Do you see what I see?

Dysmorphology Assessment in Autism

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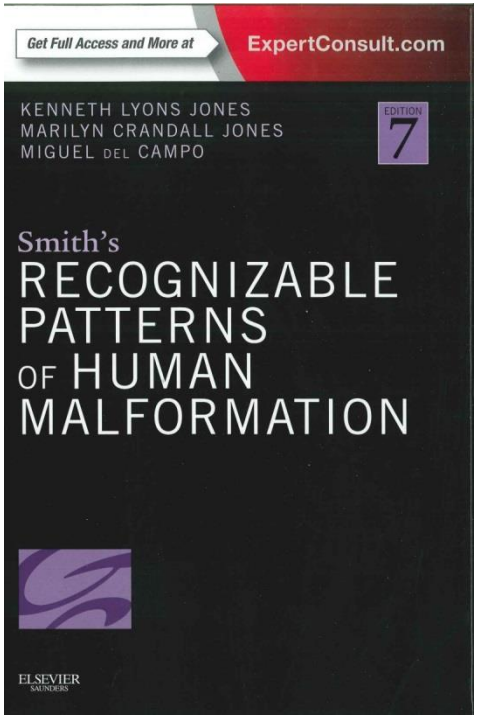
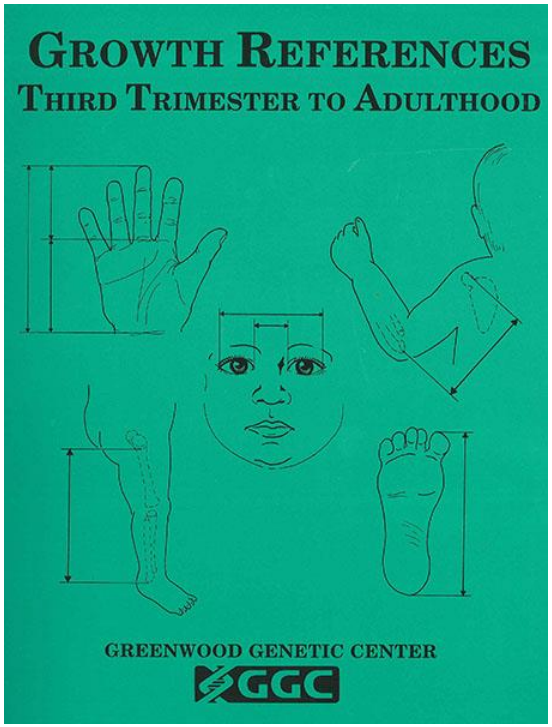
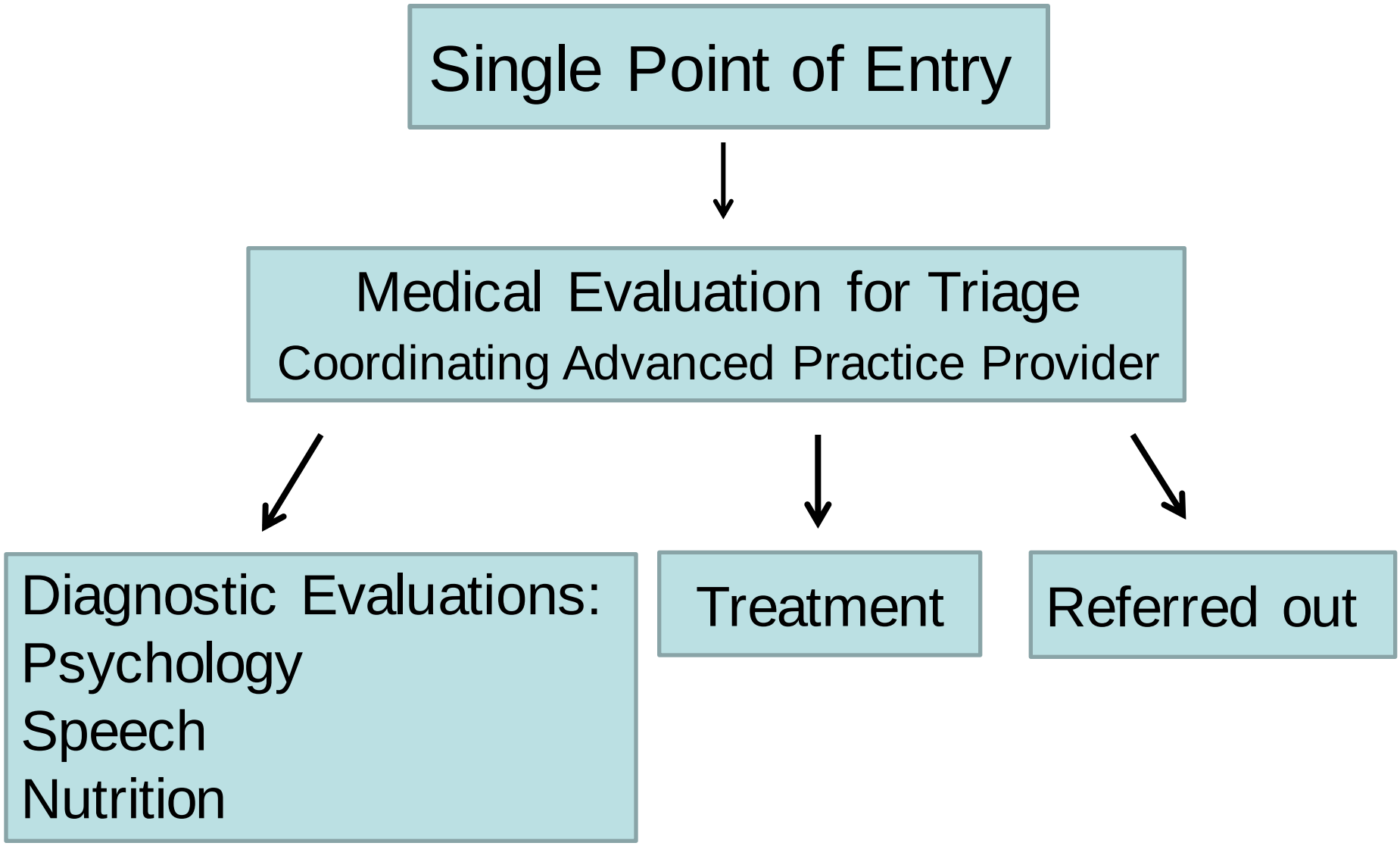
Definition of Dysmorphology

- The term “dysmorphology” was coined by Dr. David Smith in the 1960s
- “dys” (Greek) – disordered
- “morph” - shape





MAC Goal for New Clinical Patients

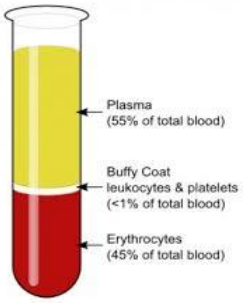


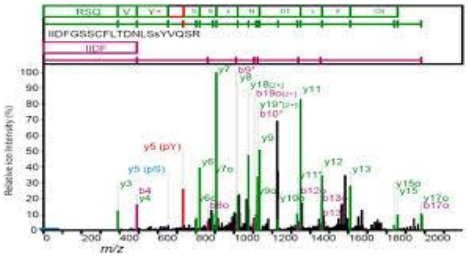
Medical Evaluation

- Growth parameters at Check In:
  - Ht, Wt, HC plotted on growth curve
- Head to Toe Physical Exam
  - General appearance: proportionate or asymmetric
  - Systems: Muscle tone, Cardiac, Abdominal exam
  - Dysmorphology
- Comparison to normal milestones
  - Delayed
  - Regression
  - Autism

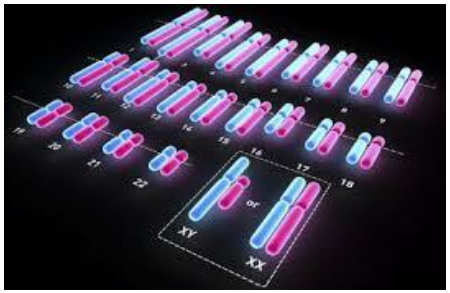
Genetic Testing

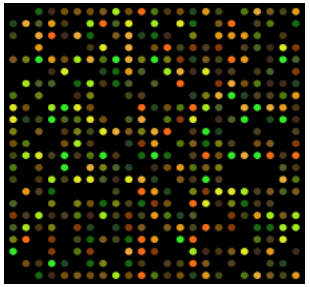
Biochemical



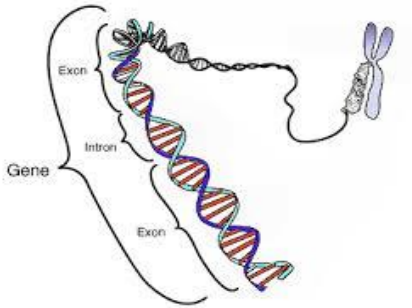


Cytogenetic





Molecular



American College of Medical Genetics

Guidelines for Autism Genetic Testing

Tier 1 Testing

- Males
  - Chromosomal microarray
  - Fragile X testing
- Females
  - Chromosomal microarray
  - Rett gene sequencing

Tier 2 Testing

Next Generation Sequencing

63 gene panel for syndromic autism

Whole Exome (WES) or Whole Genome Sequencing (WGS)

Genetic Disorders with Autism

Disorder	Autism
• Rett syndrome	61%
• Cohen	54%
• Cornelia de Lange	43%
• Tuberous Sclerosis	36%
• Angelman	34%
• CHARGE	30%
• Fragile X	males 30%; mixed sex 22%

Richards C et al. Lancet Psychiatry 2015; 2: 909-16

Other Genetic Disorders with ASD

Disorder	Autism
•Neurofibromatosis (NF1)	18%
•Down syndrome	16%
•Noonan	15%
•Williams	12%
•22q11.2 deletion	11%
•Phenylketonuria	~5-6%

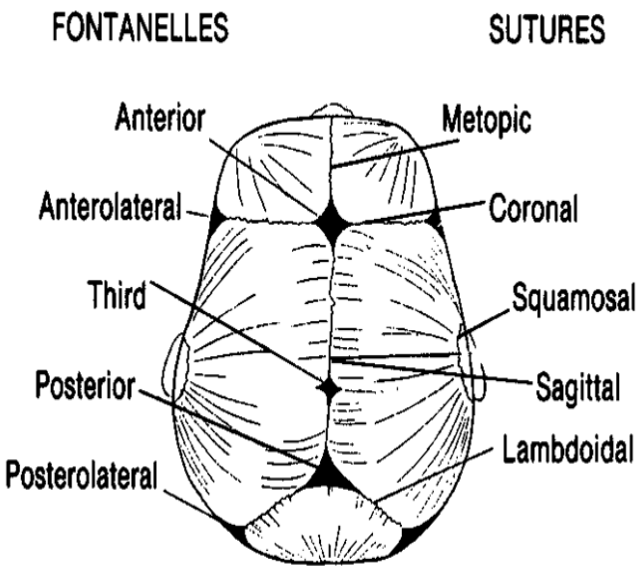
Richards C et al. Lancet Psychiatry 2015; 2: 909-16

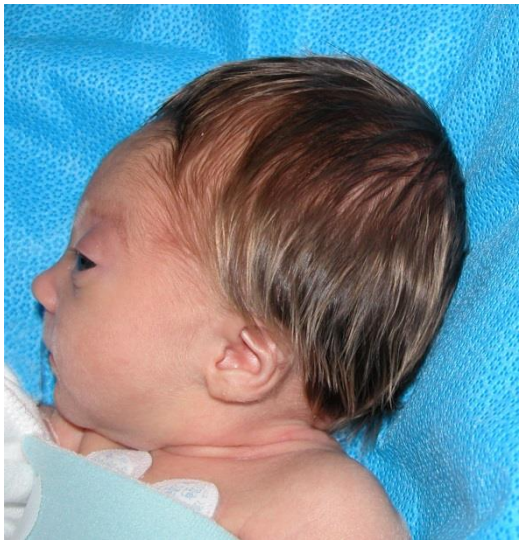
What's your role?

You may see something that no one else has seen…

- Overwhelming majority of patients referred for autism have no dysmorphic features
- If you think "something is not quite right" do they:
  - Look different from other patients at same age?
  - Look different from siblings?
  - Look different from parents?
- How to quantify your observations?
  - Head, face, and hands – we can see easily

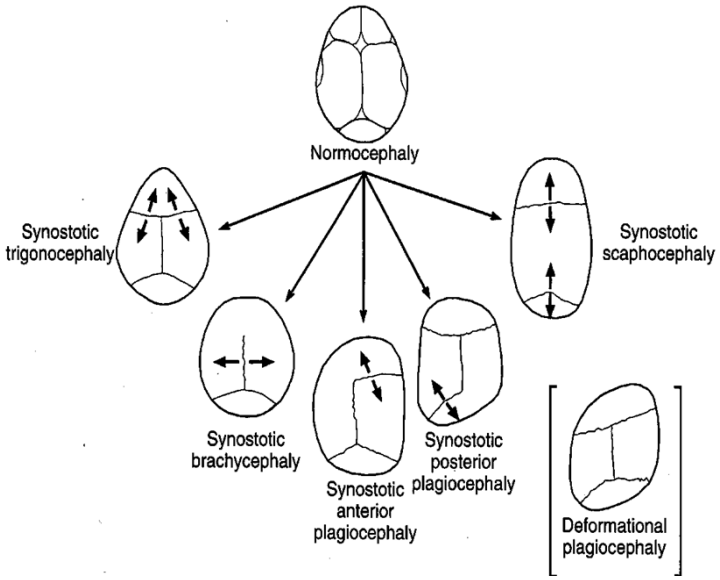
Head Shape and Size

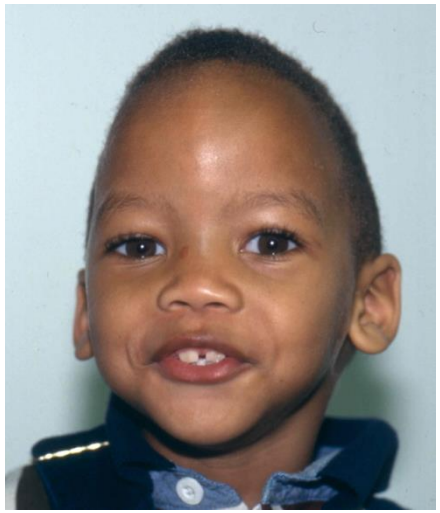


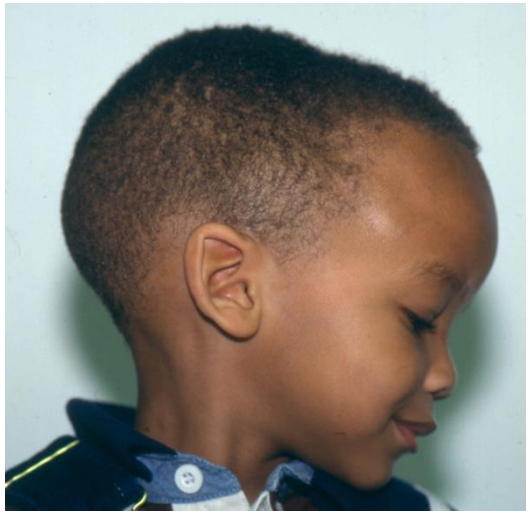


Microcephaly Macrocephaly

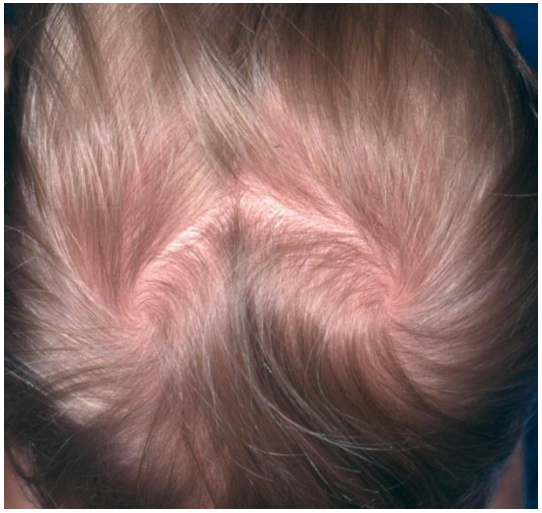
Scaphocephaly

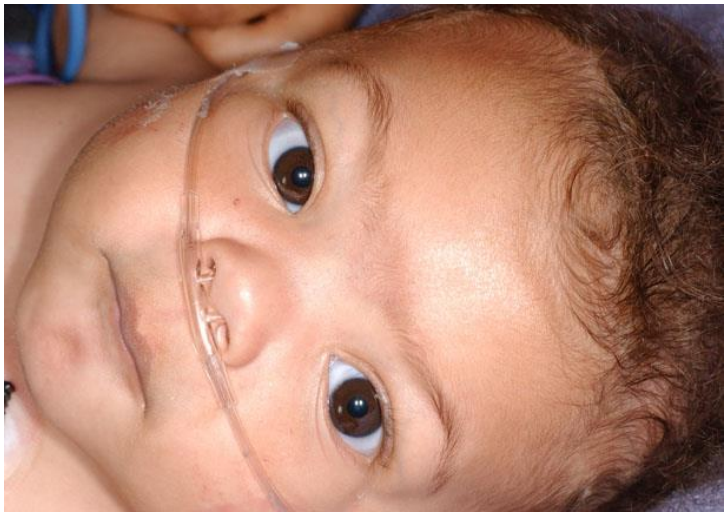




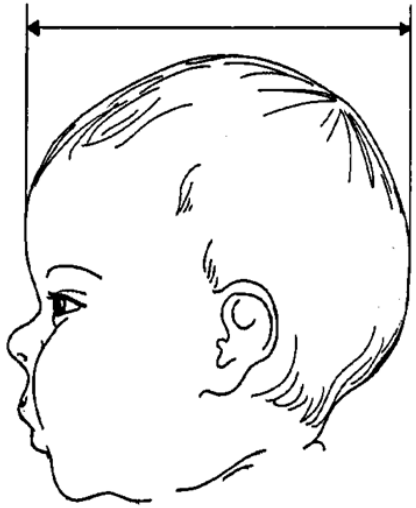


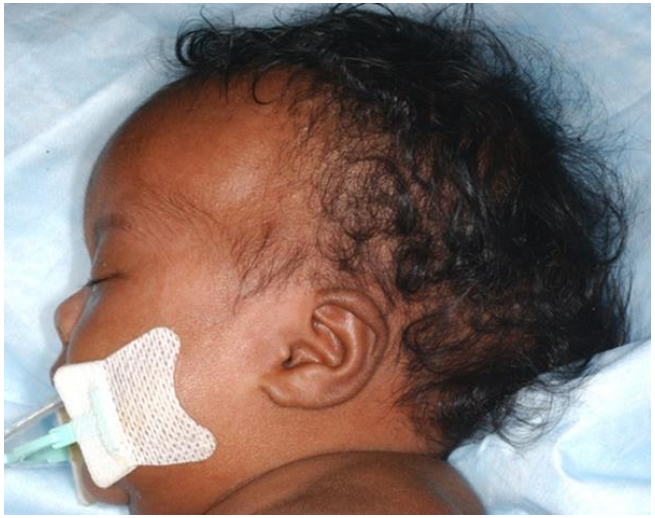
Hair whorls in unusual places





Head Profile





Ears:
posteriorly rotated

Head Profile

Nasal bridge

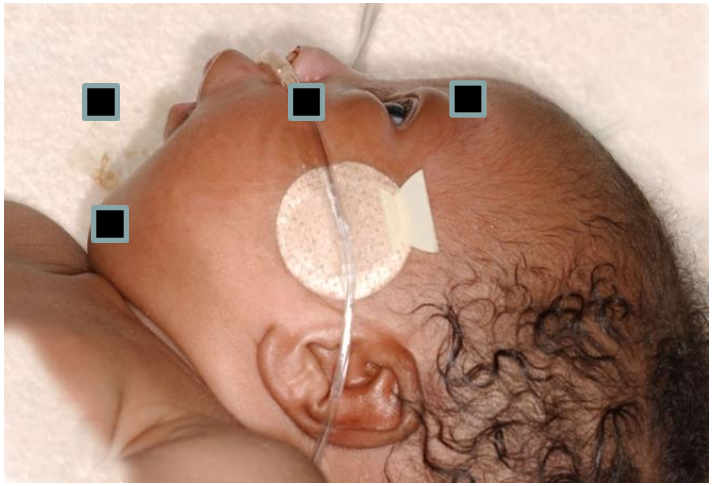
– flat vs prominent

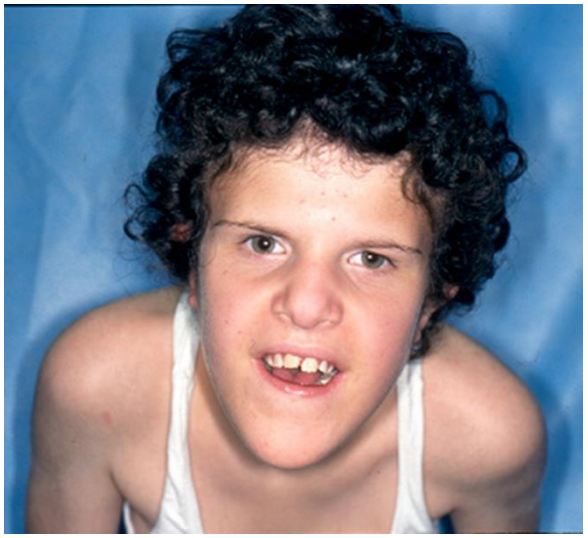
Flat mid-face

Chin development

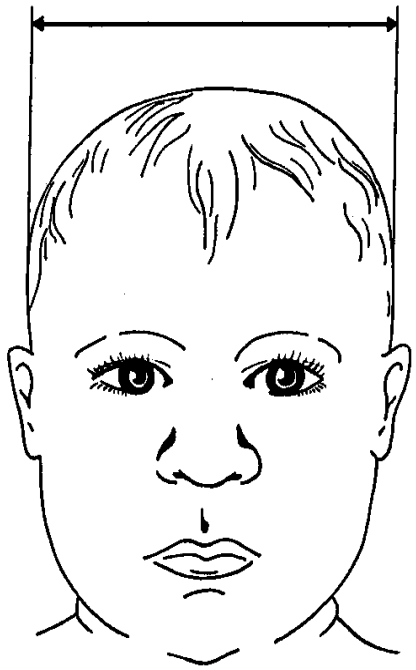
•micrognathia – small

•prognathia – prominent

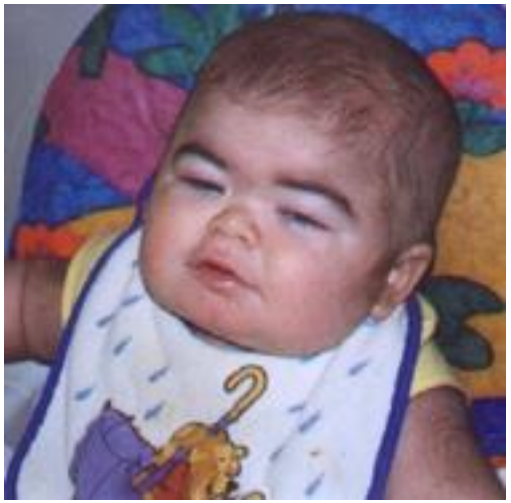


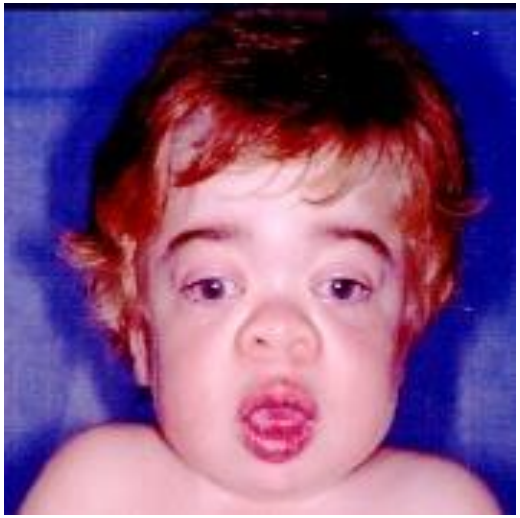


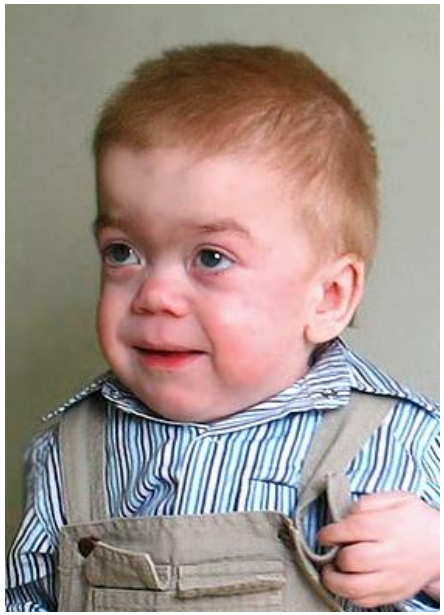
Head Width



- Bi-temporal narrowing
- Hirsutism – excessive hair
- Eyebrows: uniform, thick, medial flare
- Eye lids: colobomas, hooded, epicanthi
- Eye lashes: thick, sparse
- Iris: colobomas or small globes
- Coarse facies



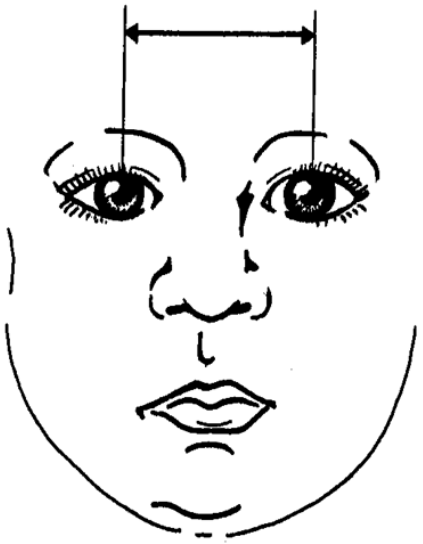


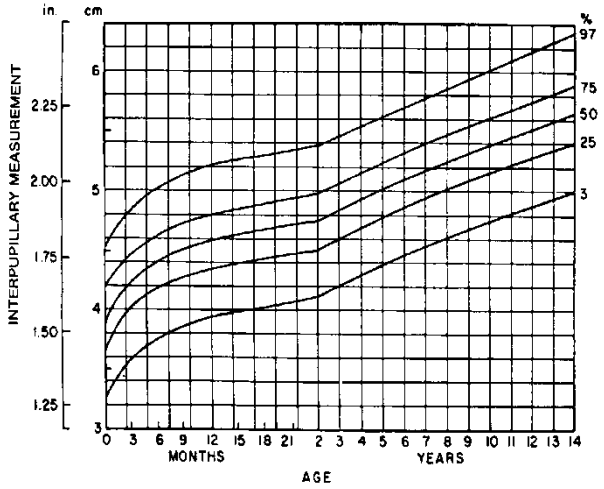


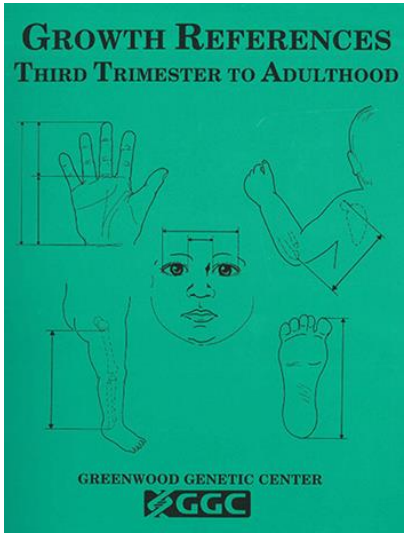
Face

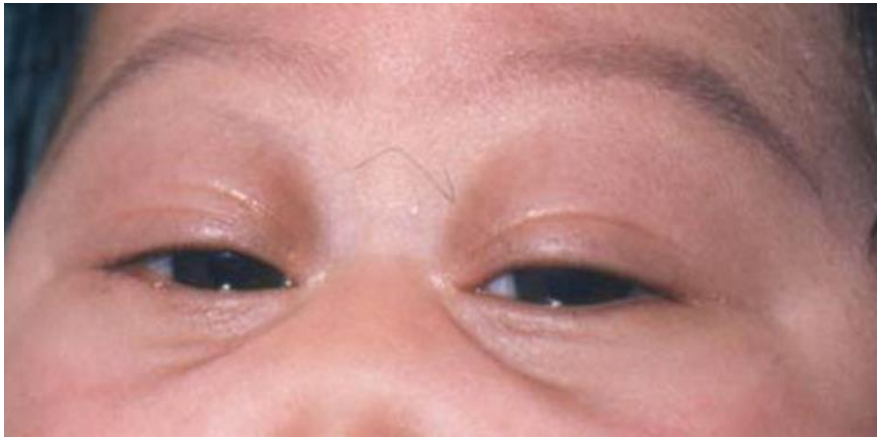
- Coarse facial features
- Depressed nasal bridge
- Up turned nares
- Thick lips
- Hirsutism

Interpupillary Measurements

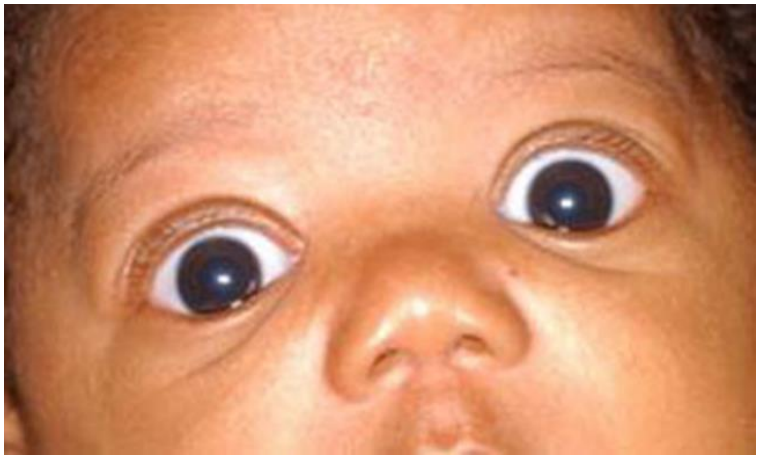








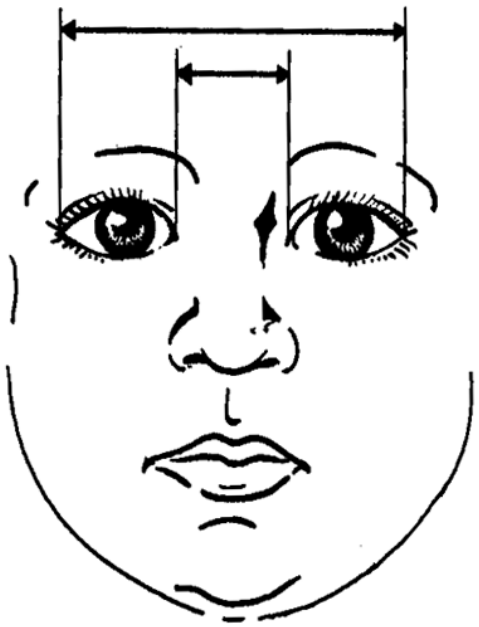
Hypotelorism

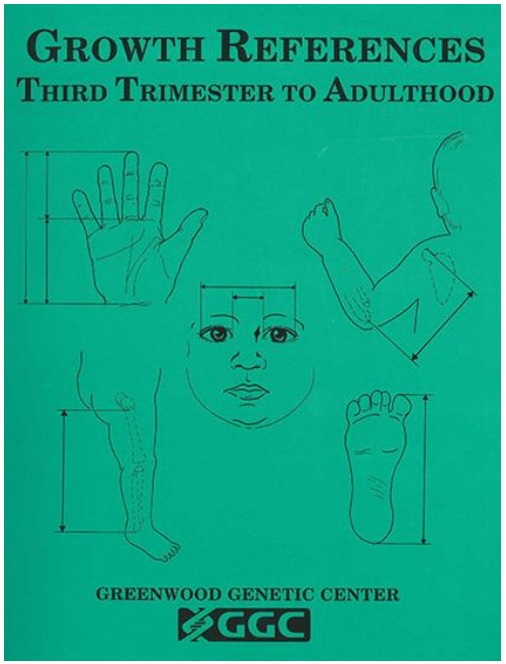


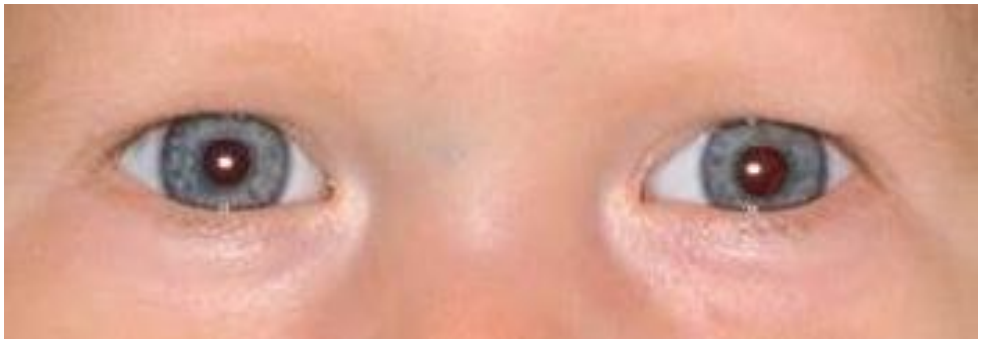
Hypertelorism

Canthal Measurements

- Inner canthus
- Outer canthus
- Palpebral Fissure Length
  - Short
  - Long
  - Narrow
- Hooded eye lids







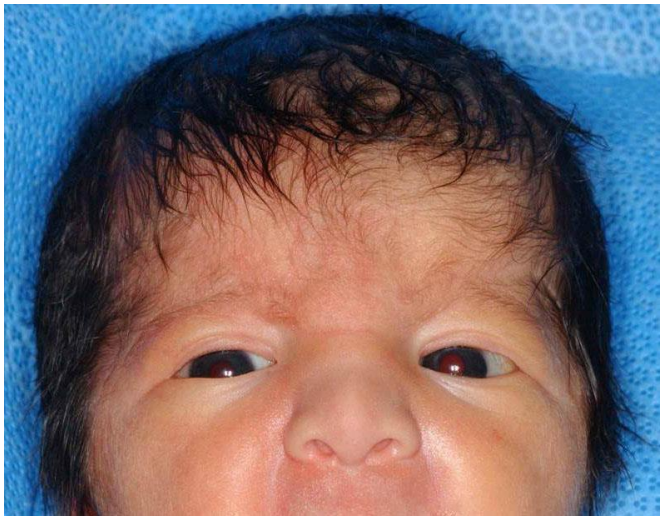
Face

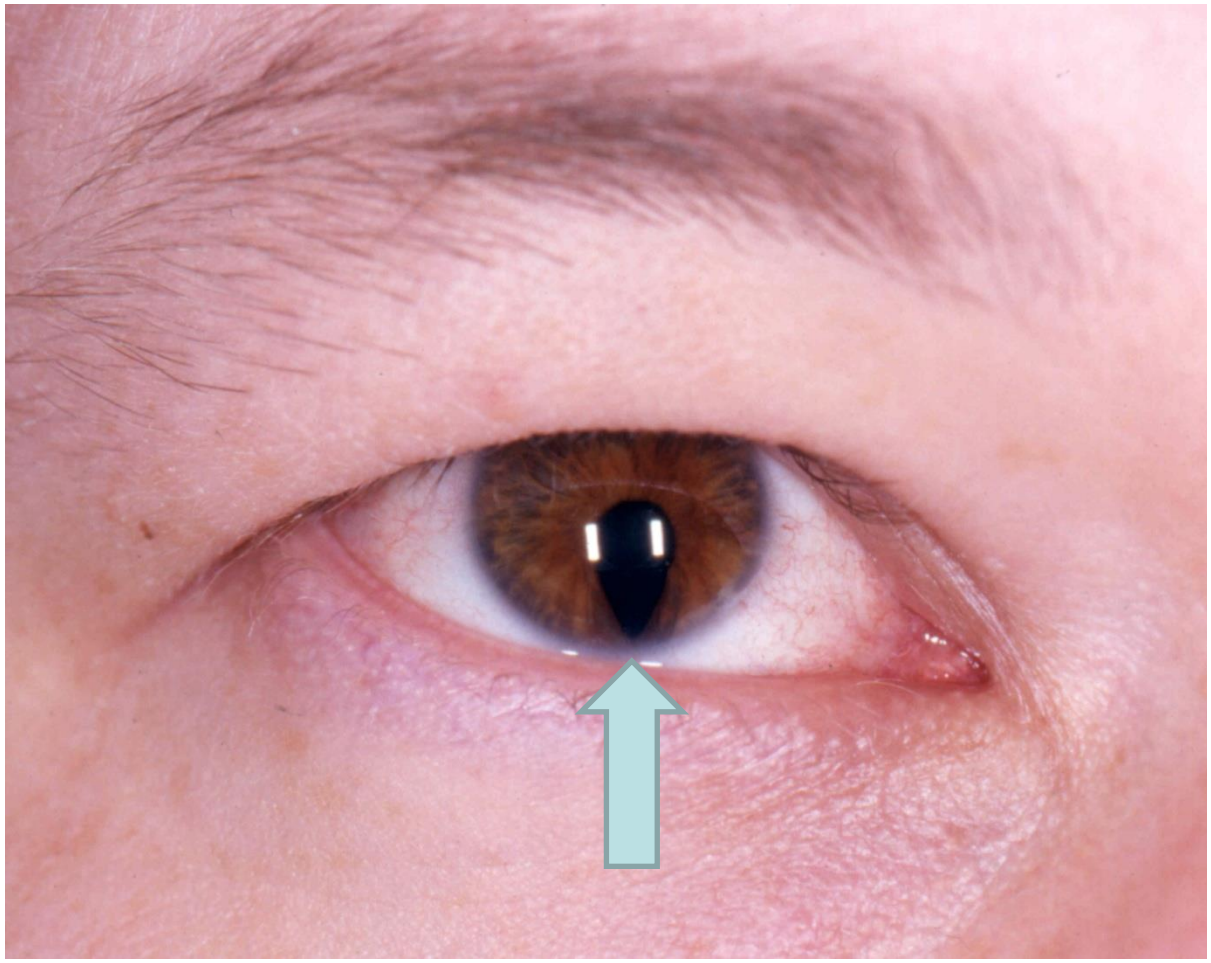
Up slanting palpebral fissures

Down slanting palpebral fissures

Epicanthal folds

Open mouth - hypotonia

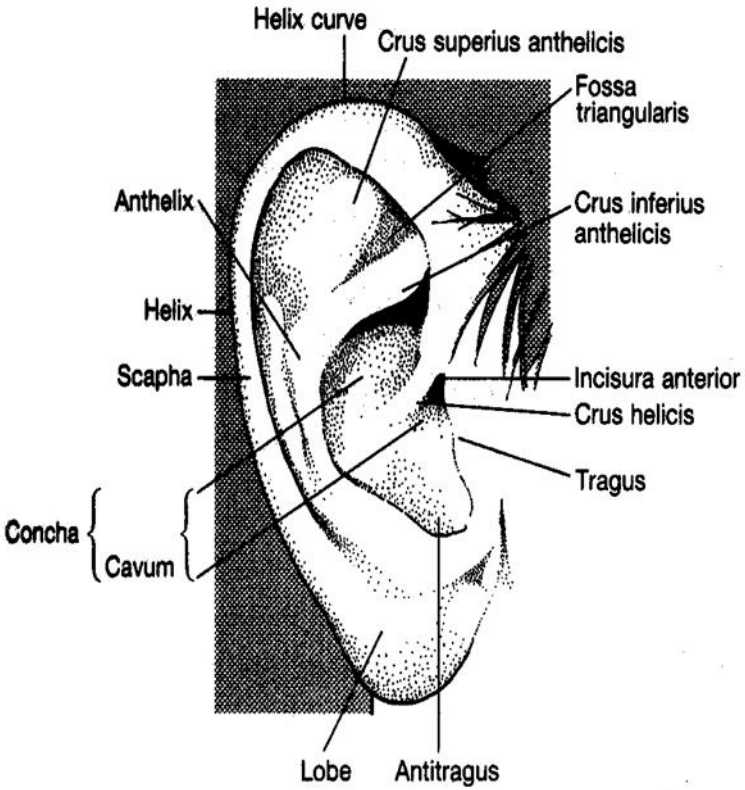




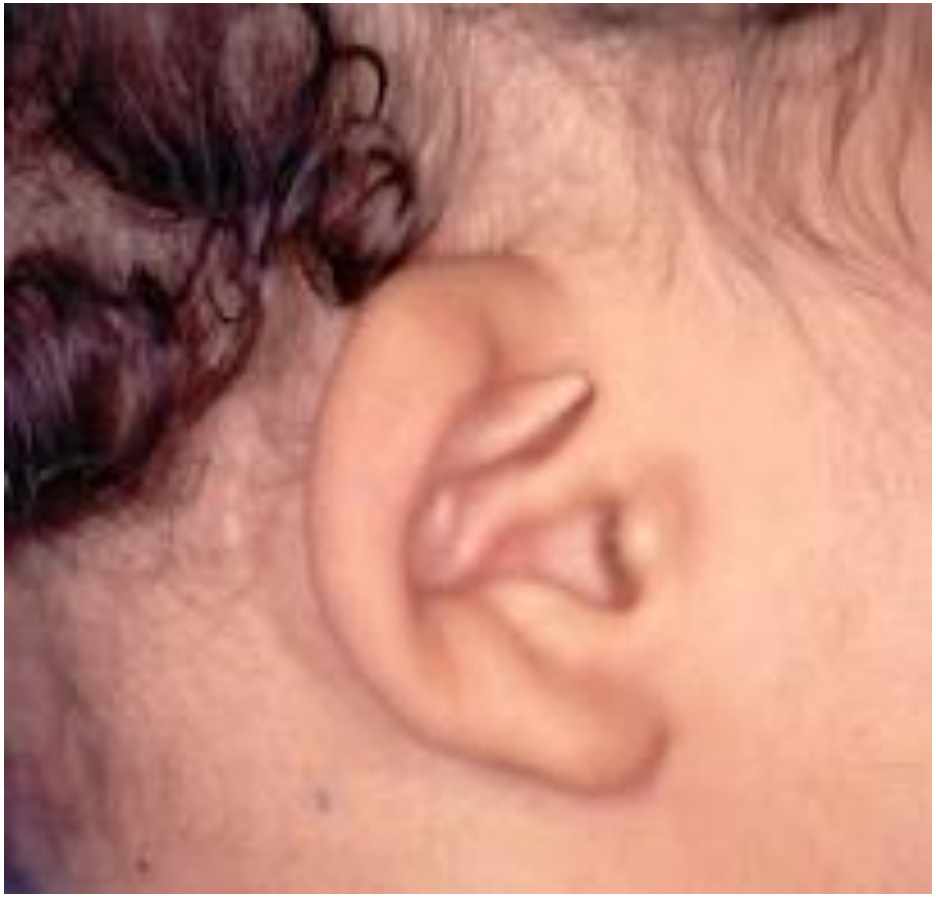
Eyes

Coloboma of the iris or retina

Ear Shape



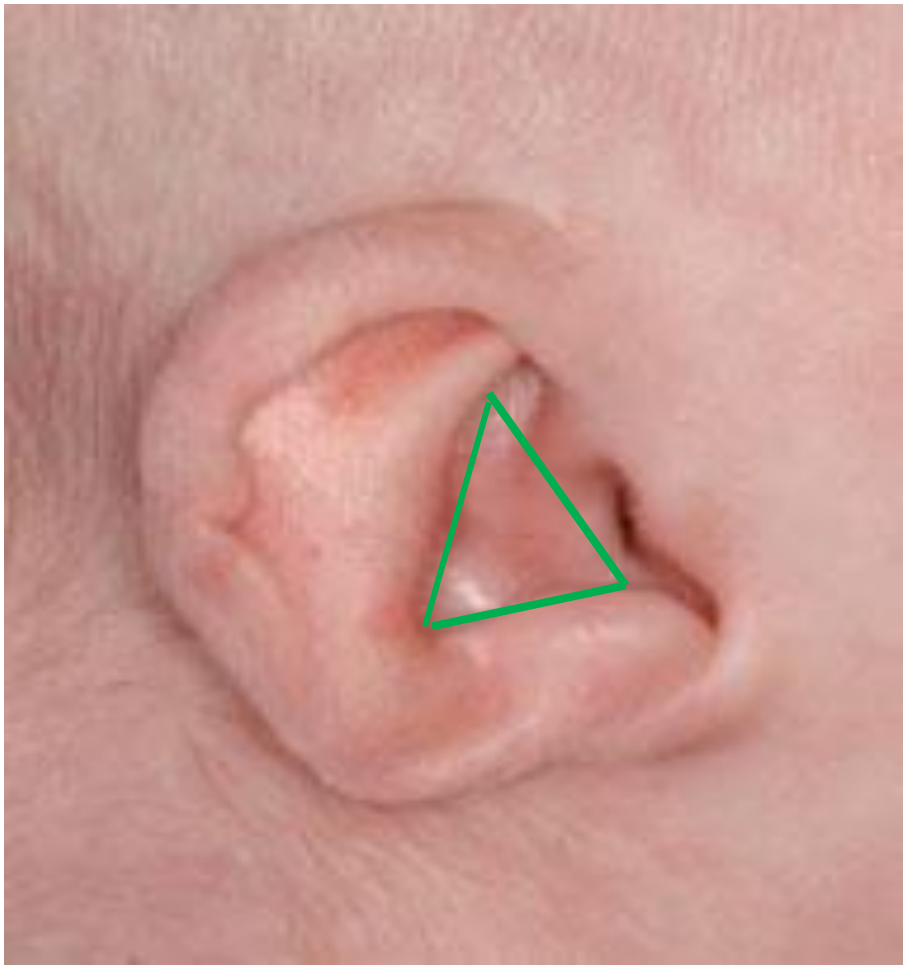
- Root
- Helix: over folded or cupped
- Lobe: absent or creased
- Size: large or small
- Preauricular area: pits or tags



22q11.2 deletion

Ears

- Deficient upper helix
- Over-folded helix
- Small ear
- C-shaped ear



Typical CHARGE syndrome ear

Ears

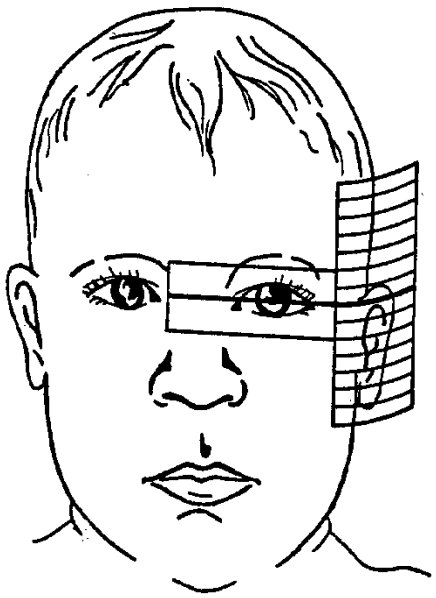
Deficient upper helix

triangular crus

absent lobes

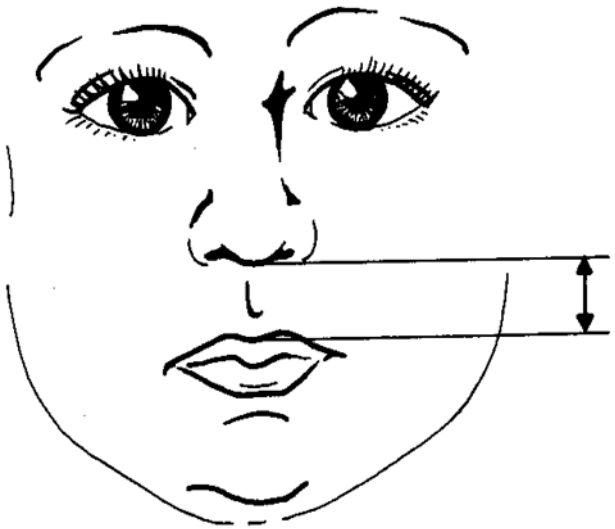
Posteriorly rotated

Ear Position



- Measure from inner canthi across to the root
- Low set
- High set
- Posteriorly rotated

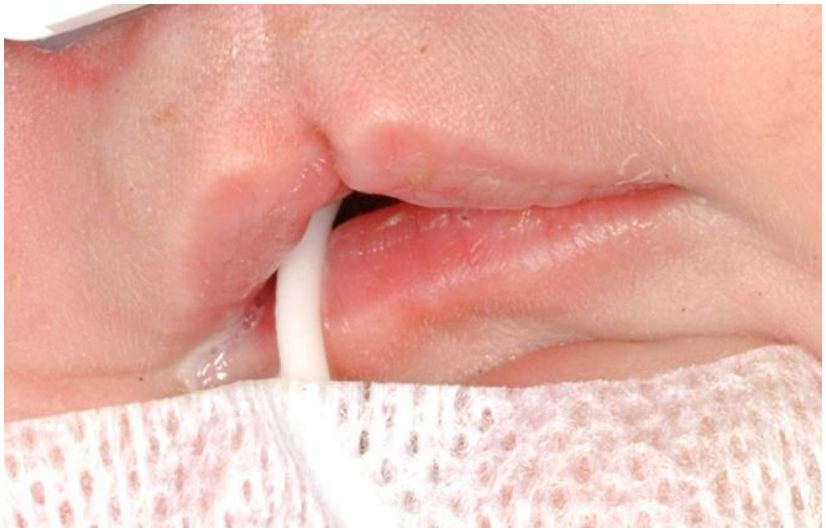
Face



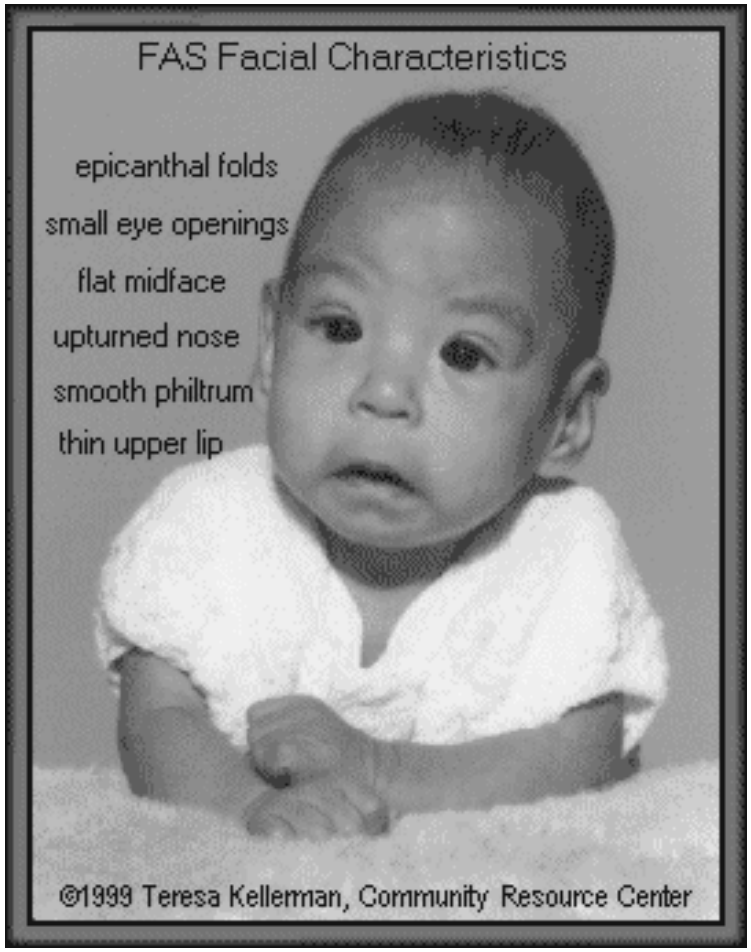
- Nasal area:
  - Short or Long nose
  - Upturned nares
  - Alae nasi formation
- Philtrum:
  - Short, Long, Smooth
- Mouth
  - Large - macrostomia
  - Small - microstomia

Mouth

- Clefting
  - Unilateral
  - Bilateral
  - Central
  - Single Central Incisor
  - Pits

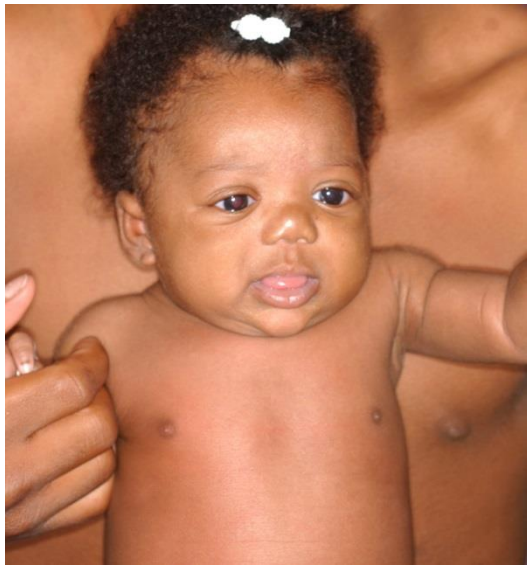


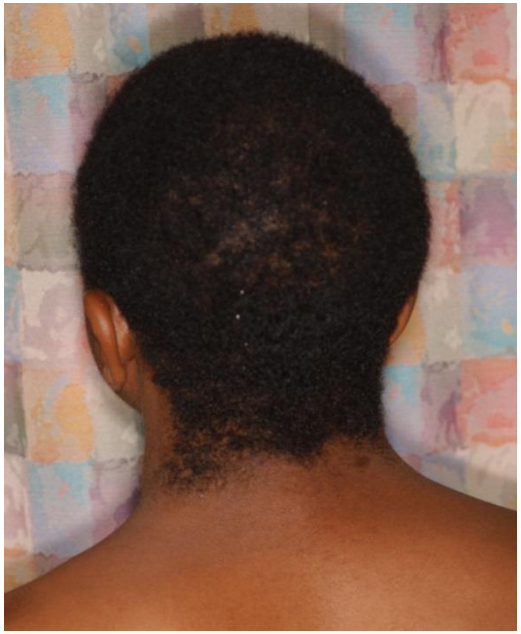
Face:

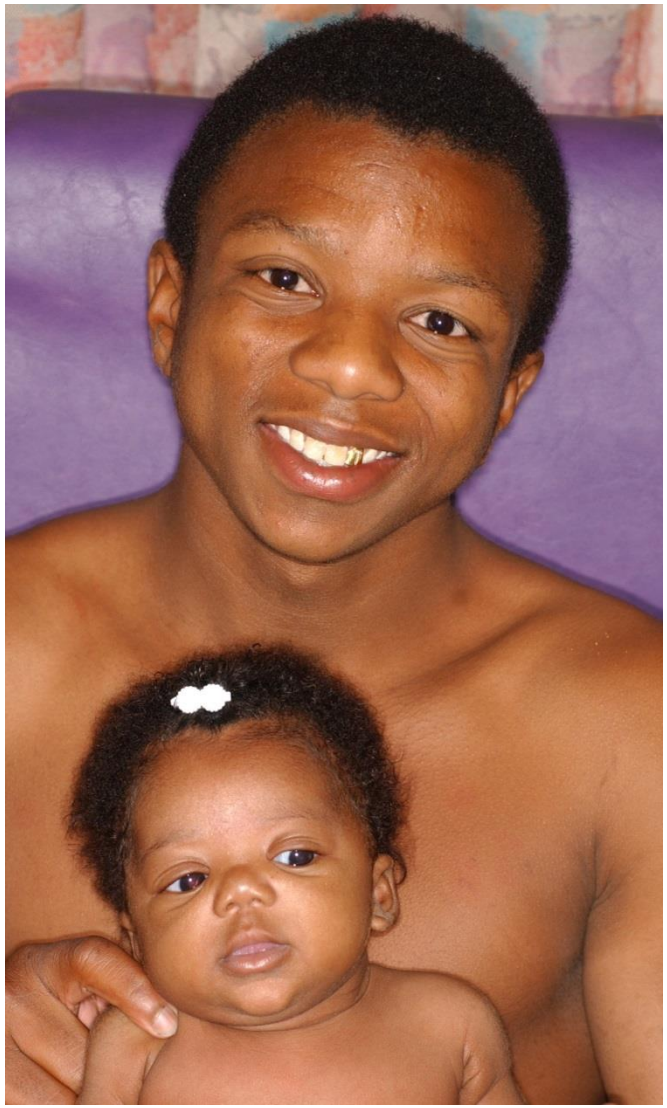


Fetal Alcohol syndrome

Neck and Chest







Pulmonary Stenosis

Short stature

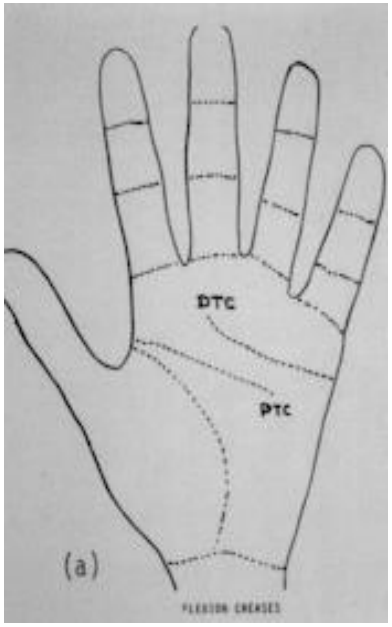
Short webbed neck

Low Posterior Hairline

Pulmonary stenosis

Noonan Syndrome - Autosomal Dominant

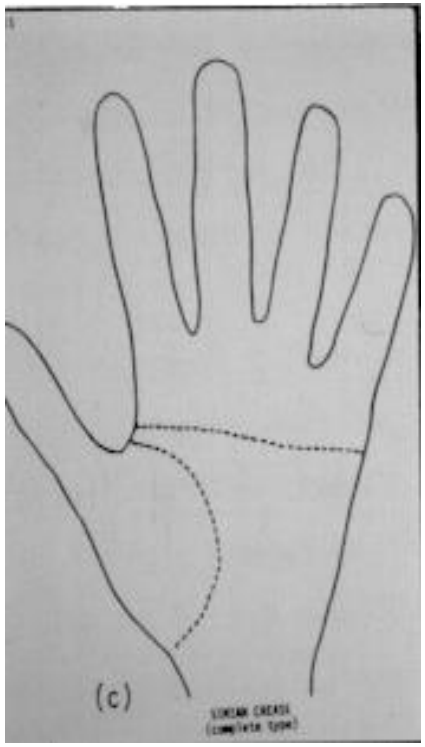
Autism diagnosed in 15%



Palmar Creases:

Three main creases in the general population

1. Proximal transverse
2. Distal transverse
3. Thenar crease

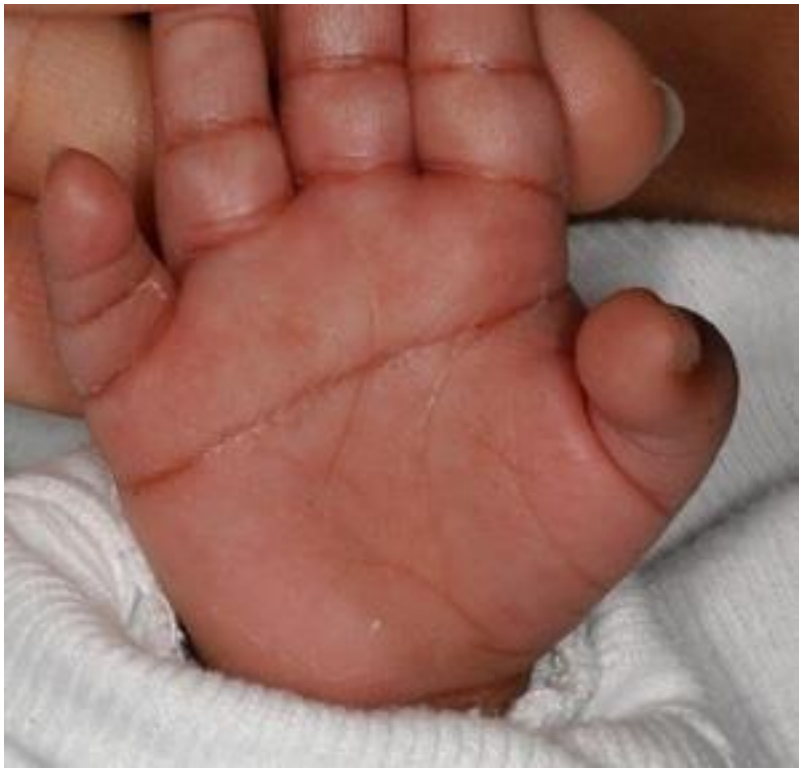


Single transverse palmer crease:

When the proximal transverse crease and the distal transverse crease merge

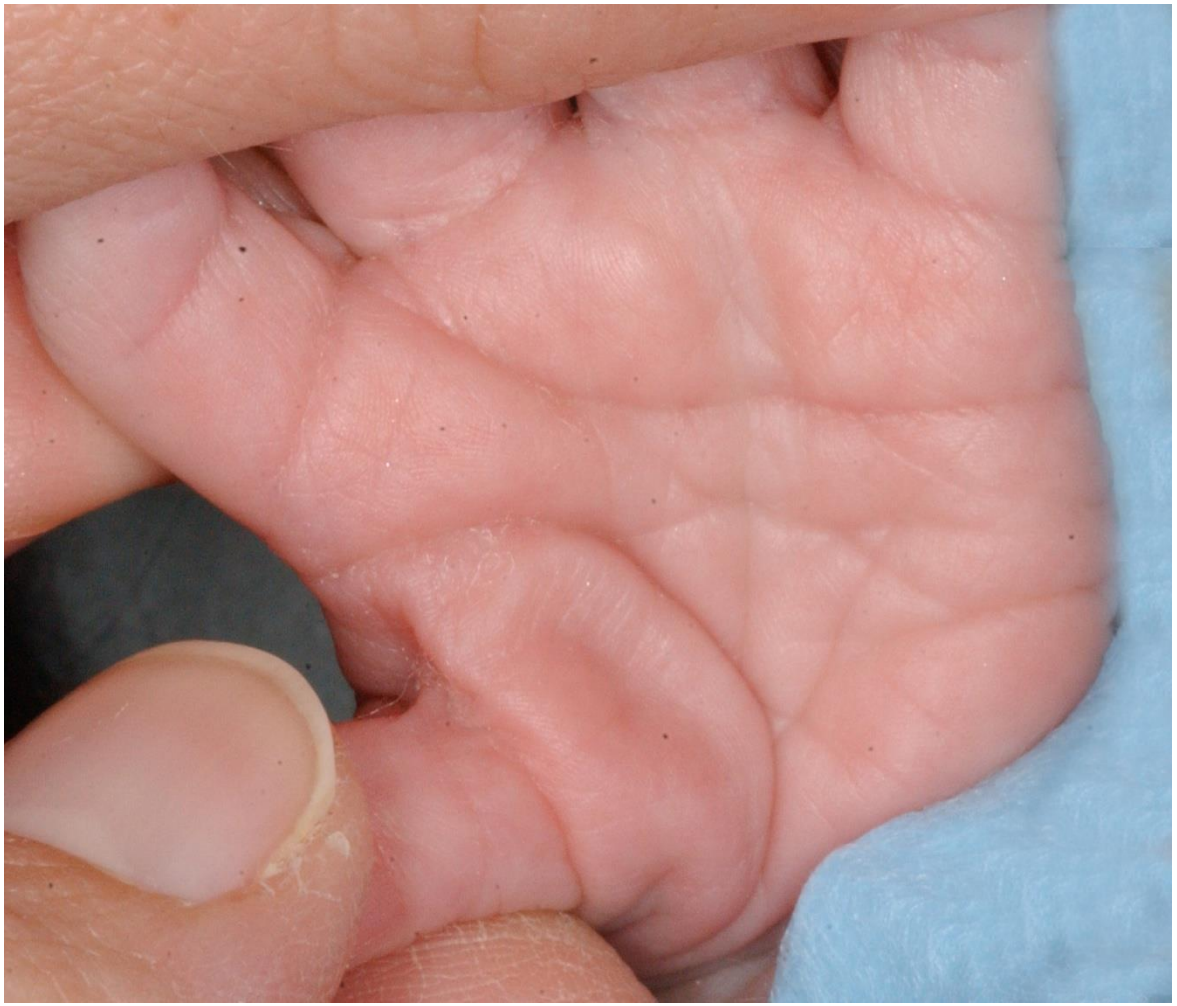
Palmar creases and finger creases

Bridge crease
+21 Down Syndrome

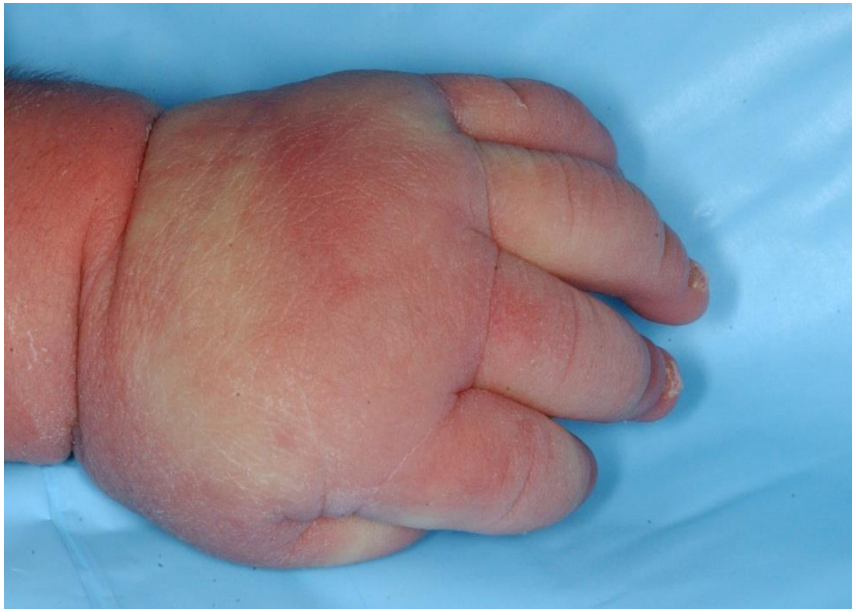


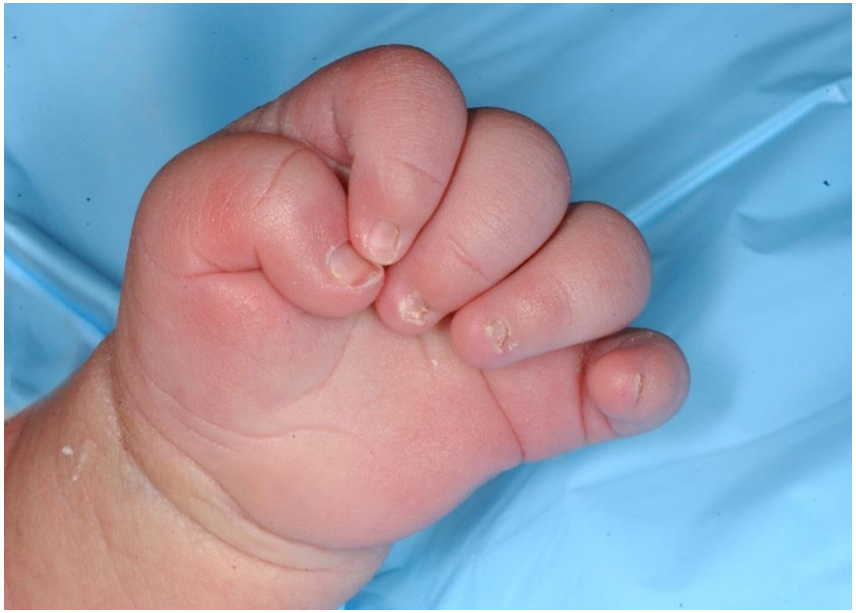
Single palmar crease
+21 Down Syndrome

Typical Fetal Alcohol Syndrome crease

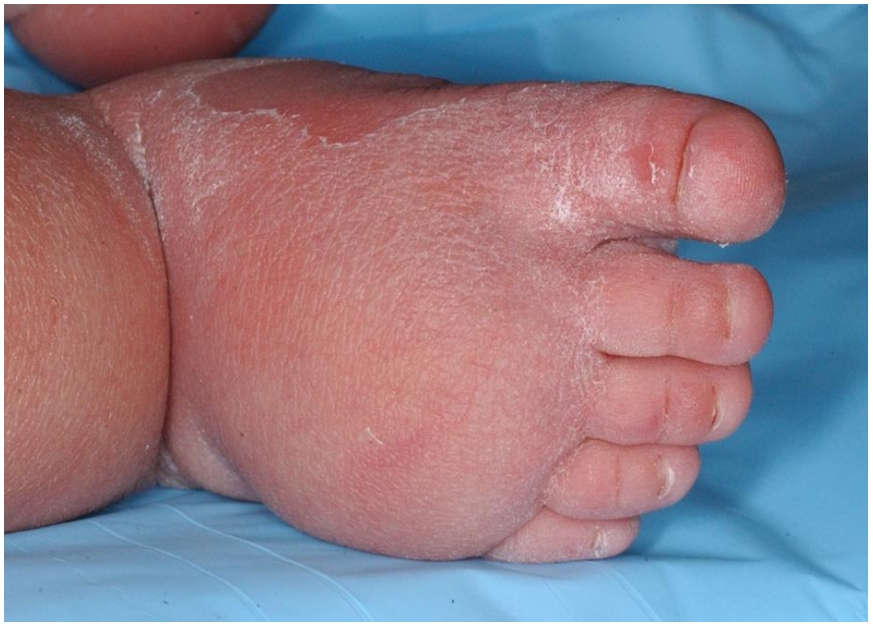


Distal transverse crease exits between fingers 2 and 3

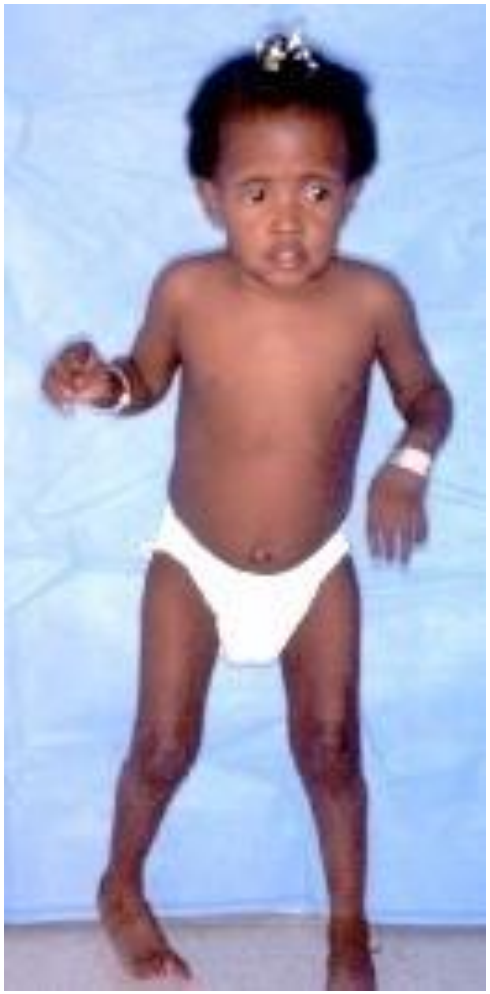




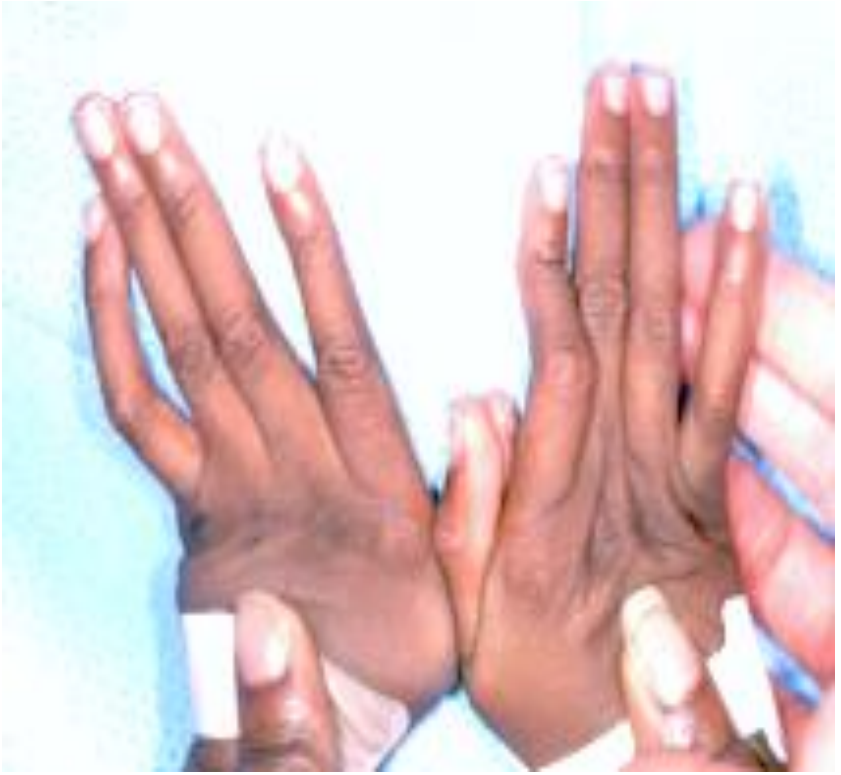
Lymphedema
Hypoplastic nails



45, X Turner syndrome



Arachnodactyly



Marfan syndrome – Autosomal Dominant

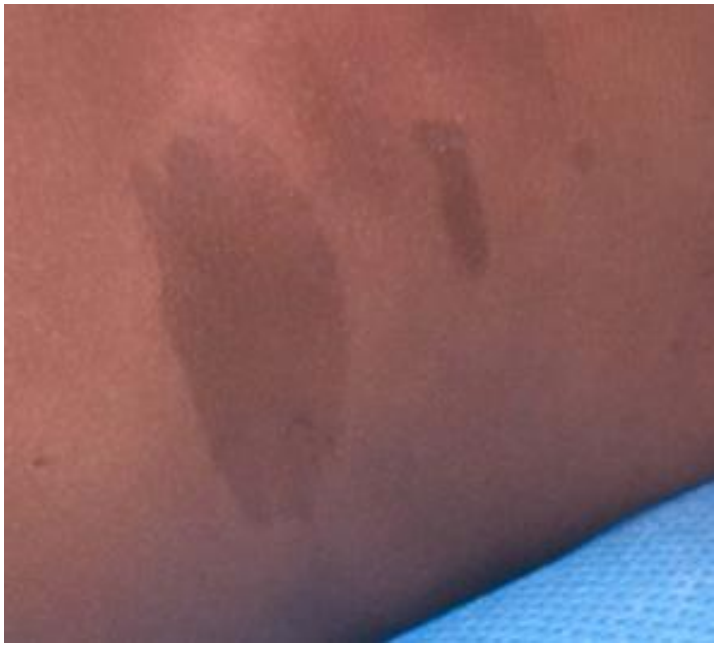
Aortopathy Clinic – Cardiology

Other family members at risk?

Skin:

café au lait spots
hyper-pigmented areas

- ≥ 6 **café-au-lait macules** over 5 mm in prepubertal individuals
- and ≥ 6 over 15 mm in postpubertal individuals



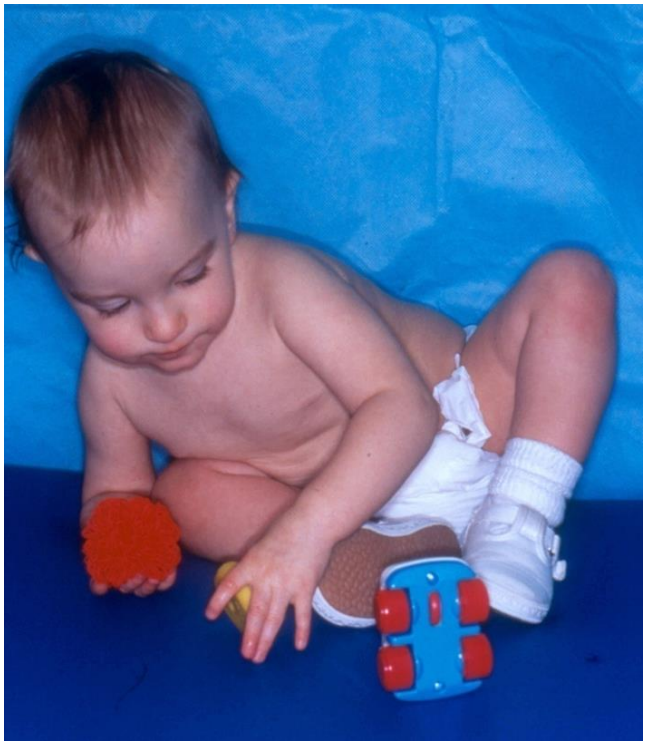
Neurofibromatosis
Autosomal Dominant
Autism diagnosed in 18%

Referred out to Genetics

- Ophthalmology exam
- X-rays
- Head Imaging
- Family History
- Gene sequencing
- Neurofibromatosis Clinic

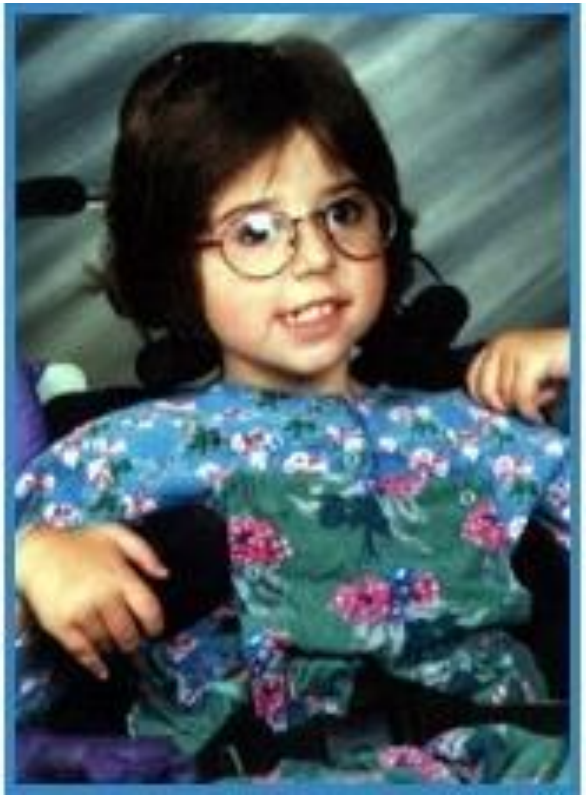
Overall Impression

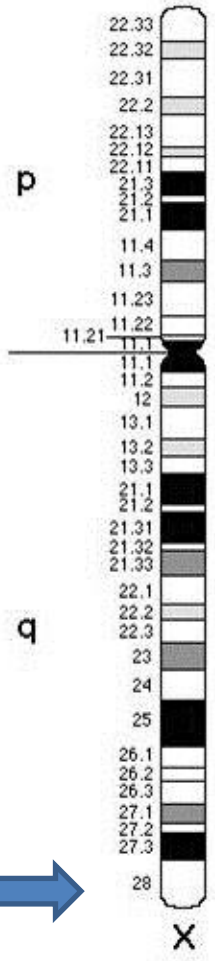
- Muscle Tone
  - Hypotonic
  - Hypertonic
- Developmental Milestones
  - Delayed
  - Regression
- Cognitive Assessment
- Autism Diagnosis



Rett syndrome:

X-linked Dominant - almost exclusively affects girls





MECP2 gene
at Xq28

Males 46,XY

Females 46,XX

Incidence ~1:22,000

99% are new mutations

Autism diagnosed in 61%

Usually not dysmorphic

Rett syndrome (RTT)

Progressive neurodevelopmental disorder

- Girls are apparently normal for first 6-18 months
- Short period of stagnation, then rapid regression, followed by long-term stability:
  - Regression
    - Loss of milestones
    - Loss of speech, communication and ability to learn
  - Loss of purposeful use of the hands:
    - wringing/squeezing
    - clapping/tapping
  - Breath Holding , Shallow breathing
    - Hyperventilation, Air swallowing

Rett syndrome

“Live with Rett syndrome”

- Time line 1:41 – 2:40
- Hand movements in Rett

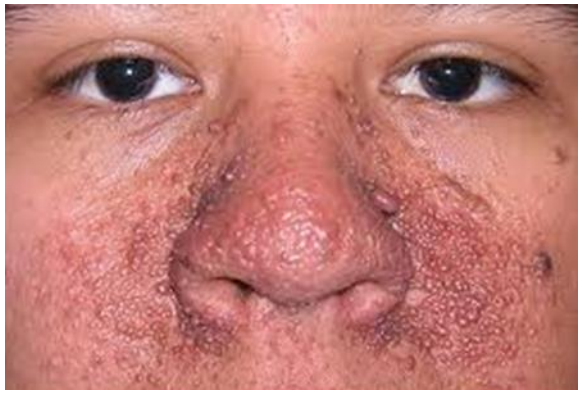
Current Research in Rett

- http://reverserett.org/research/
- Dr. Daniel Tarquinio, Pediatric Neurologist

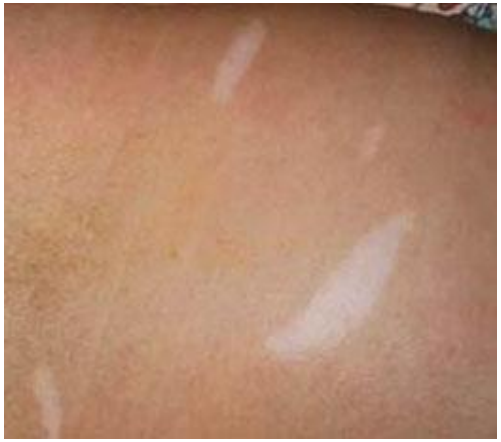
- **Rett Syndrome Clinic referrals:**
  - Call Dr. Tarquinio's cell: 207-590-6945 **(no texts)**
  - Daniel.tarquinio@emory.edu
  - danieltarq@gmail.com

Tuberous Sclerosis Complex

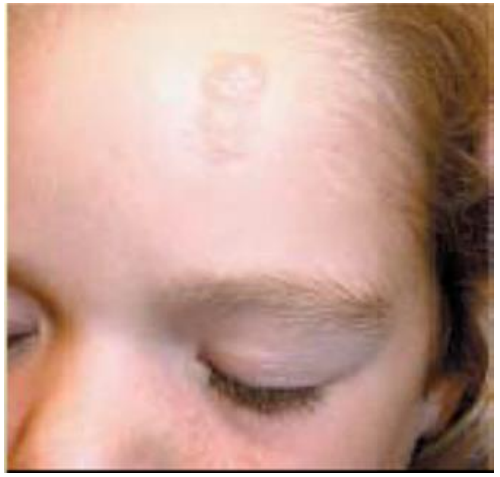
70% have Dermatology features



Angiofibromas
Malar Distribution



Ash Leaf Spots



Shagreen patches: Thickened elevated pebbly skin (orange peel) usually on lower back

Autosomal Dominant – 50% risk for recurrence
~ Two thirds are new mutations

TSC Neurological Features

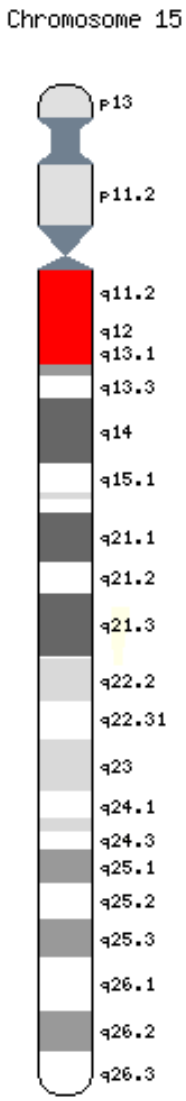
- Incidence ~1:5,000 to 10,000
- Intellectual Disability - ~40% (IQ<70)
- Epilepsy – up to 90%
- Autism diagnosed in 36%
  - Difficulty with social-emotional reciprocity; disinterest in physical contact (hugging etc)
  - Lack of eye contact
  - Problems understanding and maintaining relationships

NIH: National Institute of Neurological Disorders and Stroke

Prader Willi (PWS) & Angelman (AS) syndromes

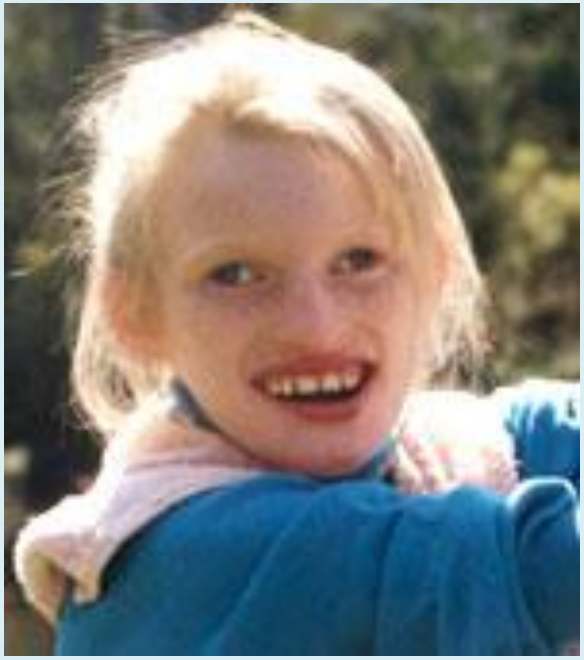
Chromosome 15q11-q13 del – <u>loss of function of the paternal copy of SNRPN gene</u>

Obesity (onset 6 months to 6 years), hypotonia, MR, small hands and feet, short stature, almond shaped eyes,



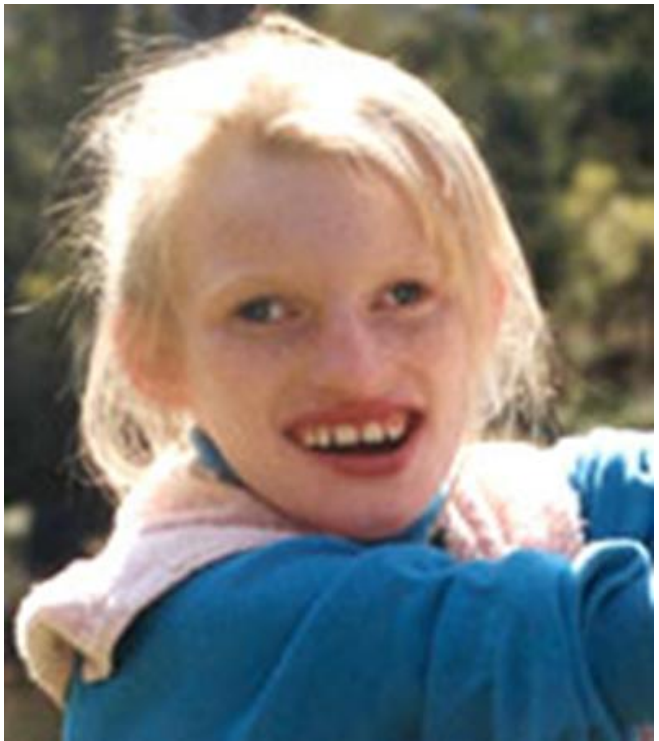
Chromosome 15q11-q13 del <u>loss of function of the maternal copy of UBE3A gene</u>

MR, seizures, short stature, hypo-pigmentation, large mouth, wide spaced teeth, prognathia,

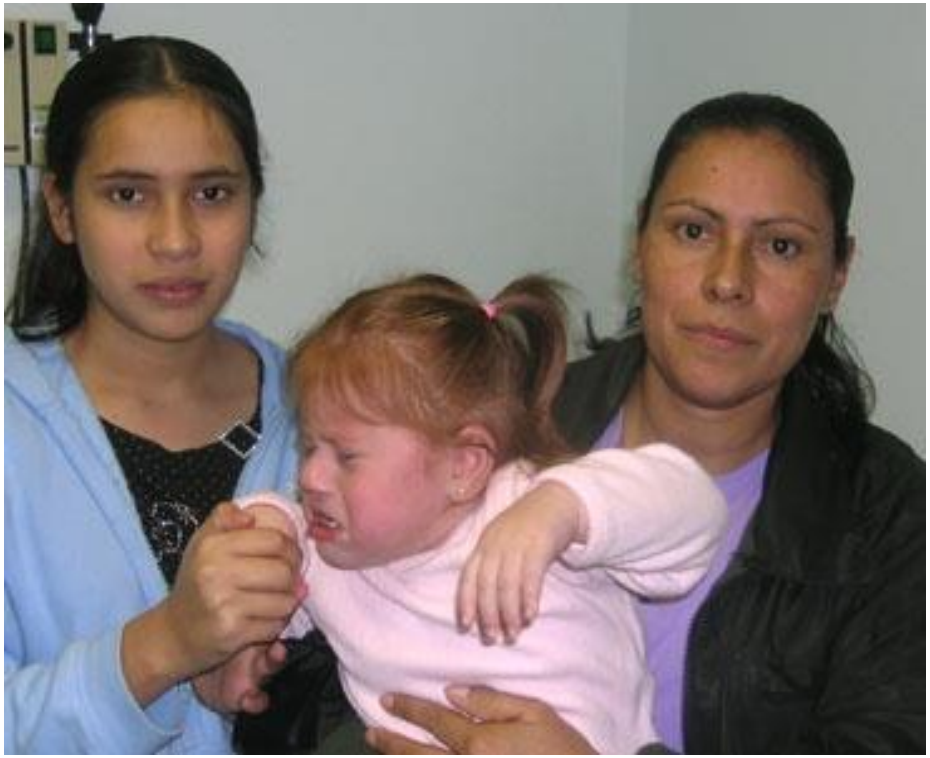


Angelman Features

- Incidence ~1:12,000 to 20,000
- Delayed development (apparent by 6-12 mos)
- Severe speech impairment
- Hypopigmented skin with light-colored hair
  - OCA2 gene associated with light-colored hair and fair skin
- Wide mouth & wide spaced teeth
- Prognathia
- Hand-flapping
- Frequent smiling & laughter
- Epilepsy
- Microcephaly
- Autism diagnosed in 34%

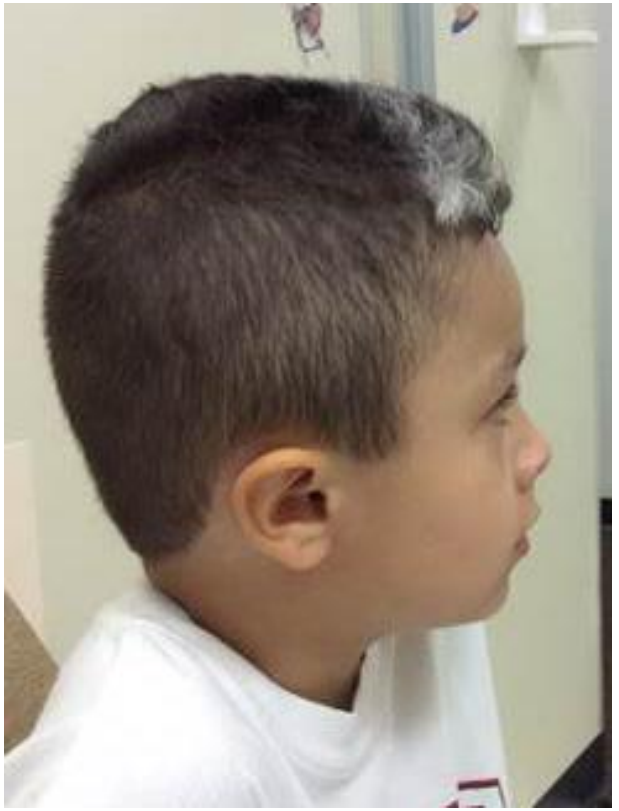


Angelman syndrome
Skin tone lighter than family background



Angelman 15q11-q13 deletion

What do you see?



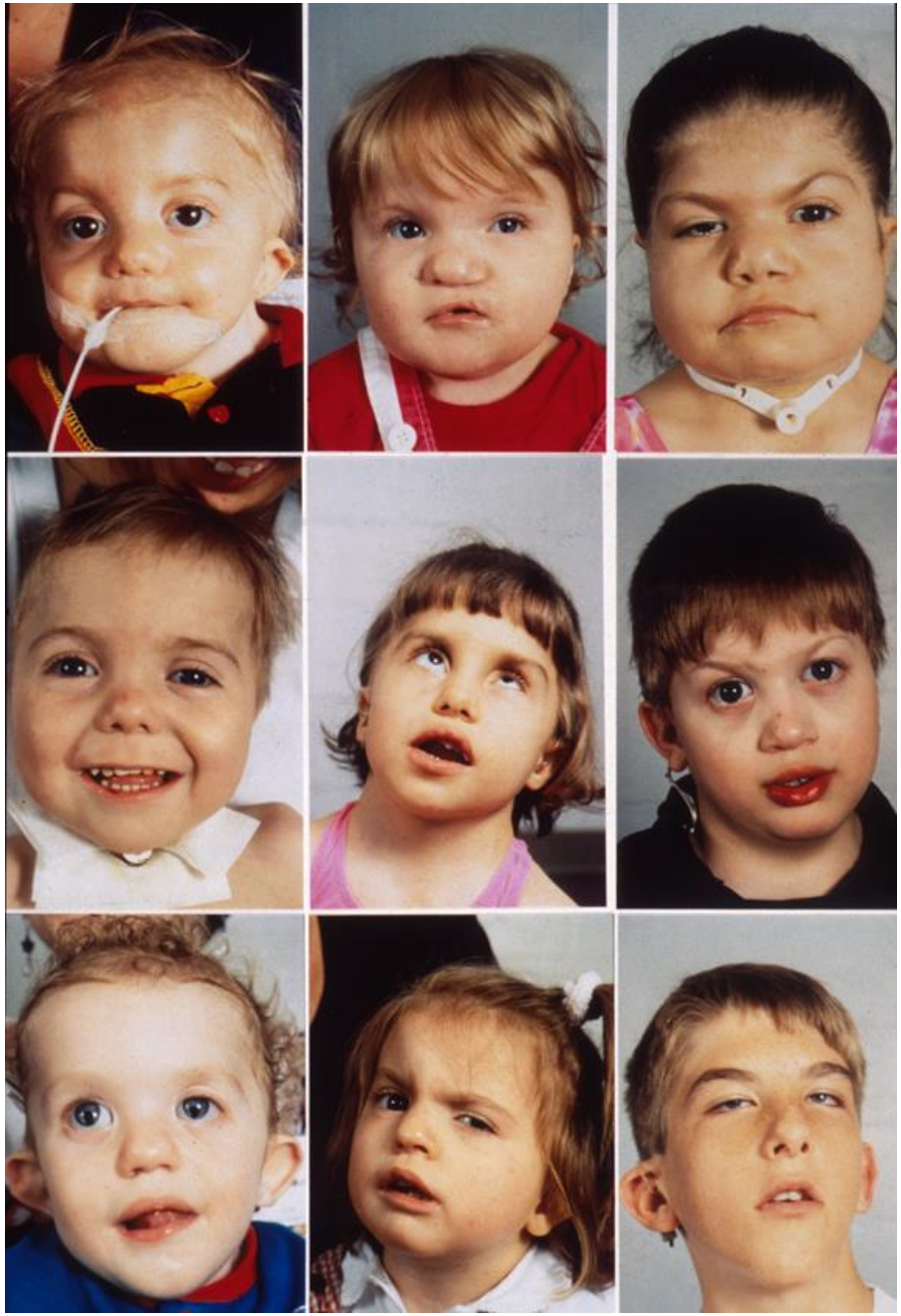
Referred out to Emory Medical Genetics:
Waardenburg syndrome
Incidence ~1:40,000

CHARGE Association

- Coloboma (79%)
- Heart Defects (85%)
- Atresia Choanae (57%)
- Retarded Growth and Development
- Genital Anomalies (34%)
- Ear Anomalies (91%), Deafness (62%)

- **Incidence ~1:8500**
- **Inheritance – Autosomal Dominant** but
  - almost all cases are *de novo* new mutations

(Tellier, et al: Am J Med Genet 76: 402-409, 1998)



CHARGE Syndrome

Face:

Iris colobomas

Ptosis

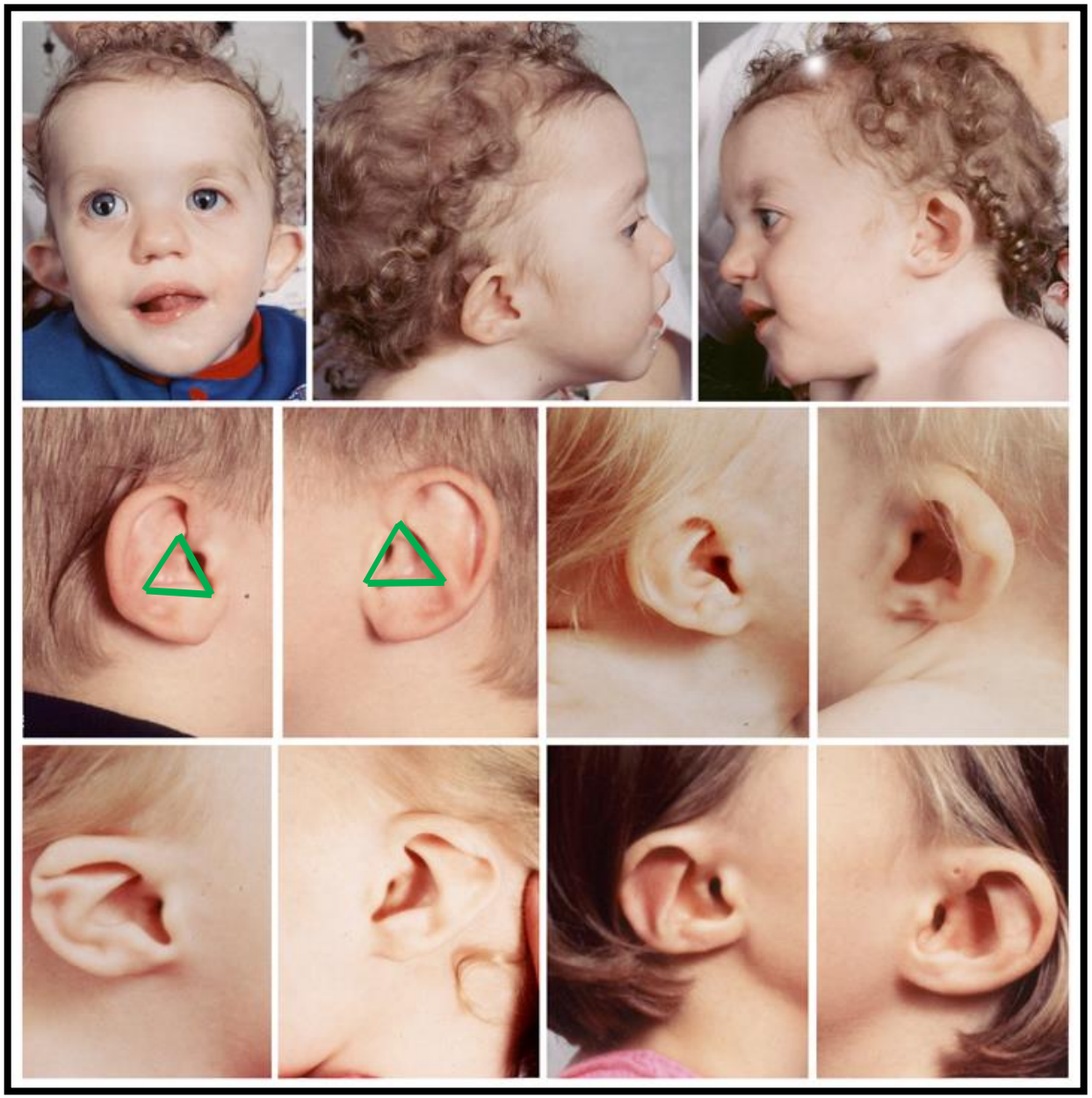
Hypertelorism

Visual Impairment

Cleft lip/palate

Microcepahly

Dull facial expression



CHARGE Syndrome

Ears:

Low set ears

Deafness

Triangular crus

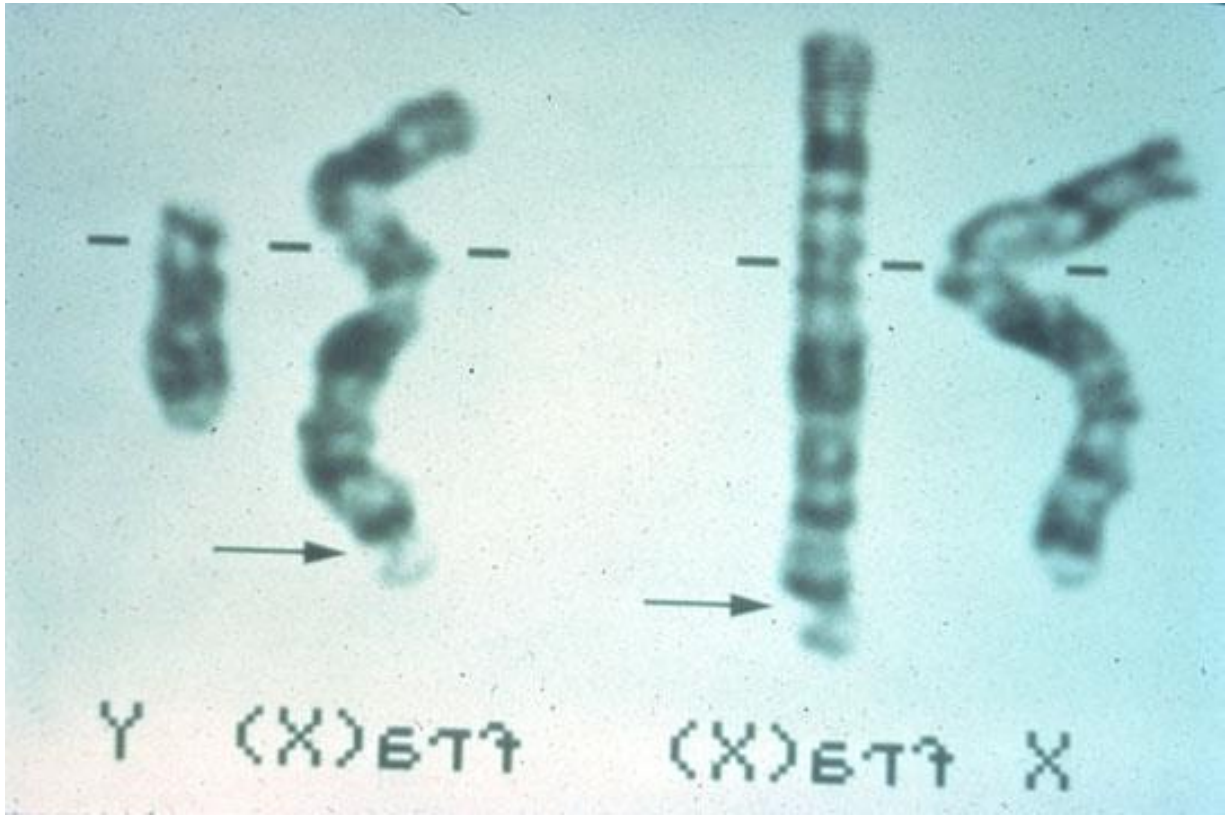
CHARGE Syndrome

- Autism diagnosed in 30%
  - Low interest in social contact
  - May show increased frustration and anxiety
  - Upset with changes in routine
  - Do things in precise manner
  - Strong need to put things in order

Am J Med Genet A. 2005 Mar 15;133A(3):257-61

Fragile X syndrome

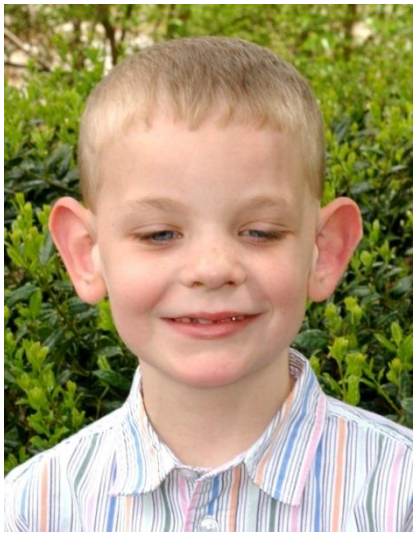
Fragile site exposed by growing cells in folate deficient media – 1969 Herbert Lubs



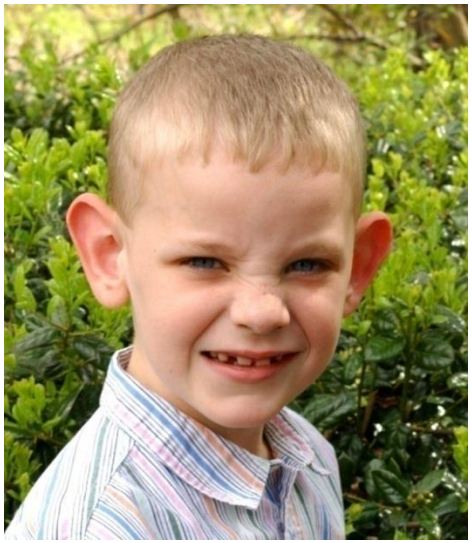
X-Linked Dominant - Fragile X

expansion of a CGG tandem repeat in the FMR1 gene

- Males:
  - Average IQ $\leq$ 50
  - Language delay
  - ADHD/ Autism spectrum
  - Post pubertal macroorchidism
  - Large ears & dysmorphisms
  - Avoidance of eye contact



- Females (milder):
  - ADD
  - Learning disabilities
  - Personality disorders
  - Premature ovarian failure (20% of females with FMR1 premutation)

Fragile X

Incidence
~1:2500-4000 males
~1:7000-8000 females

Avoidance of eye contact

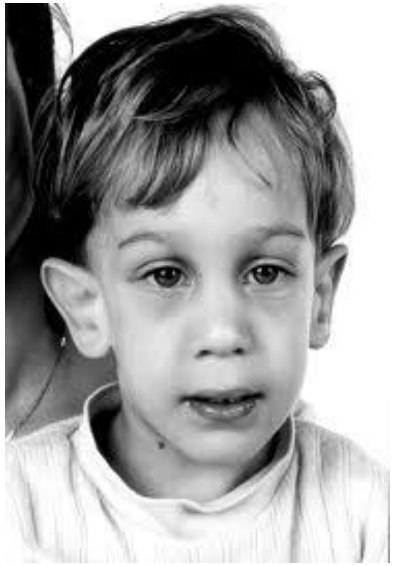
Most Common Form of Inherited Intellectual Disability

Fragile X
Development and Behavior

- Average IQ $\leq$ 50
- Hyperactivity/Distractibility – 70-80%
- Over-arousal/Hypersensitivity
- Attention Problems and Impulsivity
- Anxiety (especially social)/OCD/Perseverative
- Aggression/Self Abusive behaviors
- Autism diagnosed (30% of males; 22% in mixed sex)

Phenotype NOT Consistent



Why Seek a Diagnosis?

Connect Families to Resources

Research and Treatments

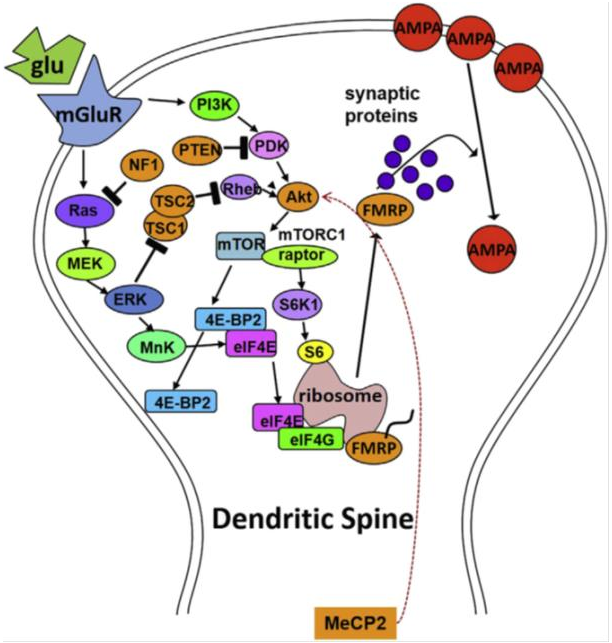
Tuberous Sclerosis Alliance
http://www.tsalliance.org/

National Fragile X Foundation
http://www.fragilex.org

Run ⊙ Walk ⊙ Roll
for
RETT SYNDROME

Proceeds to help fund
IRSF INTERNATIONAL RETT SYNDROME FOUNDATION

THE CHARGE SYNDROME FOUNDATION



Dendritic translation pathways

- Fragile X syndrome
- Tuberous sclerosis complex
- Rett syndrome
- Neurofibromatosis
- Autism/macrocephaly (PTEN)

Pediatr Neurol 2016; 65: 1-13

Why Seek a Diagnosis?

Connect Families to Specialty Clinics
Specific Guidelines for Care
Reproductive Information

- At CHOA and Emory:
  - 22q Deletion
  - Aortopathy
  - Fragile X
  - Neurofibromatosis
  - Rett
  - Tuberous Sclerosis
  - 36 Others

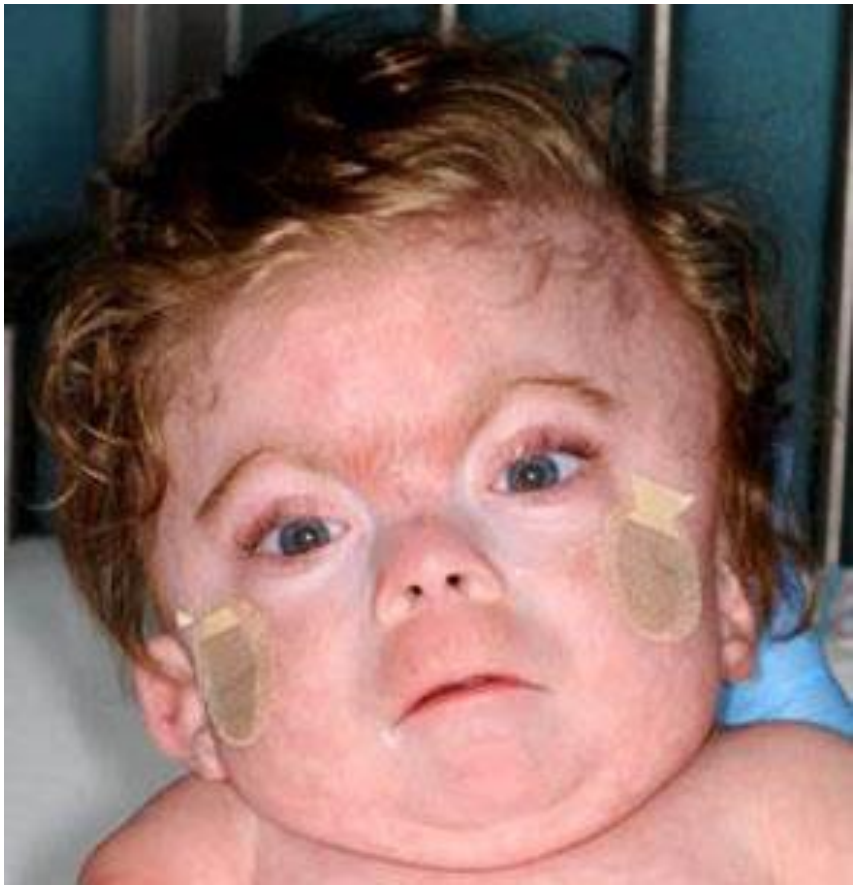
- **TSC Surveillance**
- ECHOs – cardiac rhabdomyomas
- Brain MRIs
- Renal Ultrasound, CT or MRI
- Ophthalmology
- **Fragile X, 22q, Rett**
- **Recurrence Risks and Prenatal Options**

What do you see?

- Wide mouth and hoarse voice
- Microcephaly
- Moderate ID
- Growth retardation << 3rd percentile
- Outgoing friendly personality
- Supra Valvular Aortic Stenosis
- Autism diagnosed in 12%

Williams syndome - 7q11.23 deletion

What do you see?



Hirsutism

Arched eyebrows

Long eyelashes

Thick eyelashes

Flat nasal bridge

Short nose

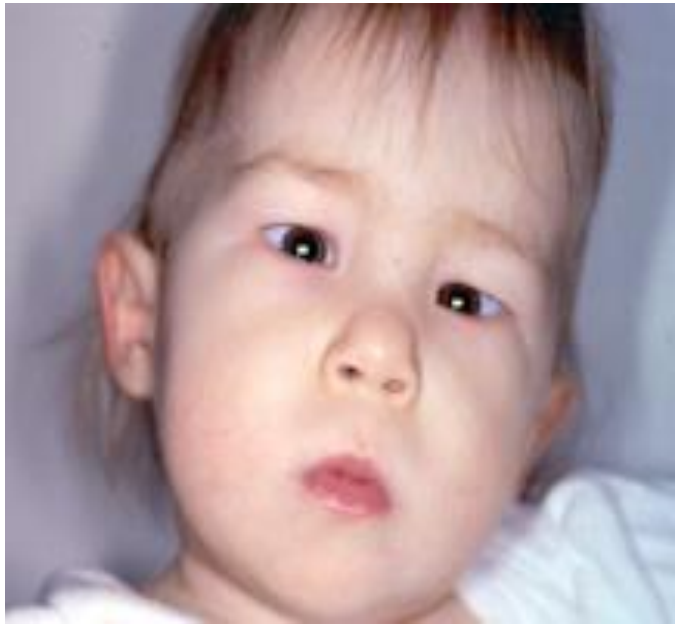
Upturned nares

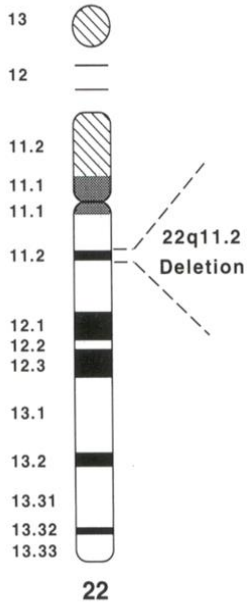
Long and Smooth philtrum

Thin lips

Cornelia de Lange syndrome – Autism diagnosed in 43%

What do you see?





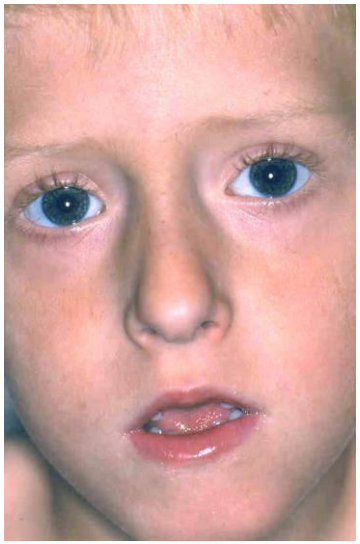
- Hooded eyelids
  - Short and narrow palpebral fissures
- Bulbous nose
- Hypoplastic alae nasi
- Long flat mid-face
- Microstomia

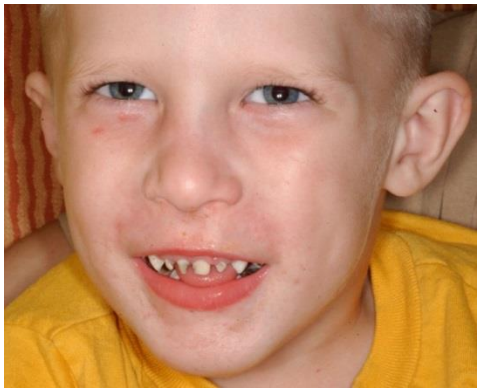
22q11.2 deletion

Autosomal Dominant
~10% are inherited
~90% are de novo
Autism diagnosed in 11%

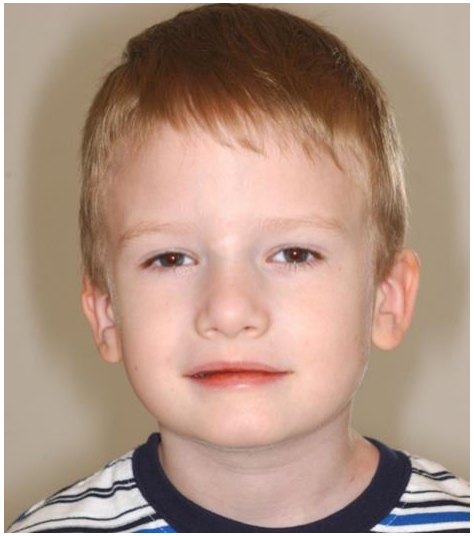
McDonald et al Nature Primer 2015

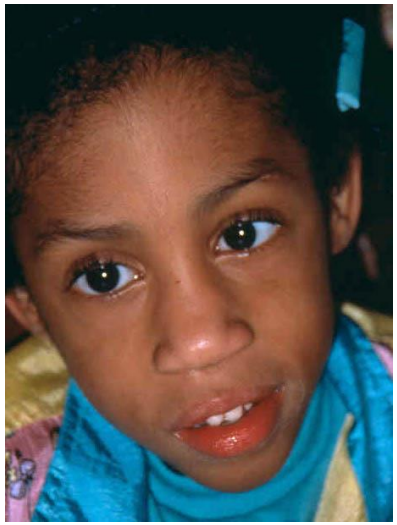
Features in older children





- Short palpebral fissures
- Deficient alae nasi
- Dull facial expression
- Developmental delay
- Special Ed classes
- Hx: Conotruncal defect
- 50% risk for recurrence





What can help you determine dysmorphology?

Comparison to Other Family Members


HELLO
my name is

Do you question something you are seeing?

- Ask someone on our medical team to look?
- Take a photo
  - Face front with camera in same plane
  - Head from the side
  - Hands
- Dr. Ramsay's Photo lab

MAC MVP Award

- Case 1: Dr. Renee Ussery
- 6 year old white male
- Referred for diagnostic clarification of strengths, weaknesses and “autistic traits”
- Seizures beginning at 18 months
- Stopped talking at age 5
- By age 6 could no longer feed himself and no longer toilet trained
- Referred Immediately to Emory Genetics

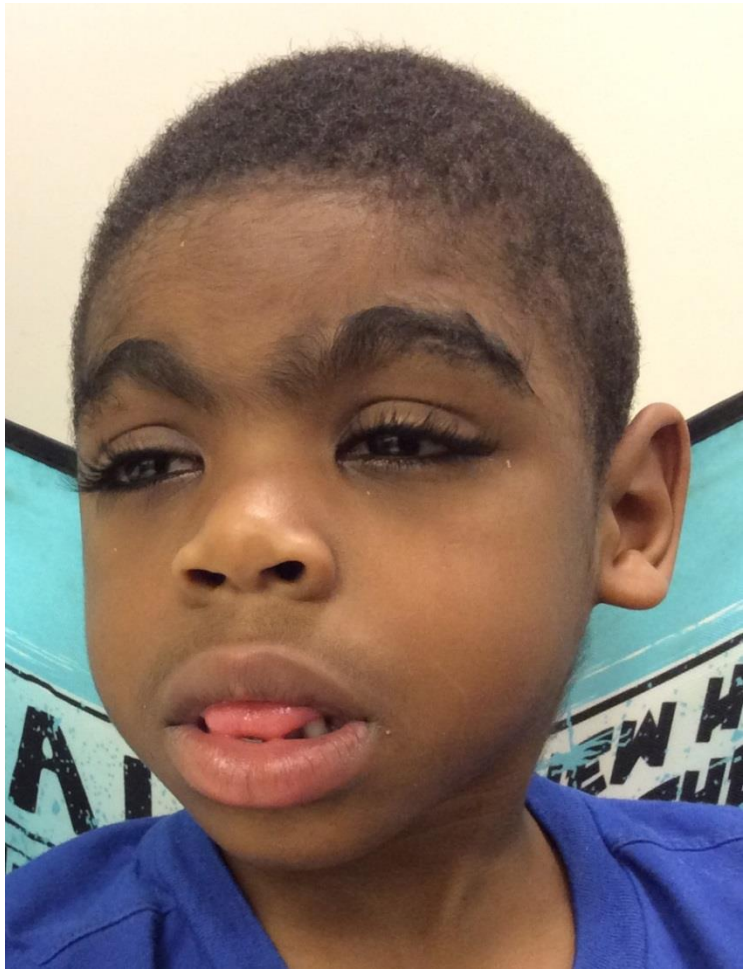
MAC MVP Award

- Juvenile Tay Sachs - very rare
- NIH offered to bring the family to Bethesda for evaluations
- Mom's response to the diagnosis:
  - No treatments and no cures
  - "Not what I wanted to hear"
  - But very appreciative to have a diagnosis
  - Family now knows what to expect
  - Stopped all unnecessary treatments
  - Focus on keeping him comfortable

MAC MVP Award

- Case 2: Dr. Meena Lambha
- 5 year old black male
- Mom concerned about developmental delays and social skill difficulties
- Markedly dysmorphic
- Marked Developmental delays

What do you see?



- Hirsutism
- Low frontal hairline
- Snophrys
- Long thick eyelashes
- Marked epicanthal folds
- Smooth philtrum
- Protruding tongue
- Autism

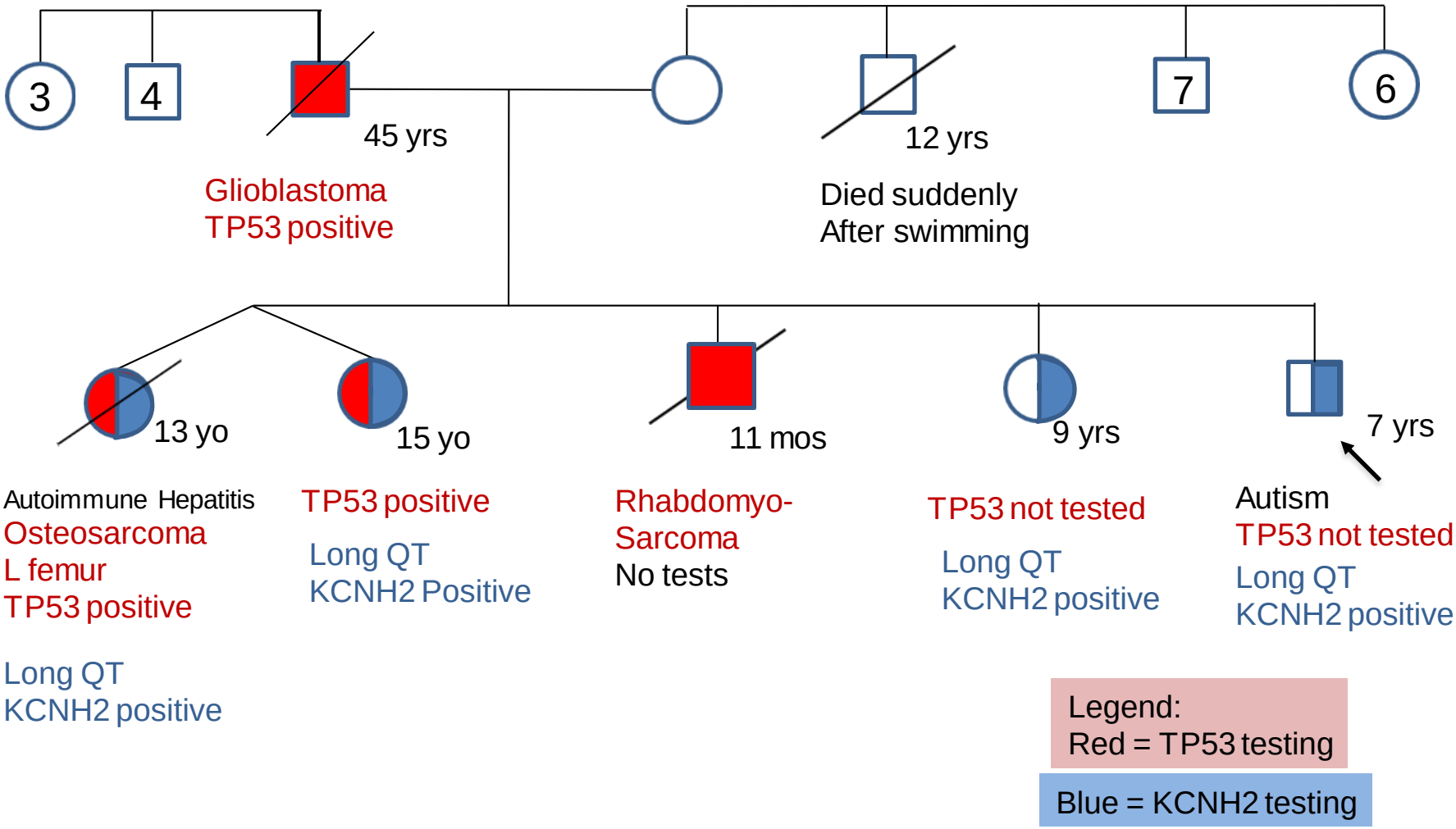
- Referred out to Emory Medical Genetics
- Concern for Lysosomal storage disorder

MAC MVP Award

- Case 3 – Monica Hannah, NP
- Li Fraumeni syndrome
- TP53 gene
- Autosomal Dominant
- Family Cancer Syndrome
  - Sarcomas
  - Leukemias
  - Adrenal cancer
  - Breast cancer

MAC MVP Award – Monica Hannah

Li Fraumeni – TP53 gene – Autosomal Dominant: Familial Cancer Syndrome: sarcomas, leukemias, adrenal, breast



What Do You See?

- Autism
- DD
- Hypotonia
- Mild DysmorphicFeatures:
  - Mild frontal bossing
  - Exotropia
  - Asymmetric mouth
- CMA and Fra X – normal
- What Next?

Whole Exome Sequencing

No Significant Changes At This Time

ATYPICAL

- Dull and Confused Facial Expression
- Asymmetry
  - Right arm much bigger than left
- Poor Life Choices
  - Madras swim suit?

MAC Hall of Fame for Clinical Observations

Lashonya

Angela

Tiffany

Bonnie

Monica

Christy

Meena

Renee

Beauty is in the eye of the beholder…..