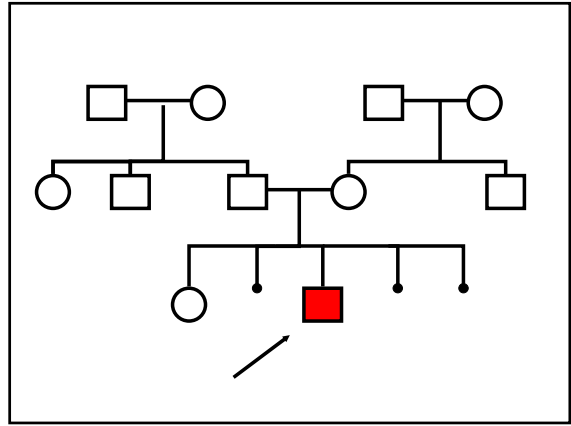
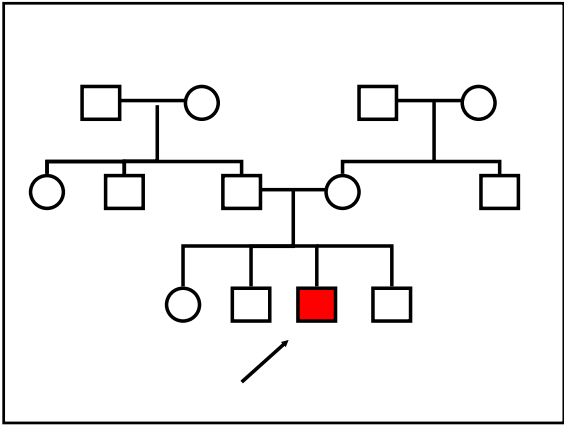
### Indications for Referral

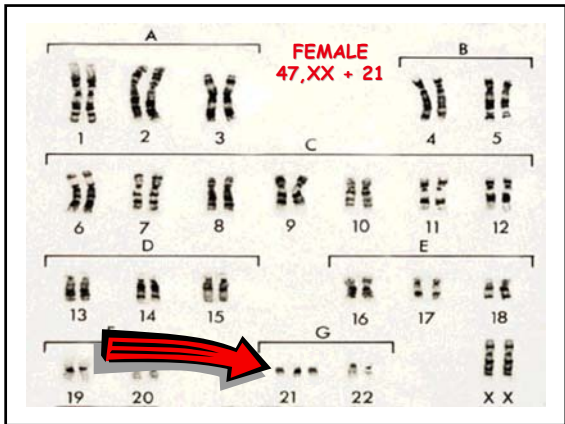
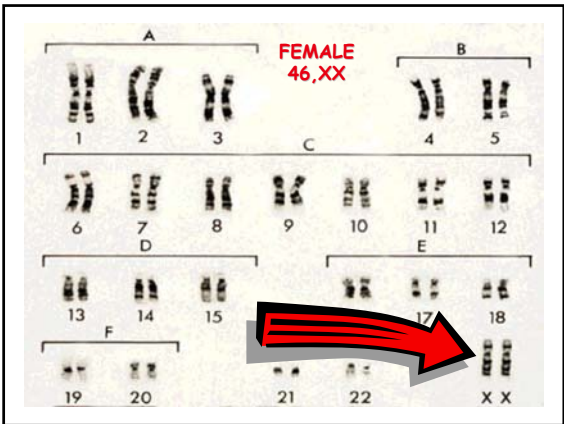
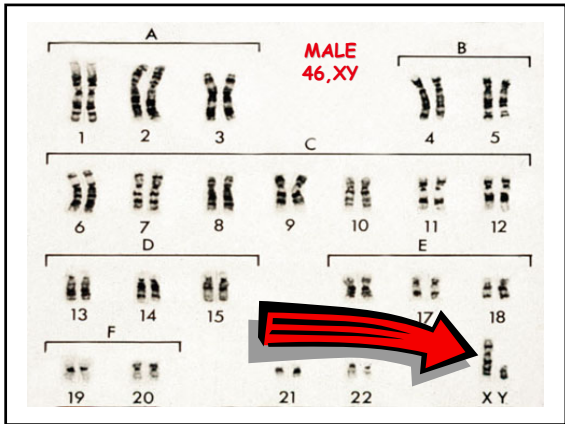
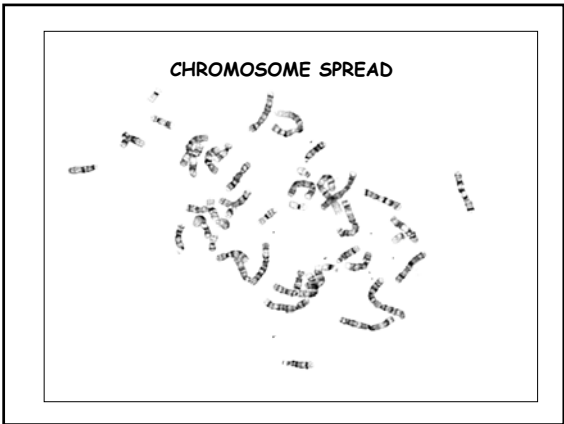
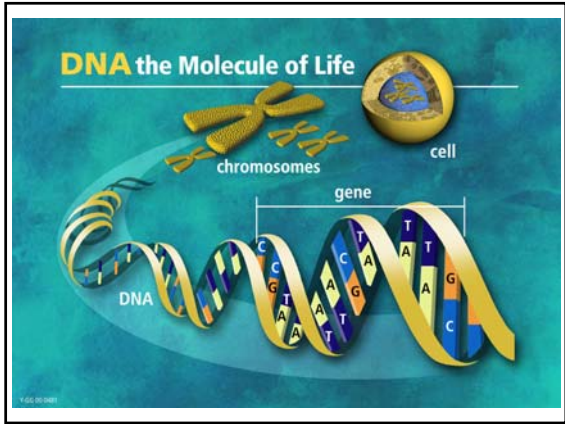
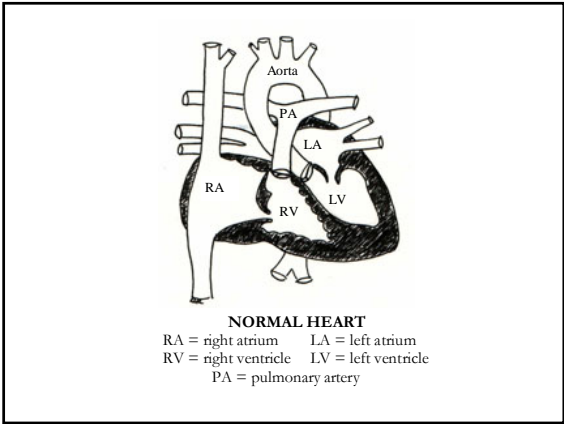
- Unusual body odor
- Excessive unexplained vomiting, lethargy
- Congenital hypotonia
- Prenatal exposure to alcohol, seizure medications, German measles, herpes, HIV or other infections
- Parents who have had stillborn children or lost other children during pregnancy, even with other partners

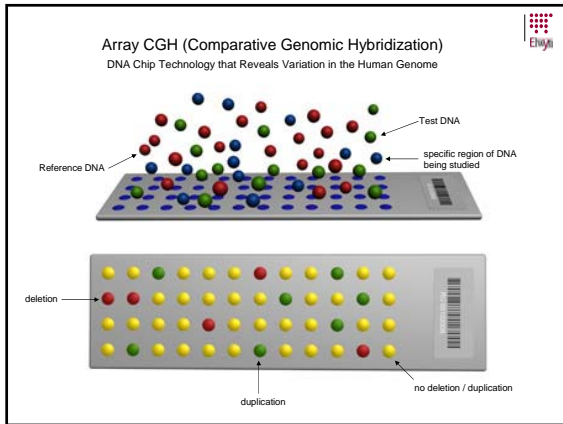


### Indications for Referral

- Parent, sibling, or other close family member with developmental, neurological, or psychiatric problems, or known genetic conditions
- Parents who are genetically related
- Mother over the age of 35 or father over 55 when the child was born
- Parents who would like to plan another pregnancy but are worried about the chance of having a child with developmental delay





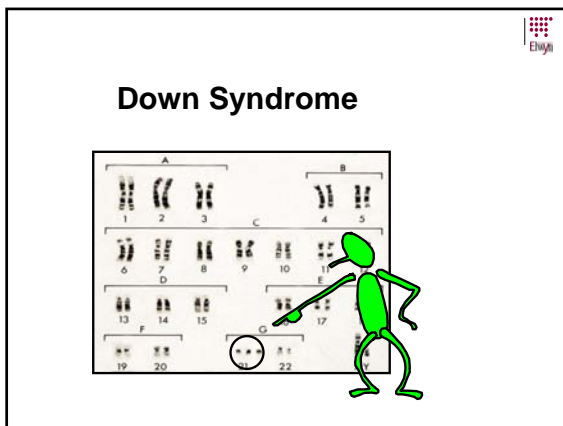


**Medical Genetics Centers**

**GeneClinics**  
www.geneclinics.org  
(state by state directory)

**National Society of Genetic Counselors**  
www.nsgc.org

**American Board of Genetic Counseling**  
www.abgc.net



**Down Syndrome**

- 1 in 660 births
- the most common diagnosable cause of ID in all populations
- associated with an extra copy (trisomy) of chromosome 21

Down Syndrome  
New Parent Support

2010 beautiful faces  
LIVING WITH DOWN SYNDROME

**www.bandofangels.com**

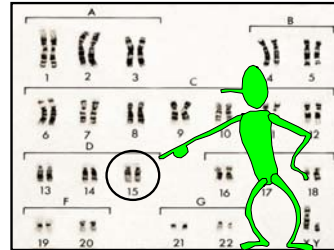
**Down Syndrome**

- relative strength in sequential processing
- tendency for depression in adolescence
- relatively few maladaptive behaviors

## Down Syndrome

NATIONAL  
DOWN SYNDROME SOCIETY  
[www.ndss.org](http://www.ndss.org)

## Prader-Willi Syndrome



## Prader-Willi Syndrome

Associated in most cases with a deletion of part of the **paternal** copy of chromosome 15q.

## Prader-Willi Syndrome

- General Population: 1 in 15,000
- Intellectual Disability: 1 in 100

Among people with ID: 1 in 150

## Developmental Course

- Hypotonia: in utero (decreased fetal movements), at delivery, in infancy
- Poor suck, failure to thrive in infancy
- Decreased arousal, weak cry in infancy
- Delayed motor milestones (walking after 2 years)

## Developmental Course

- Hyperphagia (overeating): toddlers, children, adults
- Food seeking, hoarding
- Eating inedibles, uncooked foods
- Low muscle tone leads to exercise aversion



## Intellectual Development

- Global developmental delay before age 6; mild to moderate ID or learning disabilities in older children
- Average IQ around 70 (ranges from over 100 to 40)
- Good expressive language
- Relative strength in reading
- Weakness in math, abstract reasoning



## Intellectual Development

- Strength in visual processing
  - Visual pattern construction
  - Relative strength on Block Design: Wechsler
- Simultaneous vs. sequential learners
- Short-term memory deficits but good long-term memory



## Personality

- Low tolerance for teasing
- Low energy (hypotonia)
- Low sex drive (hypogonadism)
- Always thinking about food: try to hide overeating
- Upset with changes in routine
- Like to help others, nurturing
- Need for order
- Tendency to get “stuck” on topics



## Behavioral Features

- Difficulty coping with frustration
- Socialization difficulties
- Temper tantrums
- Obsessive compulsive tendencies
- Need to put things in order, ritualistic repetition of actions over and over
- Impulsivity
- Skin Picking




## Weight Control

- Obesity can be prevented!
- 1,000 to 1,200 calorie diet; adequate calcium
- Regular exercise – at least 30 mins/day
- Environmental controls: locking up food – rights?
- Close supervision
- Consider growth hormone




## Hypotonia


- Hypotonia – low muscle tone
  - People w/PWS have to work harder to move
    - contributes to avoidance of exercise
  - Less muscle requires fewer calories for energy
- Increased body fat (lower lean body mass), regardless of weight
- Vomiting reflex often absent/delayed



## Weight Management in PWS


- Low calorie diet – 1,000 - 1,200 kcal/day
  - Can be as low as 800 kcal/day
- Food **MUST** be inaccessible
  - Refrigerator and cabinets must be locked
    - People with PWS will find food even if it seems well hidden!
    - Limiting food reduces stress for people with PWS
- **Must be vigilant and consistent!**






## PWS and Growth Hormone

- Individuals with PWS have Growth Hormone (GH) deficiency
- In 2000, GH became available as a treatment for PWS




## PWS and Growth Hormone

- Accelerates growth, increases height
- Decreases percent of body fat
- Lean body mass increases (stronger bones and muscle)
- Total body fat decreases
- Improves respiratory muscle strength
- Somewhat controversial
  - A few cases of sudden death
  - These individuals were already morbidly obese



## PWS and GH


- Somewhat controversial
  - A few cases of sudden death
    - These individuals were already morbidly obese



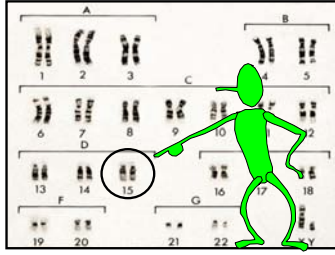
## Prader-Willi Syndrome

International Prader-Willi Syndrome Organization  
[www.ipwso.org](http://www.ipwso.org)

Prader-Willi Syndrome Association (USA)  
[www.pwsausa.org](http://www.pwsausa.org)



## Angelman Syndrome





## Angelman Syndrome

- General Population: 1 in 15,000
- Intellectual Disability: 1 in 100

Among people with ID: 1 in 150



## Angelman Syndrome

Associated in most cases with a deletion of part of the **maternal** copy of chromosome 15q.



## Prader-Willi Syndrome

Associated in most cases with a deletion of part of the **paternal** copy of chromosome 15q.



## Angelman Syndrome

- Characteristic facial appearance
- Small head size
- Tendency toward fair hair and skin
- Seizure disorder
- Tremors (shakiness)
- Often diagnosed as CP
- 1 in 15,000 newborns



## Angelman Syndrome

- Developmental delays apparent in infancy
- Lack of speech
- Unsteady gait
- Frequent laughter
- Intellectual disability
- Hyperactivity
- Sleep disturbance

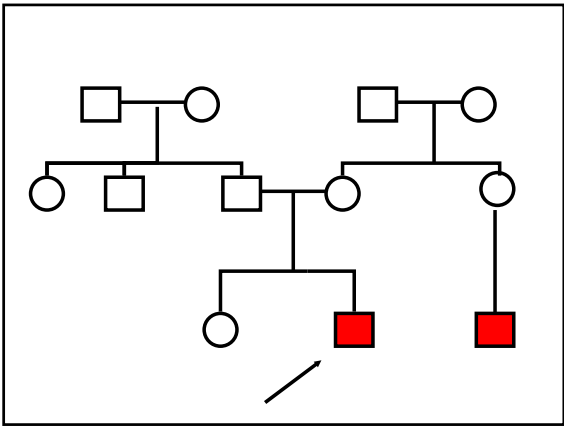
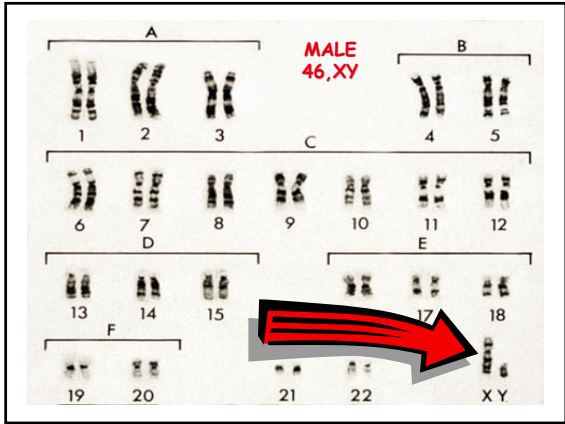
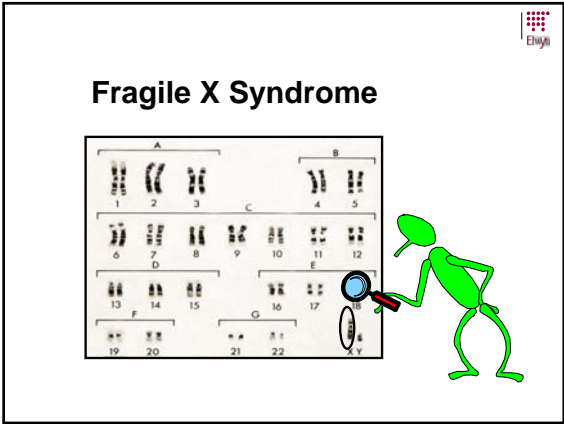


## Angelman Syndrome

ANGELMAN SYNDROME FOUNDATION  
[www.angelman.org](http://www.angelman.org)

AUSTRALIAN A.S. ASSOCIATION  
[www.angelmansyndrome.org](http://www.angelmansyndrome.org)

INT'L. A.S. ORGANISATION (IASO)  
[www.international.angelmansyndrome.org](http://www.international.angelmansyndrome.org)



**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


Finucane et al., Fragile Syndrome: A Handbook for Families and Professionals, NFXF, 2004



## 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


Hagerman & Hagerman, Fragile X Syndrome. Diagnosis, Treatment, and Research, 2002



## Behavioral Characteristics

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


Finucane et al., Fragile Syndrome: A Handbook for Families and Professionals, NFXF, 2004



## 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


McConkie Rosell et al., Journal of Genetic Counseling, 2005



## Fragile X and Autism

- Up to 21% of young boys with fragile X syndrome meet diagnostic criteria for Autistic Disorder
- A majority of males and many females with fragile X syndrome have symptoms consistent with an autism spectrum disorder

Hatton et al., American Journal of Medical Genetics, 2006  
Clifford 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

Belmonte and Bourgeron, Nature Neuroscience, 2006

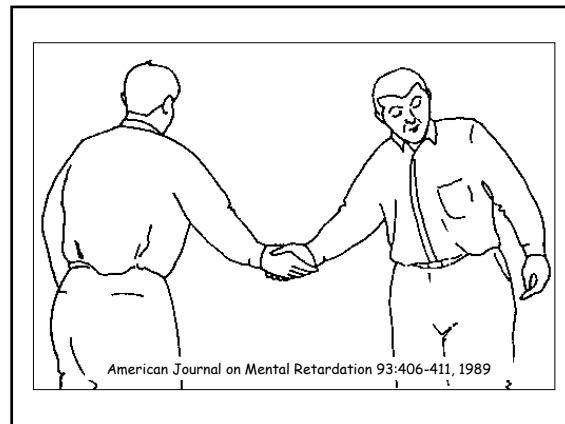
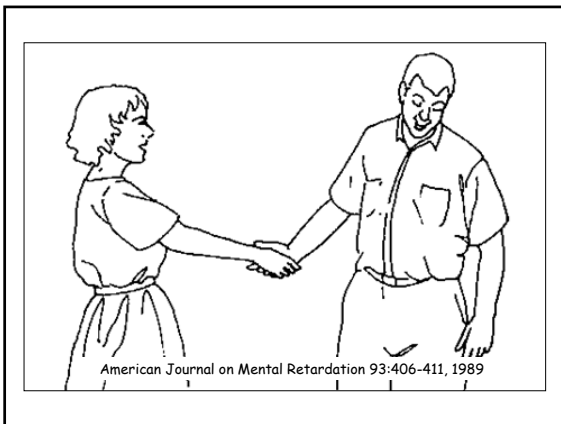
## Hyperarousal in Fragile X Syndrome

- Over-reaction to sensory stimuli
- Enhanced electrodermal response to sensory stimuli which correlates inversely with FMRP levels
- Enhanced cortisol release after stressors
- Delayed physiological recovery after hyperarousal

## 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

Hessl et al., *Journal of Child Psychology and Psychiatry*, 2006  
 Garrett et al., *Archives of General Psychiatry*, 2004  
 Cohen et al., *Journal of Child Psychology and Psychiatry*, 1988



## Gaze Aversion

- Verbal prompting and forced eye contact often exacerbate gaze aversion in males with fragile X
- When eye contact goals are de-emphasized, eye contact often improves



## 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

Scharfenaker and Stackhouse, *Nat'l Fragile X Fdn Quarterly*, 2006

## Anxiety / Hyperarousal in Fragile X Syndrome

### EARLY SIGNS:

- self-injury (hand- and wrist- biting)
- mouthing objects, clothes
- hand-flapping

### ESCALATE TO:

- task refusal
- leaving the area
- verbal aggression (often imitated phrases)

## Anxiety / Hyperarousal in Fragile X Syndrome

### ESCALATE TO:

- property destruction (threatened & real)
- breaking personal objects (glasses)
- door slamming
- throwing objects

### ESCALATE TO:

- physical aggression (threatened & real)
- punching
- slapping

## Anxiety / Hyperarousal in Fragile X Syndrome

### TRIGGERS:

- forced eye contact
- personal space issues
- tactile defensiveness
- emotional tone of peers and staff
- changes in routine
- auditory stimuli
- changes in environment

## Anxiety / Hyperarousal in Fragile X Syndrome

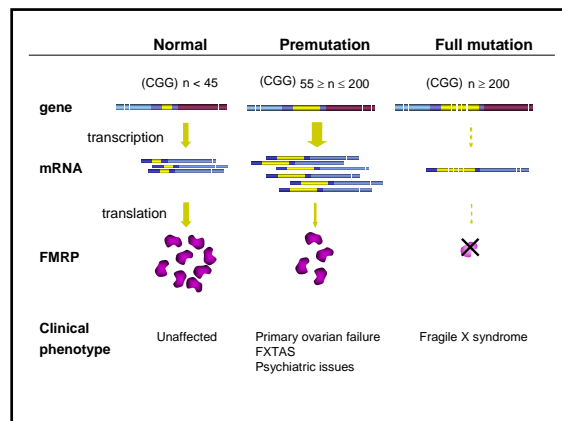
### OTHER POTENTIAL CONTRIBUTORS:

- auditory processing deficits
- delayed emotional processing
- hypersensitivity to negative correction
- performance anxiety
- poor concept of time
- strong associations (positive & negative)

## Molecular Basis

### Three FMR-1 states:

- Normal allele: 6 - <55 CGG repeats
- Premutation: >55 - <200 CGG repeats
- Full mutation:  $\geq 200$  CGG repeats



## Fragile X Premutations

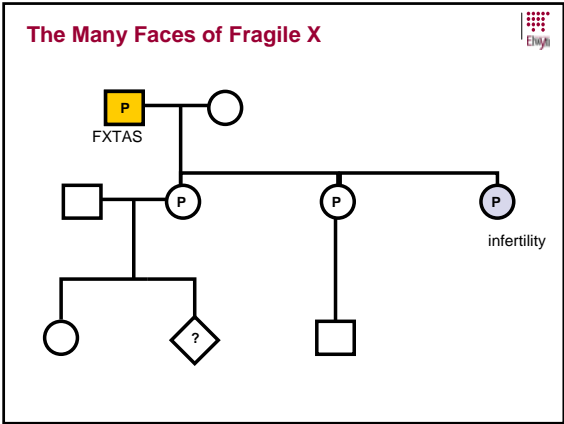
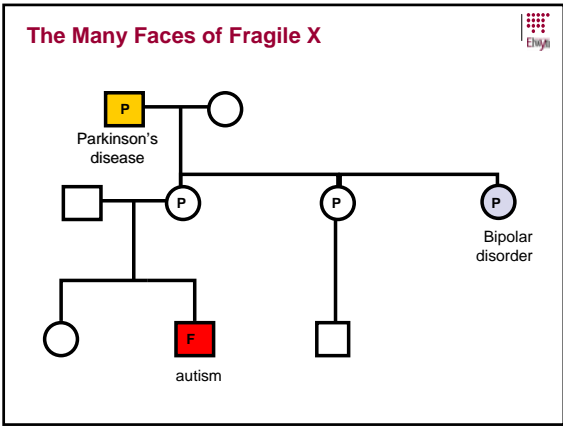
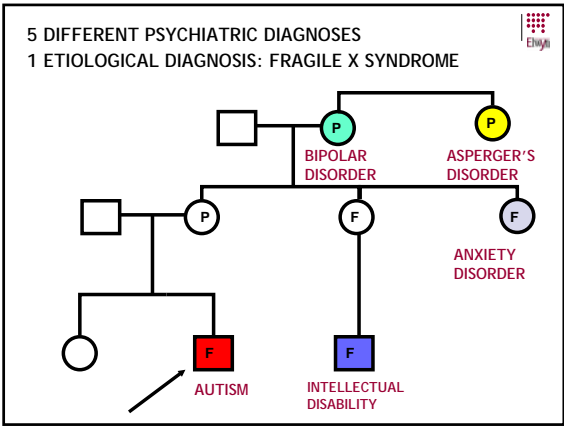
- No cognitive impairment in males or females
- Associated with symptoms of mRNA toxicity
- Females:
  - Increased risk for psychiatric symptoms – depression, social anxiety, shyness
  - Primary ovarian insufficiency (POI): early menopause, fertility issues
    - 13 – 24% of premutation carriers have menopause before age 40
  - Conversely, fraX premutations found in:
    - 2% of women with idiopathic menopause <40 years
    - 14% of women with who have POI plus family history of menopause <40

McConkie Rosell et al., Journal of Genetic Counseling, 2005

## Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

- Neurodegenerative condition in otherwise unaffected males with the fraX premutation, also some females
- First reported in 2001
- At least 1/3 males with the premutation develop FXTAS
  - Intention tremor, ataxia, atypical Parkinson's disease, dementia
- Prevalence in general population
  - Affects up to 1/3000 adult males over 50 years of age
  - Less frequent and milder in females
- Reproductive implications

Hagerman and Hagerman, Ment Retard Dev Disabil Res Rev, 2004



## A Cure for Fragile X?

- Targeted pharmaceutical treatments are currently undergoing human clinical trials and are expected to be available within the next 5 years
- New treatments target underlying biochemical pathway affected by the fragile X gene mutation
- Only those families diagnosed with fragile X syndrome will be able to benefit from these medical breakthroughs!

Penzarikano et al., Annual Review of Genomics and Human Genetics, 2007






## Research Review

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*Fragile X Research: A Status Report*  
Elizabeth Berry-Kravis, MD, PhD  
July 2008 issue of Fragile X Quarterly  
Nat'l Fragile X Foundation  
[www.fragileX.org](http://www.fragileX.org)



## Population Screening

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- Pregnant women
- Special populations
  - Children / adults with intellectual disability
  - Psychiatric patients
  - Women with infertility
  - Males or females with early onset Parkinsonian symptoms / ataxia / dementia
- Newborn screening
- Everybody ??




## Fragile Syndrome

Elwyn Fragile X Center  
[www.elwyngenetics.org](http://www.elwyngenetics.org)

National Fragile X Foundation  
[www.fragileX.org](http://www.fragileX.org)

FRAXA Research Foundation  
[www.fraxa.org](http://www.fraxa.org)



## Smith-Magenis Syndrome

## Smith-Magenis Syndrome

Chromosome deletion 17p11.2

## Smith-Magenis Syndrome

**ONYCHOTILLOMANIA**  
Nail yanking

**POLYEMBOLOKOILAMANIA**  
Orifice stuffing



## 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

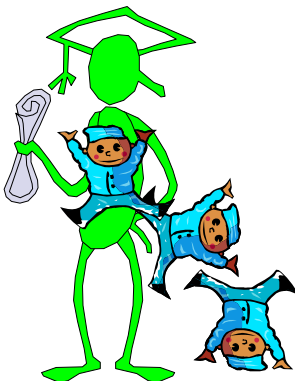
### POSITIVE ASPECTS

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

## Smith-Magenis Syndrome

### POSITIVE ASPECTS

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



**SMITH-MAGENIS SYNDROME**

relatively high cognitive and social abilities

*versus*

very young emotional development

## “EMOTIONAL TODDLER” IN SMS

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

## “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

## DEVELOPMENTAL ASYNCHRONY

- disparity between intellectual and socio-emotional development
- described in highly gifted children; not well-researched in people with intellectual disabilities
- parallel phenomenon observed in people with Smith-Magenis syndrome
- significant contributor to maladaptive behaviors in SMS

## IMPLICATIONS FOR EDUCATION

- relatively good fit between intellectual and emotional development in early childhood (preschool, K-2)
- increasing disparity in later childhood through adulthood
- emotional development grows at much slower pace
- by 3<sup>rd</sup> grade, increasing need to adapt education practices to meet both types of development



**KEYS TO SUCCESS**

- communication, staff training about developmental asynchrony
- acknowledging developmental asynchrony does NOT mean treating older individual with SMS like a young child
- individualized education / vocational / behavior plan should incorporate *relevant approaches* in early childhood education, even in older children and adults




**EARLY CHILDHOOD EDUCATION  
APPROACH**

+

**AGE / IQ-APPROPRIATE GOALS  
AND ACTIVITIES**


=

**SUCCESS FOR OLDER CHILDREN,  
ADOLESCENTS, AND ADULTS!**




**EARLY CHILDHOOD APPROACH**

- use of visual cues and schedules
- “smorgasbord” of varied, high interest activities of relatively short (~20 minutes) duration
- mix of academic, functional, and recreational activities presented in a multi-sensory way
- emphasis on concrete, hands-on learning
- well-defined areas for different activities (cooking center, quiet area, free play area, etc.)
- individual attention; staff attuned to children’s emotions




**EARLY CHILDHOOD  
APPROACH GROWN UP!**

- use of day planner with post-its; computer-based schedule; email / phone reminders
- “smorgasbord” of school, work, volunteer, and recreational activities of relatively short duration
- emphasis on hands-on, functional aspects of curriculum / work schedule
- vary work / school activities throughout the day
- vary work / school environment throughout the day
- one-to-one support as needed



**CONCLUSIONS**

- Developmental asynchrony appears to be common in children and adults with SMS and significantly contributes to maladaptive behavior
- Emotional development progresses with age, but at a much slower rate than intellectual development in SMS
- The bigger the disparity between intellectual and emotional development, the greater the potential for maladaptive behavior
- Long periods of destabilized behavior further delay emotional growth
- Long periods of success, behavioral stability enhance emotional growth



**CONCLUSIONS**

- Professionals working with adolescents and adults generally not trained in early childhood special education approaches
- Emphasis on “normalization” philosophy in adult services ignores impact of unique SMS developmental profile on functioning and quality of life
- Individualized approach that combines appropriate early childhood practices with age / IQ appropriate goals often promotes success



**BEHAVIOR CHANGE**  
**isn't just about the**  
**person with the**  
**syndrome!**

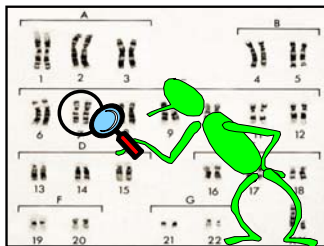


## Smith-Magenis Syndrome

Parents and Researchers Interested in  
 Smith-Magenis Syndrome  
 (PRISMS)  
[www.prisms.org](http://www.prisms.org)



## Williams Syndrome



## Williams Syndrome

- Highly characteristic facial appearance
- Small size
- High calcium levels in blood during infancy
- Often have heart defect called supravalvular aortic stenosis



## Williams Syndrome

- Well-developed verbal skills
- Friendly, sociable personality
- No fear of strangers
- Hyperacusis - unusually sensitive to noise
- Visuospatial deficits
- Attentional problems



## Williams Syndrome

- General Population: 1 in 20,000
- Intellectual Disability: 1 in 100

Among people with ID: 1 in 200



## Williams Syndrome

- Appealing face / engaging smile
- Enthusiastic
- Sociable
- Communicative
- Good expressive language
- Auditory processing strength



## Williams Syndrome

- Good short / long - term auditory memory
- Relative strength in musical ability
- Strength in facial recognition



## Williams Syndrome

- Short attention span
- Hyperactivity
- Distractibility
- Impulsivity



## Williams Syndrome

- Anxiety
- Hyperacusis
- Fearful of heights / uneven surfaces
- Emotionally labile



## Williams Syndrome

- Difficulty with transitions
- Phobias
- Irrelevant chatter
- Perseveration on favorite topics



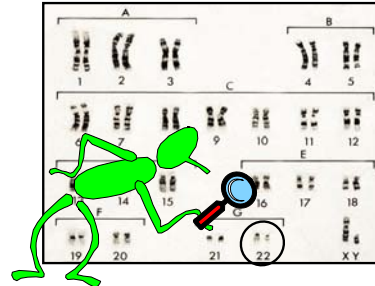
## Williams Syndrome

- Difficulty building friendships
- Poor visual motor integration
- Poor motor planning
- Fine motor deficits
- Medically fragile

## Williams Syndrome

WILLIAMS SYNDROME  
ASSOCIATION  
[www.williams-syndrome.org](http://www.williams-syndrome.org)

## 22q11.2 Deletion Syndrome

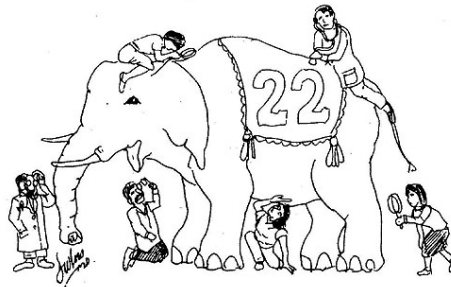


## ALSO KNOWN AS.....

~~DIGEORGE SYNDROME  
ABSENT THYMIC HYPOCALCEMIA, CARDIAC  
CONOTRUNCAL ANOMALY OF FACE (CTAF) SYNDROME  
CARDIAC, CHARACTERISTIC FACE  
VELOCARDIOFACIAL SYNDROME  
CHARACTERISTIC FACE, CARDIAC, CLEFT, LD~~

22q11.2 DELETION SYNDROME

## 22q11.2 DELETION SYNDROME



## 22q11.2 Deletion Syndrome

- Highly variable multiple congenital anomaly syndrome
- Common cause of LD, ID, psychiatric symptoms
- Males and females equally affected
- 1 in 2000 - 5000 births
- Associated with microdeletion of 22q11.2

## 22q11.2 Deletion Syndrome

- 80% BORN WITH CARDIAC DEFECTS RANGING FROM MINOR TO SEVERE
- MOST COMMON TYPES:
  - TETRALOGY OF FALLOT
  - INTERRUPTED AORTIC ARCH
  - TRUNCUS ARTERIOSUS
  - VSD



## 22q11.2 Deletion Syndrome

- CHARACTERISTIC FACIAL APPEARANCE
- HYPERNASAL VOICE
- EAR MALFORMATIONS
- IMMUNE DEFICIENCY
- FEEDING / SWALLOWING PROBLEMS
- HYPOCALCEMIA
- GROWTH HORMONE DEFICIENCY



## 22q11.2 Deletion Syndrome

- 62% BORN WITH PALATAL ANOMALIES RANGING FROM MINOR TO SEVERE
- 2%: CLEFT LIP + PALATE
- 11%: CLEFT PALATE
- 14%: SUBMUCOSAL CLEFTS
- 5%: BIFID UVULA
- 30%: VELOPHARYNGEAL INCOMPETENCE (VPI)



## 22q11.2 Deletion Syndrome

- EARLY CHILDHOOD**
- 15% NO LANGUAGE DELAY
  - 46% BORDERLINE DELAY
  - 39% DEFINITE DELAY
  - 20 - 40% HAVE ID (USUALLY MILD)
  - VIQ > PIQ
  - 60 - 80% NORMAL IQ / LD (NON VERBAL LD)



## 22q11.2 Deletion Syndrome

- SCHOOL AGE:**
- ADD
  - IMPULSE CONTROL DISORDER
  - OCD
  - ANXIETY DISORDER
  - PDD-NOS, AD
  - DEPRESSION (? FACIAL HYPOTONIA)



## 22q11.2 Deletion Syndrome

- ADOLESCENCE / ADULTHOOD:**
- PULVER ET AL. (1994): 29% met DSM criteria for schizophrenia / schizoaffective disorder
  - PAPOLOS ET AL. (1998): 64% met criteria for bipolar spectrum disorders
  - BASSETT et al. (2005): schizophrenia in 25%, indistinguishable from that of other causes



## Neuropsychological Profile

### Strengths

- Verbal IQ
- Verbal Comprehension
- Rote Verbal Learning
- Rote Verbal Memory
- Initial Auditory Attention
- Simple Focused Attention
- Auditory Perception and Memory
- Word Reading
- Word Decoding

## Neuropsychological Profile



### Weaknesses

- Nonverbal processing
- Visuospatial skills
- Complex verbal memory
- Attention, working memory, executive functioning
- Motor functions Simple Focused Attention
- Visual-spatial memory
- Facial processing and recall

## Neuropsychological Profile



### Weaknesses

- Phonological processing
- Language processing
- Mathematics
- Reading comprehension
- Social skills
- Emotional functioning
- Adaptive functioning

## 22q11.2 Deletion Syndrome

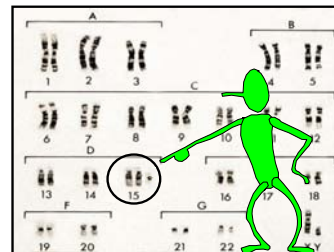


The International 22q11.2  
Deletion Syndrome Foundation  
[www.22q.org](http://www.22q.org)

VCSF Educational Foundation  
[www.vcfsef.org](http://www.vcfsef.org)

22q and You Center  
Children's Hospital of Philadelphia  
Phone: 215-590-2920

## Duplication 15q Syndrome



## Duplication 15q Syndrome

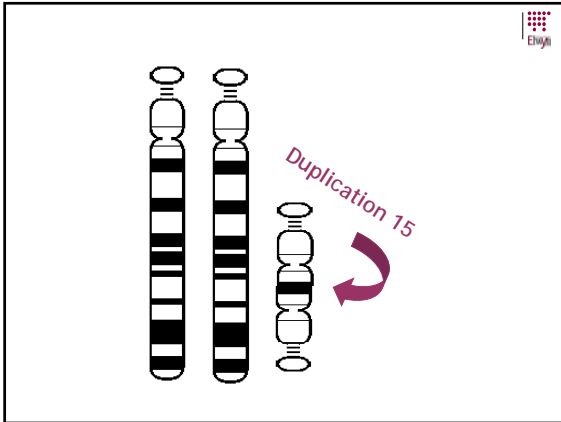


- aka: isodicentric 15
- idic(15)
- inverted duplication 15
- supernumerary marker
- bisatellited supernumerary
- tetrasomy 15
- partial trisomy 15
- related disorder: interstitial duplication 15

## Duplication 15q Syndrome



- EXTRA "BISATELLITED" CHROMOSOME 15
- DUPLICATION OF ALL OF THE p ARM
- DUPLICATION OF PART OF THE q ARM
- OUTCOME RANGES FROM NO EFFECT TO FULL SYNDROME
- SEVERITY CORRELATED WITH SIZE OF MARKER
- PRESENCE OF 15q11-q13 (PWS/AS CRITICAL REGION)
- PARENT OF ORIGIN: ALWAYS MATERNAL



## Duplication 15q Syndrome

- SEVERE HYPOTONIA / DECREASED FETAL MOVEMENTS
- STRUCTURAL ORGAN ABNORMALITIES IN MINORITY
- MILD GROWTH RETARDATION
- CHARACTERISTIC FACIAL APPEARANCE
- ID (OFTEN SEVERE) BUT SOME PEOPLE WITH HIGHER IQ
- SEIZURE DISORDERS, PARTICULARLY INFANTILE SPASMS
- AUTISM SPECTRUM DISORDERS IN MAJORITY
- SUDDEN UNEXPLAINED DEATH

## Autistic Features in Duplication 15q Syndrome

- MOTOR STEREOTYPIES (HAND FLAPPING)
- ACT AS IF DEAF
- POOR EYE CONTACT
- REPETITIVE OR POORLY-DEVELOPED SPEECH
- NEED FOR 'SAMENESS' IN ENVIRONMENT, DAILY ROUTINE
- UNUSUAL ATTACHMENTS TO INANIMATE OBJECTS

## Autistic Features in Duplication 15q Syndrome

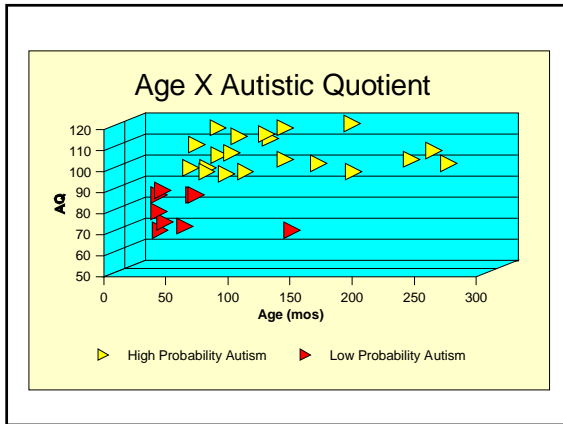
Rineer S; Finucane B; Simon EW (1998).  
 Autistic symptoms among children and young adults with isodicentric chromosome 15.  
*Am J Med Genet* 81:428-33.


## Autistic Features in Duplication 15q Syndrome

- Gilliam Autism Rating Scale - GARS
- Questionnaire format
- Normed for people with autism and for those with ID and no autism
- Study Cohort:
  - 29 individuals with dup(15)
  - GENDER: 14 MALES / 15 FEMALES
  - AGE: RANGE = 36 TO 253 months, MEAN = 98.76 months

## Study Results

- 20 of 29 individuals received an autism rating at or above that of a normed group of people known to have autism
- Scores for people with dup(15) were significantly higher than those of a normed group with ID but no autism
- Significant difference in social interaction scores between younger vs. older age groups (younger group more sociable)






### Conclusions

- dup(15) associated with autistic symptoms at all ages
- Individuals with dup(15) who are not autistic are likely to be young
- Young, non-autistic children with dup(15) are more sociable than others


Could autistic symptoms in dup(15) be age-related??



### Follow-Up Study

Study Cohort:


- Of 9 non-autistic, 7 available for follow-up
- Gender: 3 Males / 4 Females
- Age: RANGE = 111 TO 144 months  
MEAN = 124.86 months



### Conclusions

- Over 6 year period, all 7 showed increase in autism score, with all but 1 now within the autistic range
- Significant increase in social interaction subscores (i.e. less sociable) at follow-up
- Confirms original hypothesis

WHY DO CHILDREN WITH DUP(15) PRESENT AS LESS SOCIABLE WITH AGE?



### Duplication 15q Syndrome

Isodicentric 15 Exchange,  
Advocacy, and Support  
(IDEAS)  
[www.idic15.org](http://www.idic15.org)