Name That Syndrome!

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Disclosure

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Acknowledgement

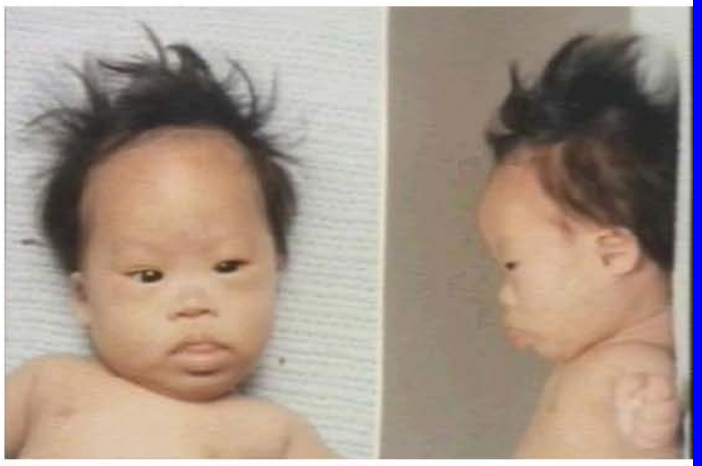
Pedro Sanchez, MD – Pediatric Geneticist

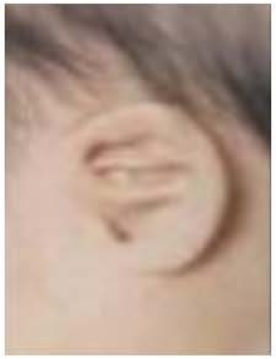
Objectives

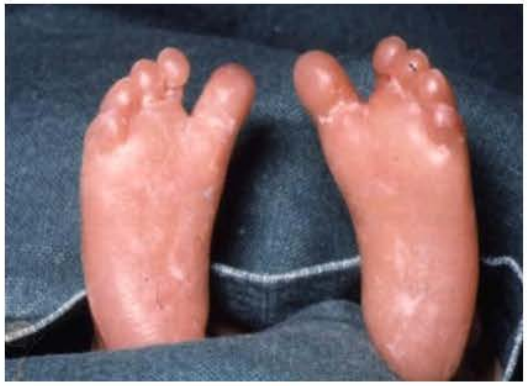
- Discuss characteristics of common genetic syndromes
- Describe diagnostic criteria and/or testing for common genetic syndromes
- Identify current guidelines for primary and specialty care for common genetic syndromes

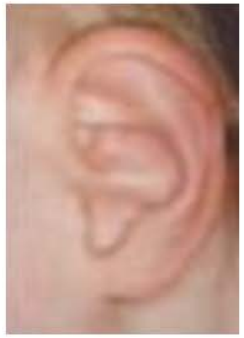
Name That Syndrome!

- 1 month old female
- Normal birth history
- Some feeding problems
- PE:
  - Small mouth and ears
  - Redundant neck folds
  - Noisy breathing
  - Somewhat hypotonic









Common Physical Features

- Brachycephalic
- Epicanthic folds
- Flat nasal bridge
- Upward slanting palpebral fissures
- Brushfield spots
- Small mouth
- Small ears
- Excessive skin at nape of neck
- Single transverse palmar crease
- Short fifth finger with clinodactyly
- Hypotonia

Newborn Period

- Feeding problems
- 60% have eye disease
- 75% have hearing loss
- ↑ incidence of URI's; 50-75% have OSA
- 50% have cardiac defects → need echo
- 12% develop obstructive bowel anomalies
- 15% have thyroid disease; 1% congenital
- Hypotonia
- Importance of early intervention

Infancy

- 50-70% develop serous OM
  - Behavioral audiogram at 1 year
- Check for strabismus, cataracts, nystagmus
  - Peds ophthalmology by 6 months of age
- Repeat thyroid function screen at 6 and 12 months then annually
- Routine immunizations – consider Synergis

Early Childhood

- Growth and development
- If unable to visualize TM's audiogram every 6 months up to 3 years – ENT referral
- Annual vision screening → refer to ophtho for exam every 2 years
- Cervical x-ray at 3-5 years
- Review s/s OSA & refer to ENT prn
- Screen for celiac disease at 2-3 years
- Dental screening every 6 months

Late Childhood

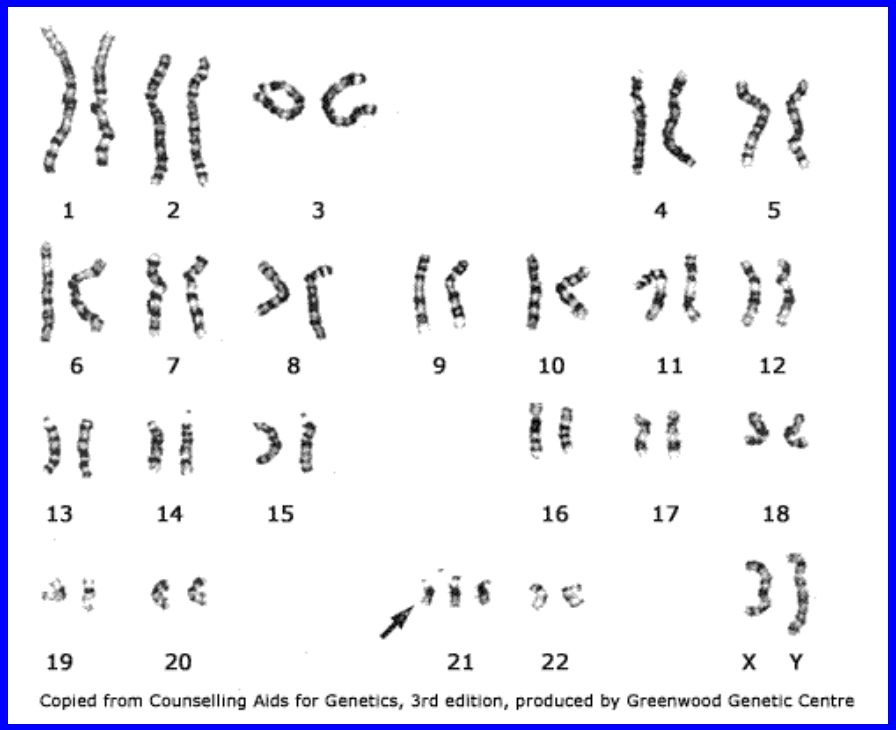
- Assess growth and development
- Annual audiologic evaluation
- Annual ophthalmologic evaluation
- Annual thyroid screening
- Review skin problems prn

Adolescence – Early Adulthood

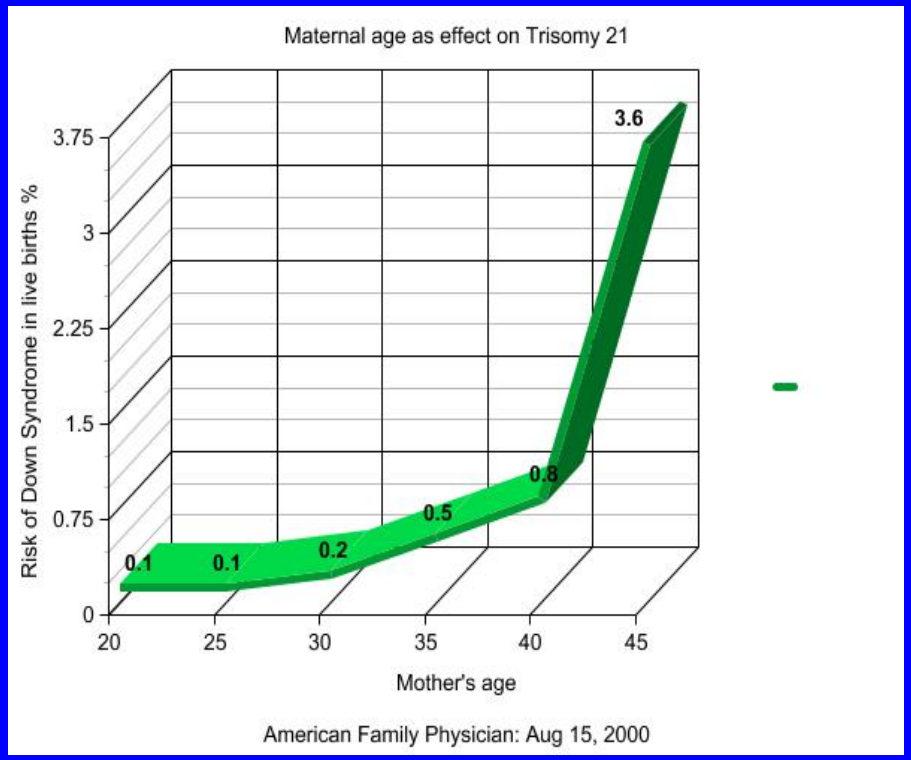
- Physical exam
  - CBC
  - Thyroid function test
- Annual audiologic evaluation
- Annual ophthalmologic evaluation
- Recommend routine gynecologic care
- Transfer to adult medical care

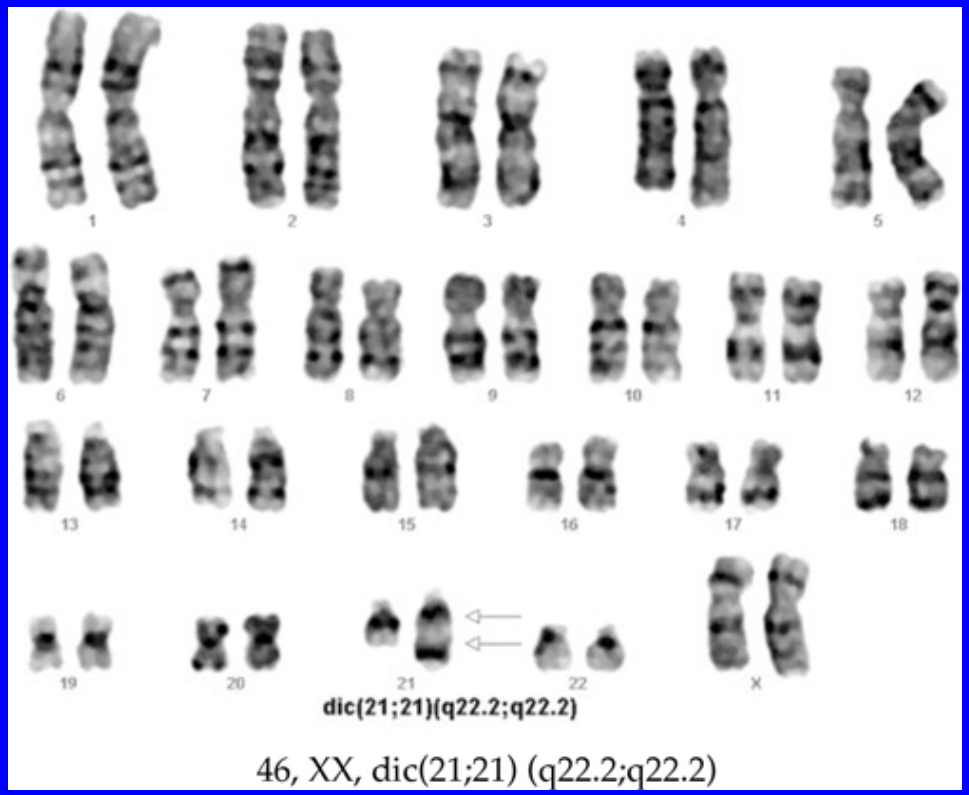
Diagnostic Testing for Down

- Prenatal screening
  - Nuchal translucency
  - Nuchal thickness
  - Triple screen
  - Quadruple screen
- Prenatal & Post-natal testing
  - Chromosomes



Robertsonian Translocation



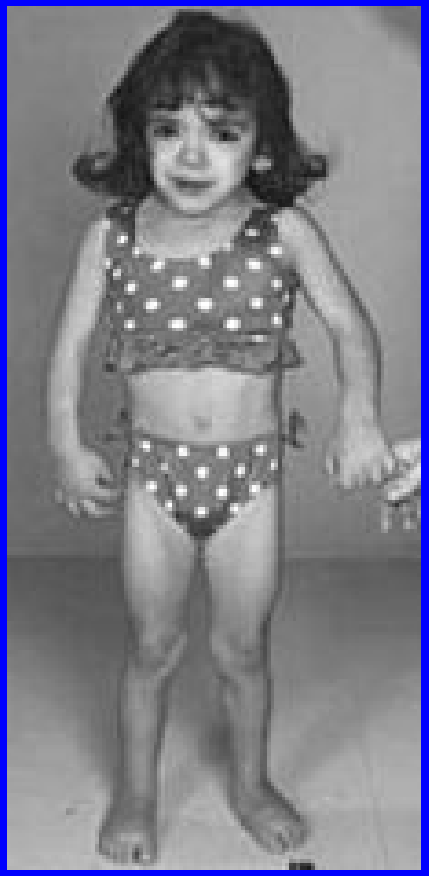


100% recurrence risk

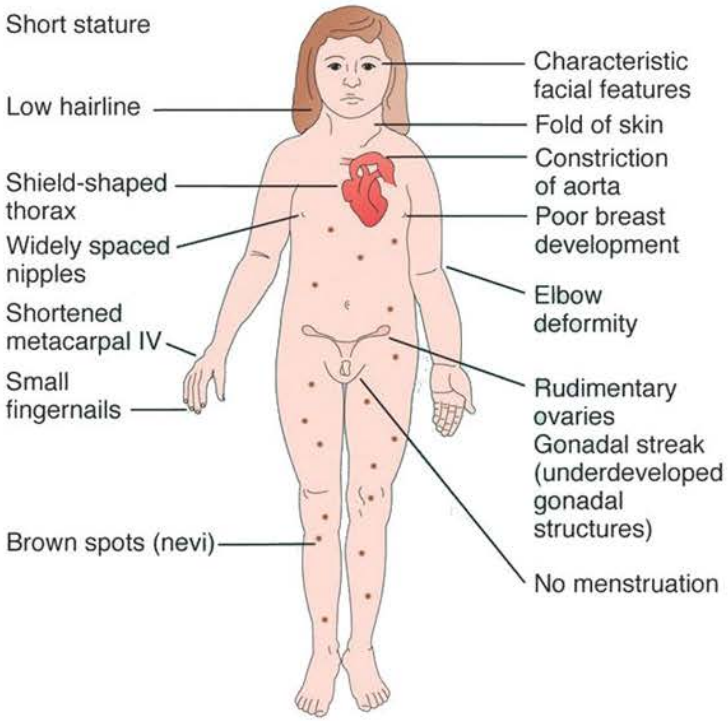
Resources for Down Syndrome

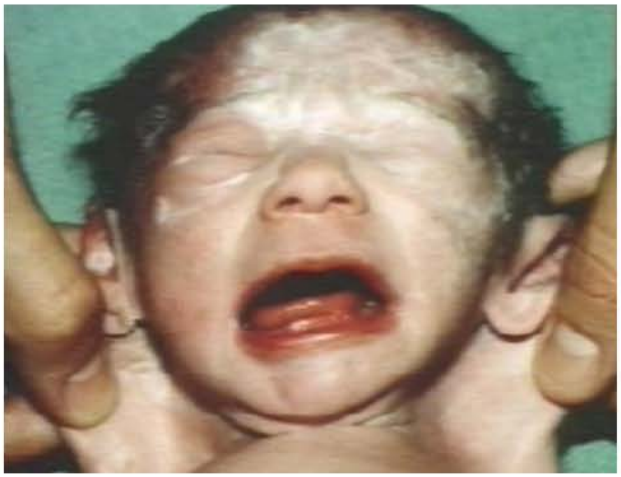
- Growth Charts
  - http://adc.bmj.com/cgi/content/full/87/2/97
- AAP Health Supervision Guidelines
  - http://www.aap.org/policy/re0016.pdf
- For parents
  - http://www.dsala.org

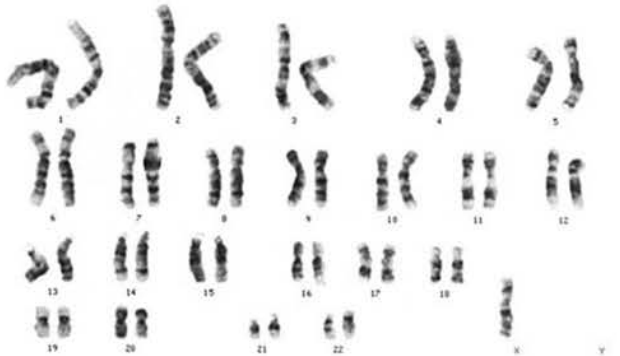
Name That Syndrome!

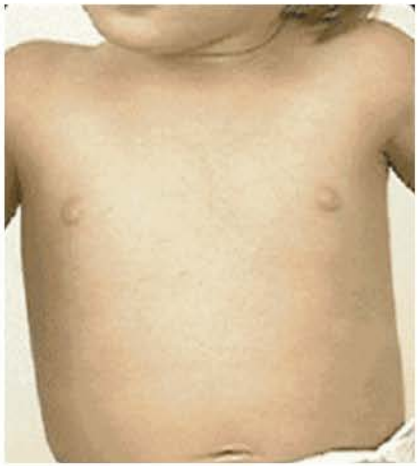


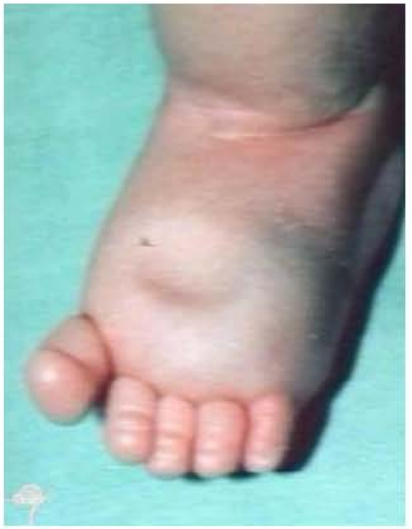
- 3 year old female just moved here from Mexico
- No significant birth hx
- PE
  - Short stature
  - Heart murmur


Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small fingernails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation









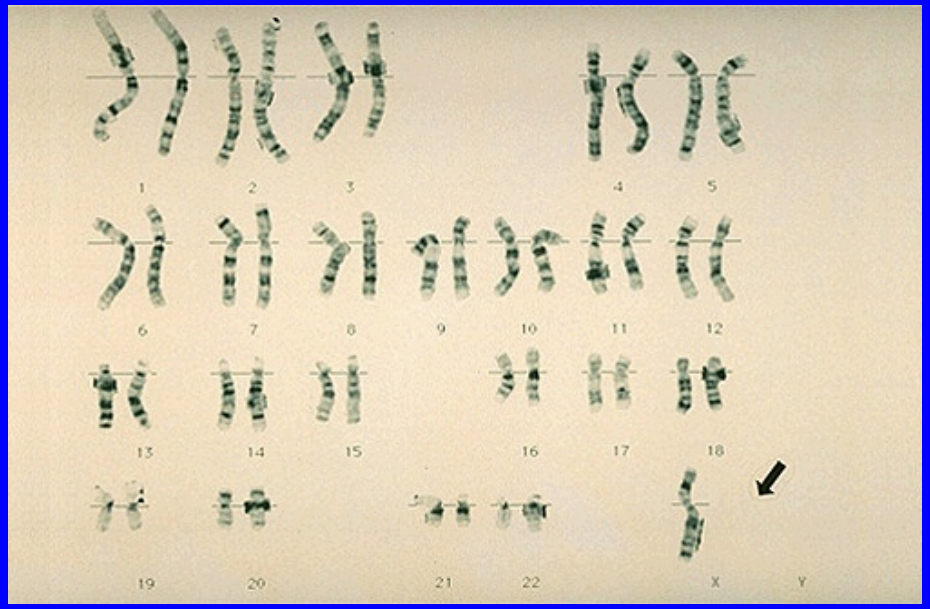
Turner Syndrome Care

- Evaluate cardiac anatomy - echo
- Evaluate renal anatomy - UTZ
- Monitor blood pressure
- Thyroid function
- Refer to Endocrine

- Evaluate hearing
- Evaluate vision
- DDH & scoliosis common
- Predisposed to obesity
- Short stature
- 90% gonadal failure
- ↑ risk for keloids

Diagnostic Testing for Turner

- Chromosomes

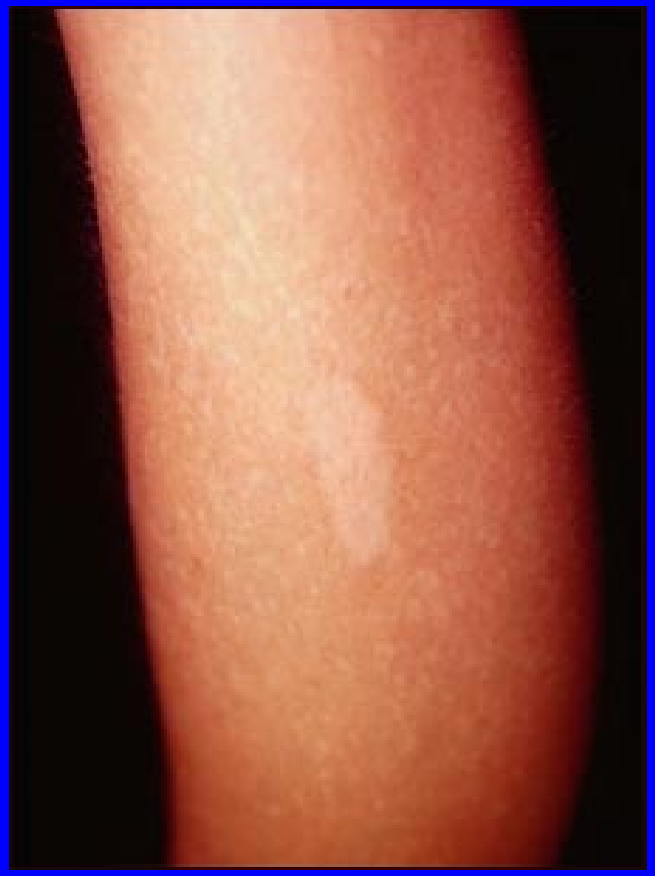


Resources for Turner Syndrome

- www.turnersyndrome.org

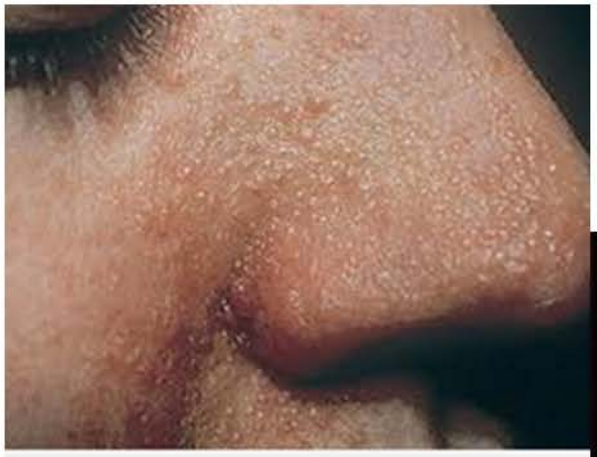
Name That Syndrome!

- 4 month old male
- Prenatal history
  - Cardiac rhabdomyoma now resolved
- Mom describes some strange posturing
  - Baby bends in two
- PE
  - See photo

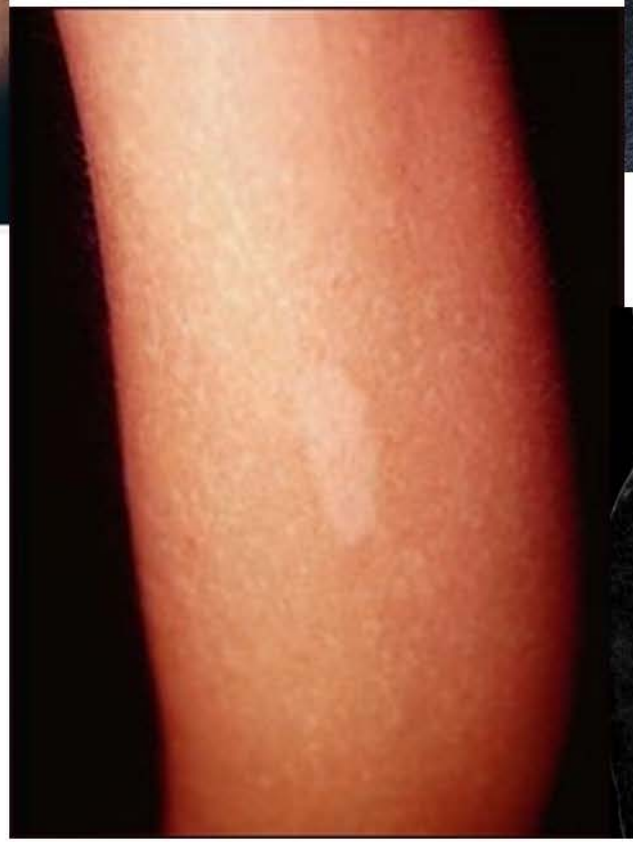


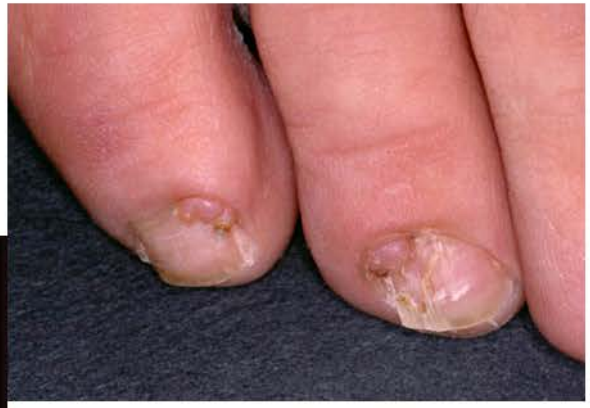
Diagnostic Criteria – Tuberous Sclerosis

- **Major features**
  - Facial angiofibromas
  - Ungual or periungual fibroma
  - Hypomelanotic macules
  - Shagreen patch
  - Cortical tuber
  - Subependymal nodule
  - Subependymal giant cell astrocytoma
  - Multiple retinal nodular hamartomas
  - Cardiac rhabdomyoma
  - Lymphangiomyomatosis
  - Renal angiomyolipoma
- **Minor features**
  - Multiple randomly distributed pits in dental enamel
  - Hamartomatous rectal polyps
  - Bone cysts
  - Cerebral white-matter “migration tracts”
  - Gingival fibromas
  - Nonrenal hamartoma
  - Retinal achromic patch
  - “Confetti” skin lesions
  - Multiple renal cysts

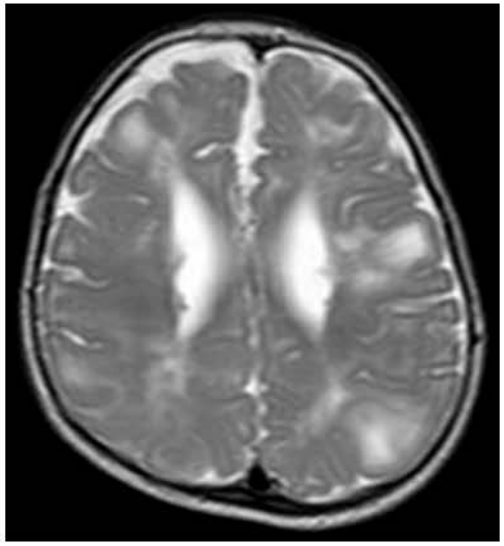


Adenoma sebacium

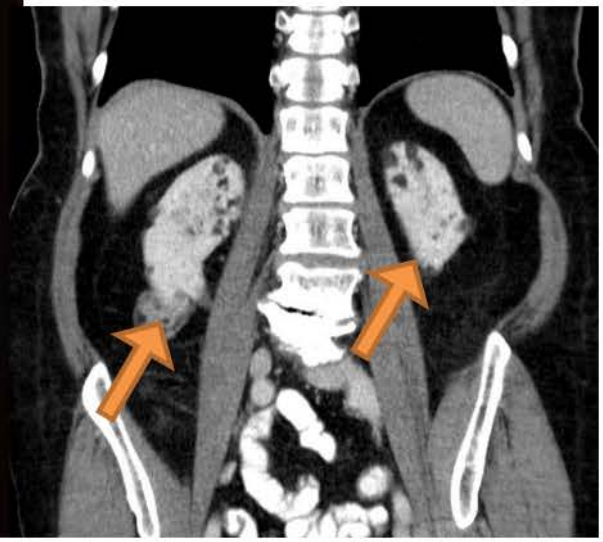




periungual fibroma



UBOs
Unidentified Bright Objects



Kidney Angiolipomas

Diagnostic and Surveillance Screening in TSC

	"Asymptomatic" parent, child or 1st degree relative at time of diagnosis of affected individual	Suspected case or initial diagnostic evaluation	CHILD		ADULT	
			Known case, no symptoms in referable organ	Known case, symptoms or findings previously documented	Known case, no symptoms in referable organ	Known case, symptoms or findings previously documented
Fundoscopic Examination	X	X	—	X	—	X[d]
Brain MRI	X[a]	X	X[b]	X	X[c]	X[e]
Brain EEG	—	—[d]	—	X[e]	—	X[e]
Cardiac EKG and ECHO	—[f]	X	—	X[g]	—	X[e]
Renal MRI, CT or Ultrasound	X[b]	X	X[i]	X[g]	X[b]	X[g]
Dermatologic Screen	X	X	—	X[e]	—	X[e]
Neurodevelopmental Testing	—	X[j]	X[k]	X[e]	—	X[e]
Pulmonary CT	—	—	—	X[e]	X[l]	X[e]

[a] With a negative physical examination, computed tomography is recommended

[b] Every 1 to 3 years

[c] Probably less frequently than in children

[d] Unless seizures are suspected, generally not useful in diagnosis

[e] As clinically indicated

[f] Unless needed for diagnosis

[g] Every 6 months to 1 year until involution or size stabilization

[i] Ultrasound generally recommended due to cost although local imaging expertise may vary

[j] Every 3 years until adolescence

[k] Generally for children only

[l] Recommended for children at the time of beginning 1st grade

[l] For women at age 18

Hyman, MH & Whittemore, VH. National Institutes of Health Consensus Conference: Tuberous Sclerosis Complex. *Arch Neurol* 2000; 57:662-665.

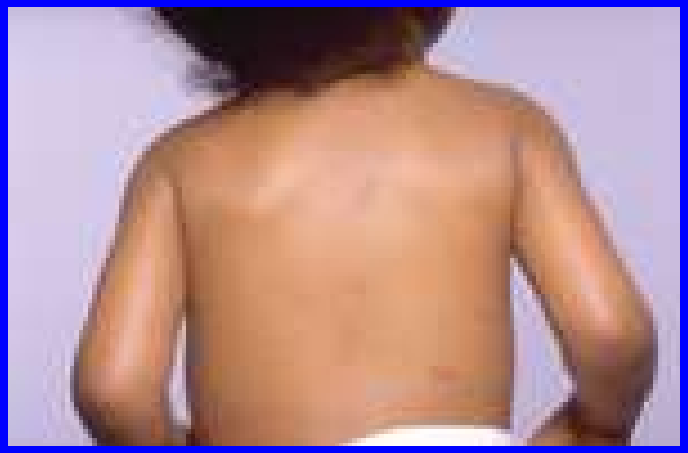
Diagnostic Testing for TS

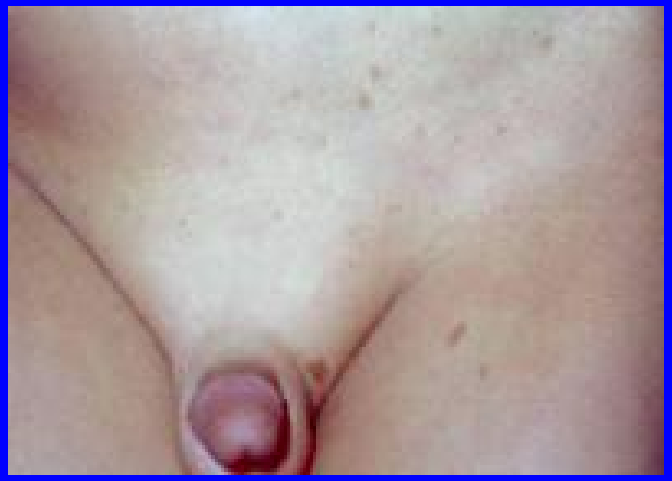
- TSC1 Gene
- TSC2 Gene

Resources for Tuberous Sclerosis

- www.tsalliance.org

Name That Syndrome!

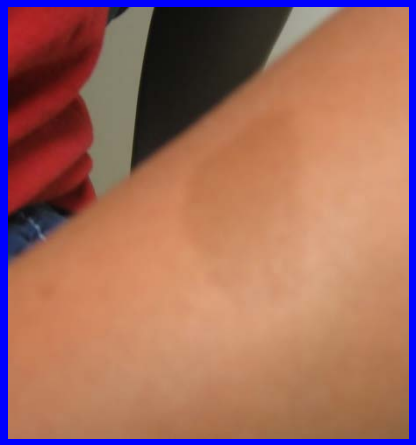




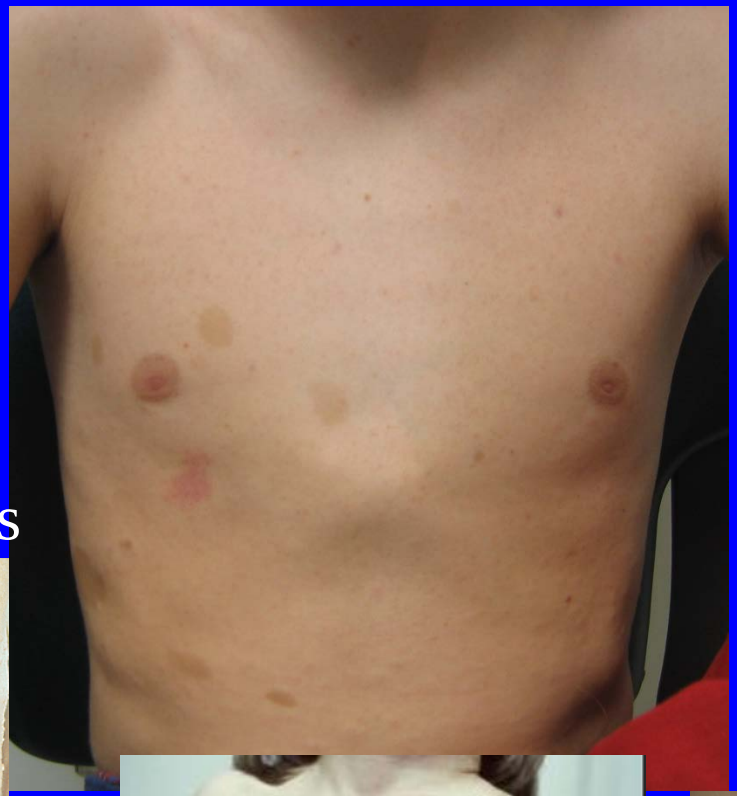
- 2 year old male new to your practice
- Negative birth hx
- PE:
  - Macrocephalic
  - Mild hypotonia
  - See photos

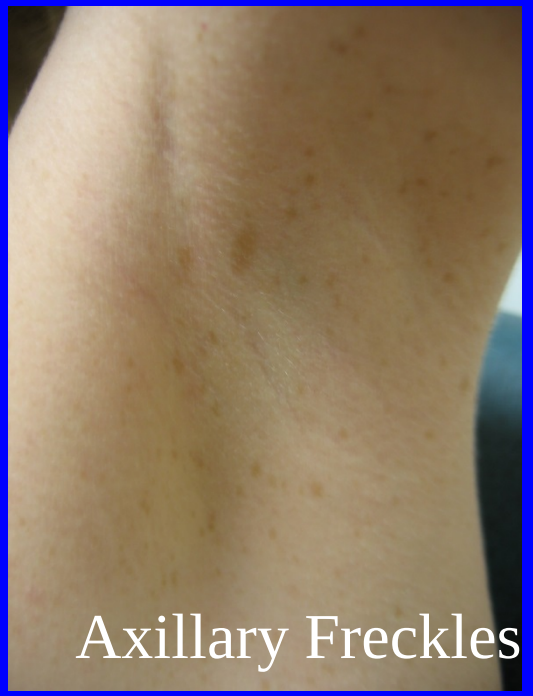
Diagnosing NF1

- Must have 2 or more of the following:
  - 6 or more CLMs
  - 2 or more neurofibromas or 1 plexiform NF
  - Axillary or inguinal freckling
  - 2 or more Lisch nodules
  - Distinctive bony lesions
  - Affected first-degree relative

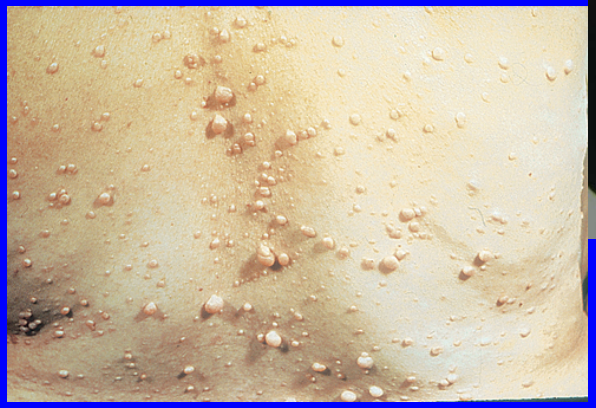


Café au lait macules

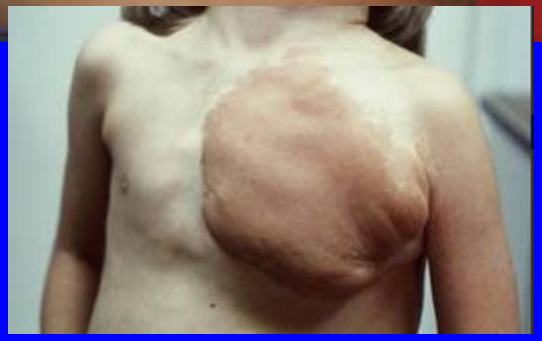




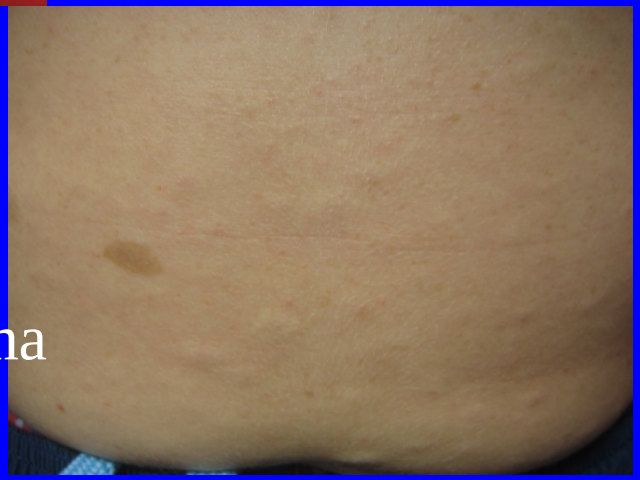
Axillary Freckles



Neurofibromas



Plexiform neurofibroma



Subcutaneous skin changes

Management of NF1

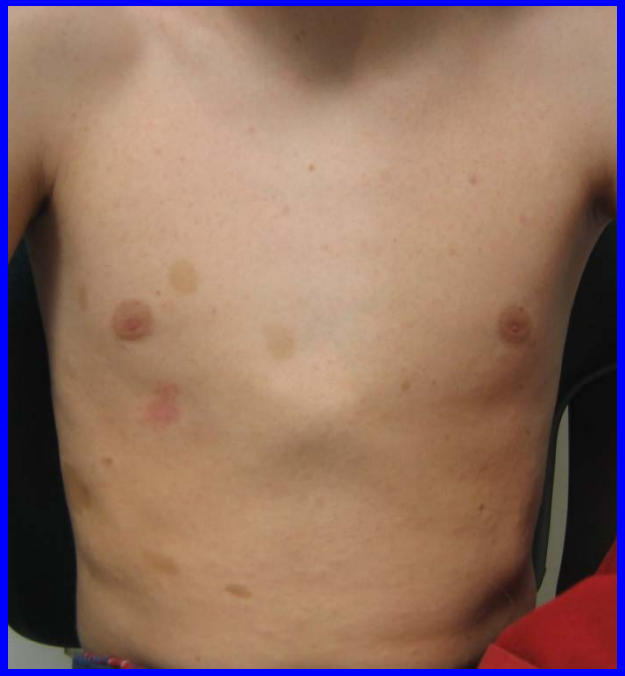
- Evaluate for new neurofibromas and progression of lesions
- Monitor blood pressure
- Evaluate neurodevelopmental progress
- Evaluate for skeletal changes
- Yearly ophthalmologic evaluations
- 40-50% have learning disabilities

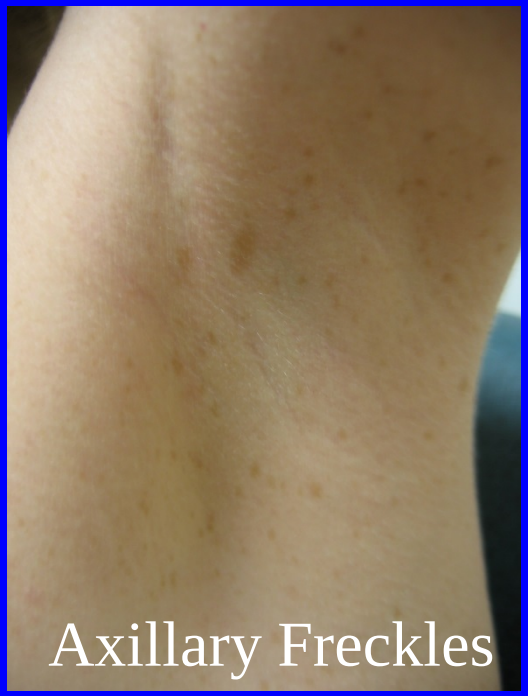
Complications of NF1

- Direct involvement by neurofibromata
- Optic gliomas
- Hypertension
- Scoliosis/kyphosis
- Learning disabilities
- Hypertension
- Risk for malignancies

Diagnostic Testing for NF1

- Clinical diagnosis
- Gene sequencing or FISH for deletion





Must differentiate from Legius Syndrome (SPRED1 gene) if the patient has no neurofibromas

Clinical features include:

- Multiple Café au lait macules
- Axillary freckling
- Macrocephaly
- Autosomal dominant

NO RISK OF NEUROFIBROMAS OR SKIN TUMORS

Usually requires genetic testing for mutations in the **SPRED1 gene**

Resources for NF1

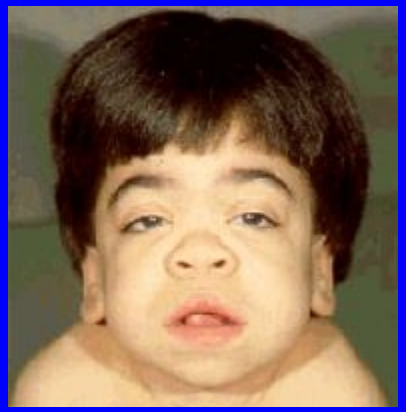
- www.ctf.org
- www.nfinc.org
- Growth charts
  - American Journal of Medical Genetics (1999) 87:317-323 (Clementi, M., Milani, S., et al)

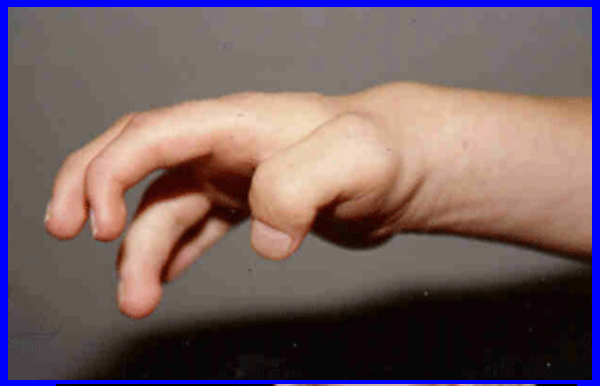
Name That Syndrome!

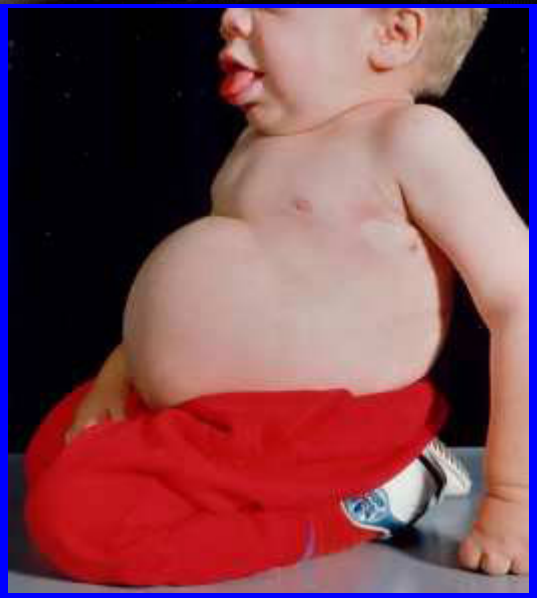
- 6 month old female
- Birth hx normal
  - 9 lb 14 oz
- PDA ligation 4 weeks
- Off the charts for weight, height, hc
- On PE:
  - Bilateral OM
  - Corneal clouding

Common Characteristics for MPS

- Coarse facial features
- Short stature
- Dysplastic bones
- Thickened skin
- HSM
- Hernias
- Progressive joint stiffness
- Recurring respiratory infections
- OSA
- Heart disease
- Corneal clouding
- Some mental retardation/dev delays
- Hearing loss








2y
5y
9y
11y
19y

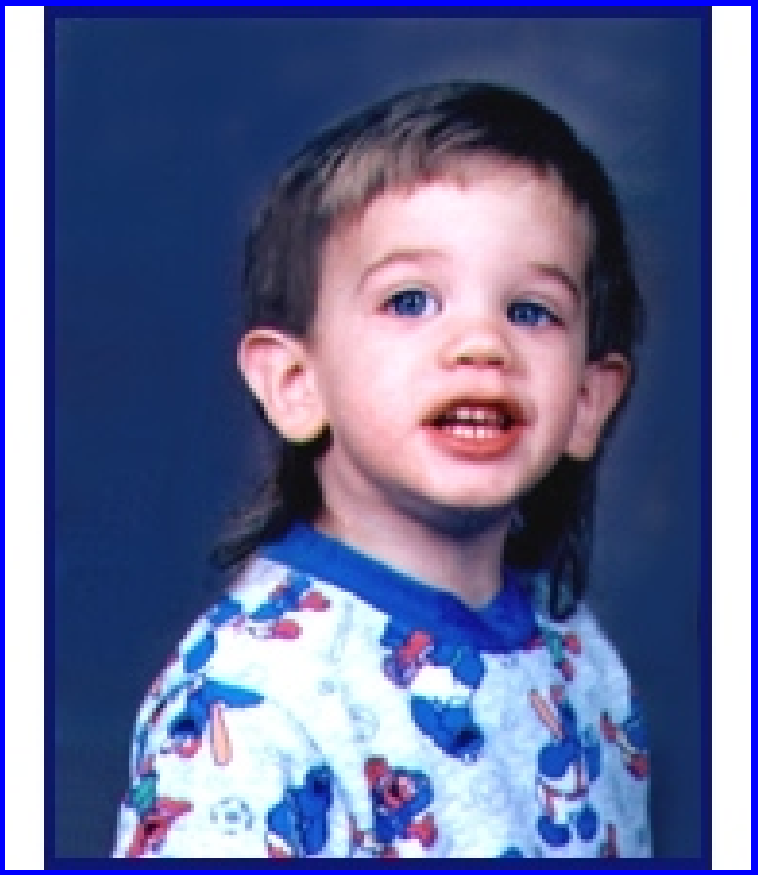
Diagnostic Testing for MPS

- Screening if suspect MPS
  - Urinary GAG
- More definitive testing depends on which type of MPS is suspected

Resources for MPS

- http://www.mpssociety.org/

Name That Syndrome!



- 4 year old male
- Birth history normal
- In speech therapy
- Mild mental retardation
- PE
  - Large ears
  - Prominent jaw

Characteristics of Fragile X

- Physical features
  - Prominent jaw
  - Large ears
  - Large testes
- Connective tissue
  - Double jointed
  - Flat feet
- Mitral valve prolapse
- Cognitive delays
- Behavioral challenges
  - ADHD
  - Hand flapping
- Sensory integration problems
- Living skills problems
- Speech & language problems

Diagnostic Testing for Fragile X

- Fragile X DNA
  - Suspect in any male with mental retardation
  - Suspect in any autistic male

Resources for Fragile X

- http://www.fragilex.org/

Name That Syndrome!

- 2 month old male
- Birth history
  - Spent a few days in NICU for NG feeds
- PE:
  - hypotonia

Diagnostic Criteria

- **Major**
  - Infantile central hypotonia
  - Infantile feeding problems and/or FTT
  - Rapid weight gain age 1-6 years
  - Narrow bifrontal diameter, narrow nasal bridge, down-turned mouth
  - Hypogonadism
  - Developmental delay/MR
- **Minor**
  - Infantile lethargy
  - Sleep disturbance or apnea
  - Short stature (teen)
  - Hypopigmentation
  - Small hands and feet
  - Narrow hands with straight ulnar border
  - Esotropia/myopia
  - Thick viscous saliva
  - Skin picking

Evaluation

- Management of hypotonia/poor feeding
- Evaluation for hypogonadism and/or hypopituitarism – refer to Endocrine
- Management of obesity
  - Risk for Type II diabetes
- Monitor for scoliosis
- Behavioral interventions
- Nutritional evaluation

Diagnostic Testing for PWS

- Methylation Studies

Table 1 Nutritional phases in Prader-Willi syndrome

Phases	Median ages	Clinical characteristics
0	Prenatal to birth	Decreased fetal movements and lower birth weight than sibs
1a	0–9 months	Hypotonia with difficulty feeding and decreased appetite
1b	9–25 months	Improved feeding and appetite and growing appropriately
2a	2.1–4.5 years	Weight increasing without appetite increase or excess calories
2b	4.5–8 years	Increased appetite and calories, but can feel full
3	8 years to adulthood	Hyperphagic, rarely feels full
4	Adulthood	Appetite is no longer insatiable

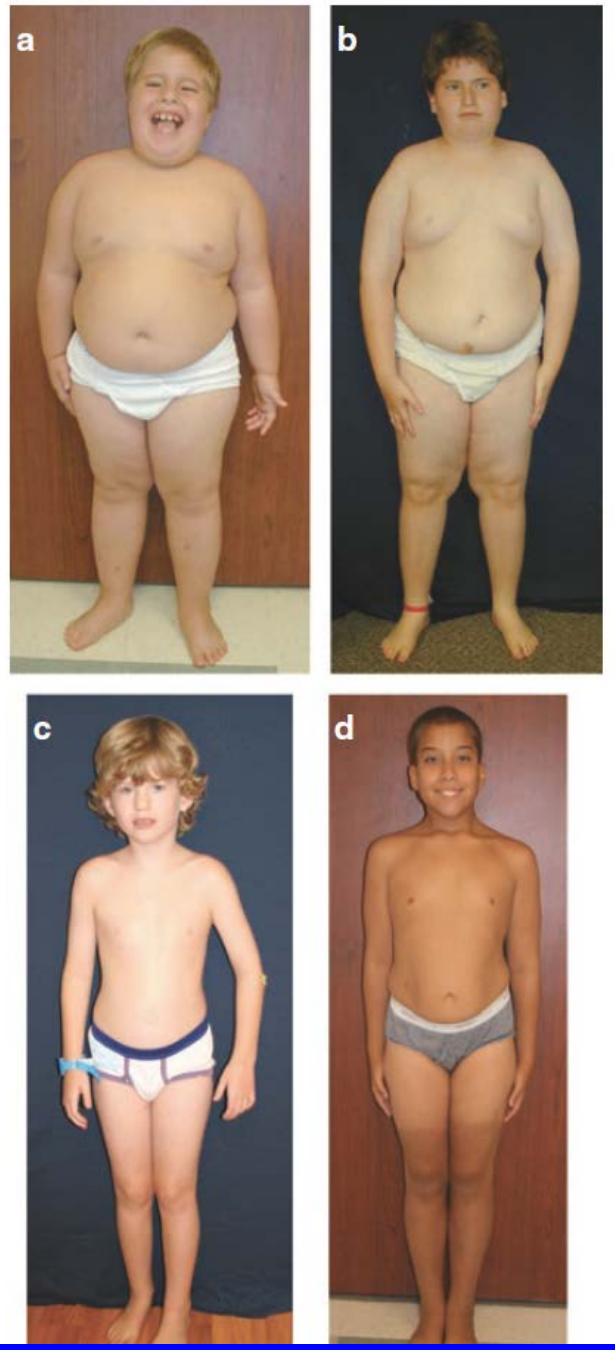
Modified from *Am J Med Genet A*.[3]

Figure a & b: **without**

Growth hormone

Bottom c & d **WITH**

Growth hormone treatment



Genet Med 2012:14(1):10–26

Resources for Prader-Willi

- www.pwsausa.org

Name That Syndrome!

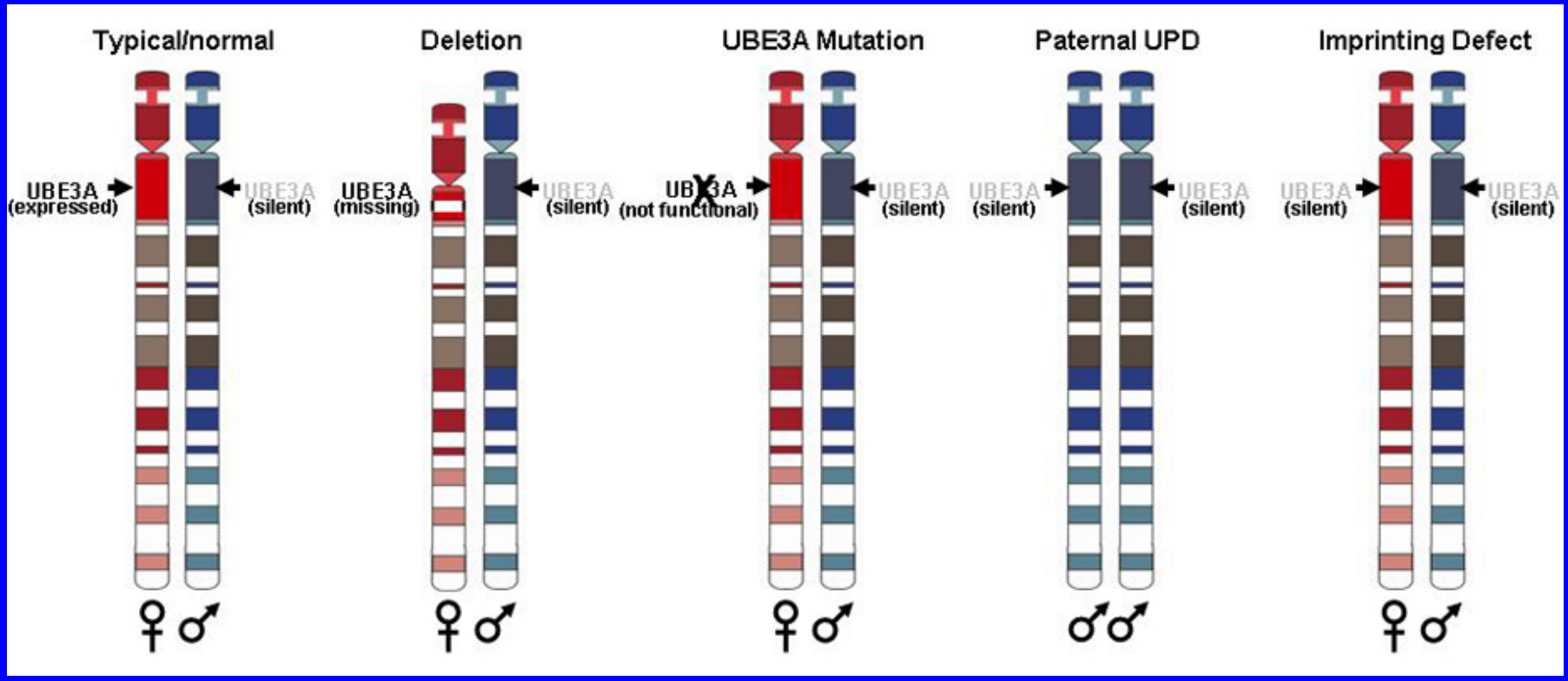
- 1 year old female
- Hx feeding problems
- No words yet
- Not walking yet
- 1st episode tonic-clonic seizure

Characteristics of Angelman

- Severe developmental delay
- Speech impairment
- Ataxia
- Behavioral uniqueness
  - Laughter
  - Hand flapping
  - ↑ excitability
- Typical facies
  - Flat occiput
  - Prognathia
  - Almond-shaped eyes
  - Wide mouth
- Suck/swallow disorder
- Strabismus
- Sleep disturbance

Diagnostic Testing for Angelman

- Methylation studies



Resources for Angelman

- www.angelman.org
- www.international.angelmansyndrome.org

Goodhue