

# The Dysmorphology of Childhood Cancer Syndromes

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# Dysmorphology of Cancer Syndromes

- Genetic alterations cause cancer
- “Cancer predisposition”: increased cancer risk related to constitutional mutations in growth-regulating or DNA repair genes
- Some pediatric cancer syndromes have associated dysmorphology
- Recognition of a cancer-associated syndrome allows for screening and genetic counseling

# Dysmorphology & Cancer Syndromes

## Learning Objectives: See Handout for last two

- Describe 3 congenital anomalies associated with childhood cancer
- Describe a tumor surveillance program for children with sporadic aniridia
- Explain the type of genetic test available for multiple endocrine neoplasia 2B and know how to access [www.genetests.org](http://www.genetests.org)

# Dysmorphology of Childhood Cancer Syndromes Outline

- Present a number of syndromes associated with **childhood cancer**
- Use a body systems approach based on **physical examination findings**
- Summary of genetics and screening recommendations for 12 syndromes

# Outline of Physical Examination

- Somatic overgrowth
- Somatic undergrowth
- Cranium: macrocephaly
- Cranium: microcephaly
- Skin: general
  - **Skin: hyperpigmentation**
  - **Skin: photosensitivity**
- Face
- Eyes
- Mouth and Lips
- Tongue and Jaw
- Cardiac
- Gastrointestinal
- Renal
- Male genitalia
- Skeletal

**Some disorders represented in several body areas**

# Somatic Overgrowth

- Isolated hemihyperplasia (HH)
- Beckwith-Wiedemann syndrome +/- HH
- Sotos syndrome
- Wilms tumor, hepatoblastoma, adrenocorticocarcinoma, neuroblastoma
  
- Simpson-Golabi-Behmel syndrome
- Wilms tumor

# Isolated Hemihyperplasia



2.5 yo with R leg  
hemihyperplasia  
(at screening visit)



2 yo with R leg hemihyperplasia  
and Wilms tumor (no screening)



# Beckwith-Wiedemann syndrome



Somatic overgrowth,  
flat orbital area,  
macroglossia,  
truncal hemihyperplasia  
organomegaly

Screened with q3mo  
abdominal u/s and  
serum AFP: early  
diagnosis of Stage 1  
hepatoblastoma

# Sotos syndrome (cerebral gigantism)



**Somatic overgrowth**  
**Macrocephaly (+4 SD)**  
**broad forehead and**  
**pointed chin, neurologic**  
**impairment, advanced**  
**bone age**

**Low incidence of**  
**embryonal tumors**  
**No formal screening but**  
**teach parents abdominal**  
**exam.**

# Simpson-Golabi-Behmel syndrome



X-linked recessive  
Mild somatic overgrowth,  
nephromegaly,  
macroglossia,  
congenital heart disease  
Distinguish from Beckwith-  
Wiedemann syndrome

Increased risk for  
**Wilms tumor**

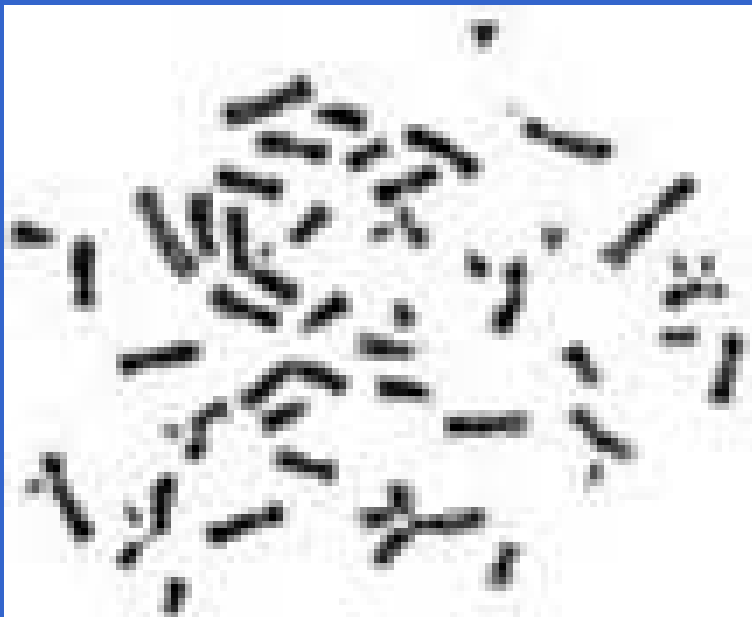
# Undergrowth

- Fanconi anemia syndrome
- Bloom syndrome
- Leukemia, lymphoma
  
- Ataxia telangiectasia (postnatal)
- Lymphoreticular cancer

# Fanconi anemia syndrome



Autosomal recessive  
Mild growth restriction  
Minor and major anomalies in 3/4:  
skin hyperpigmentation,  
radial, renal, cardiac defects,  
esophageal atresia.



Lab dx: Chromosomal breaks  
with diepoxybutane

Pancytopenia 5-10 yo,  
myelodysplasia, leukemia

# Bloom syndrome



Autosomal recessive DNA repair disorder

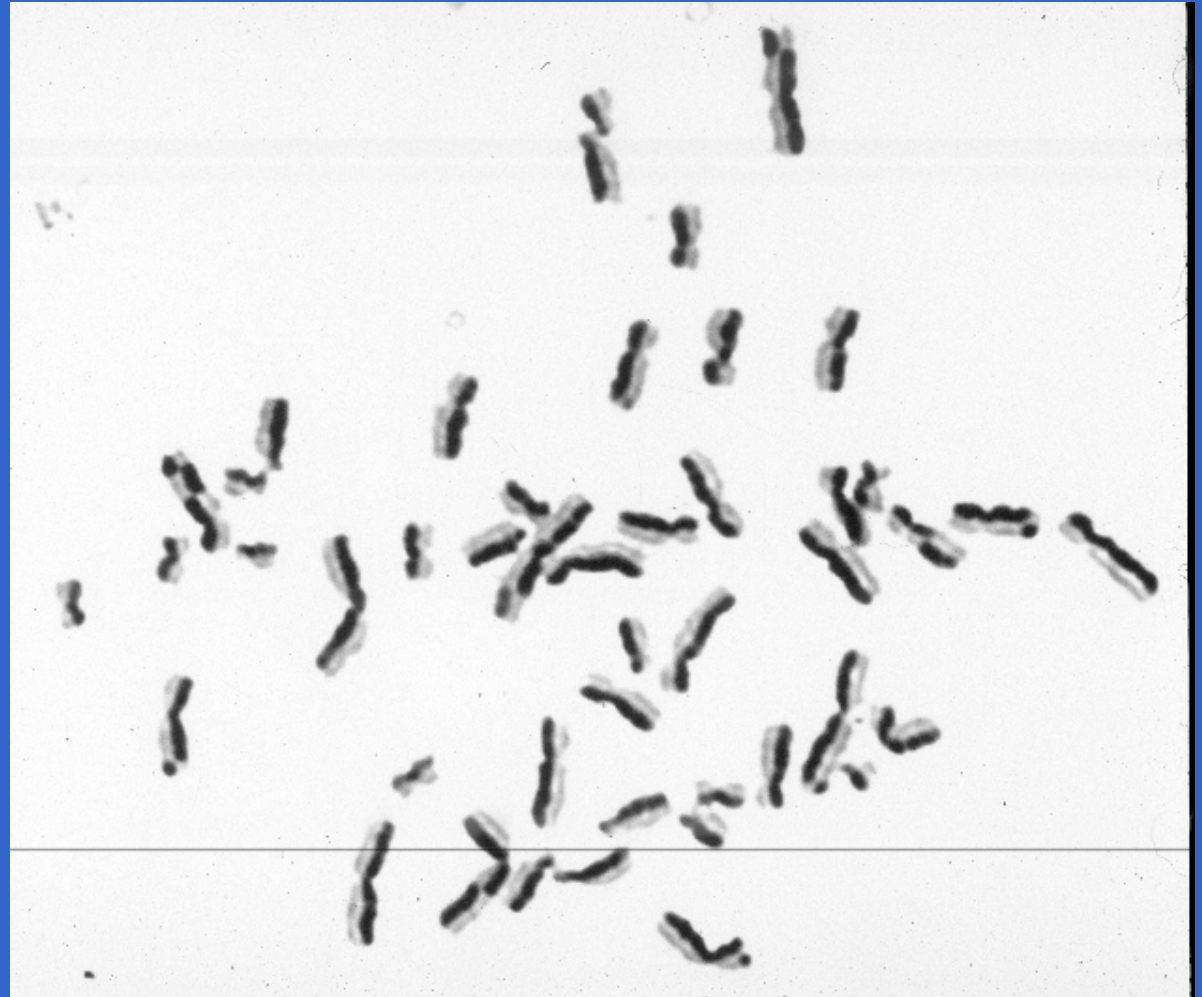
Growth restriction, sun sensitive hypo- and hyperpigmented skin, café au lait spots

Leukemia (leukopenia); Wilms tumor; lymphoma; stomach, colon, breast cancers



# Bloom syndrome

Lab: increased sister chromatid exchange; decreased immunoglobulins



# Cranium: Macrocephaly

- Sotos syndrome
- Wilms tumor, neuroblastoma, hepatoblastoma
- Basal cell nevus syndrome (Gorlin syndrome)
- Medulloblastoma, basal cell carcinoma
- Simpson-Golabi-Behmel syndrome
- Macrocephaly mild but helps distinguish from Beckwith-Wiedemann syndrome (normal OFC)
- Wilms tumor



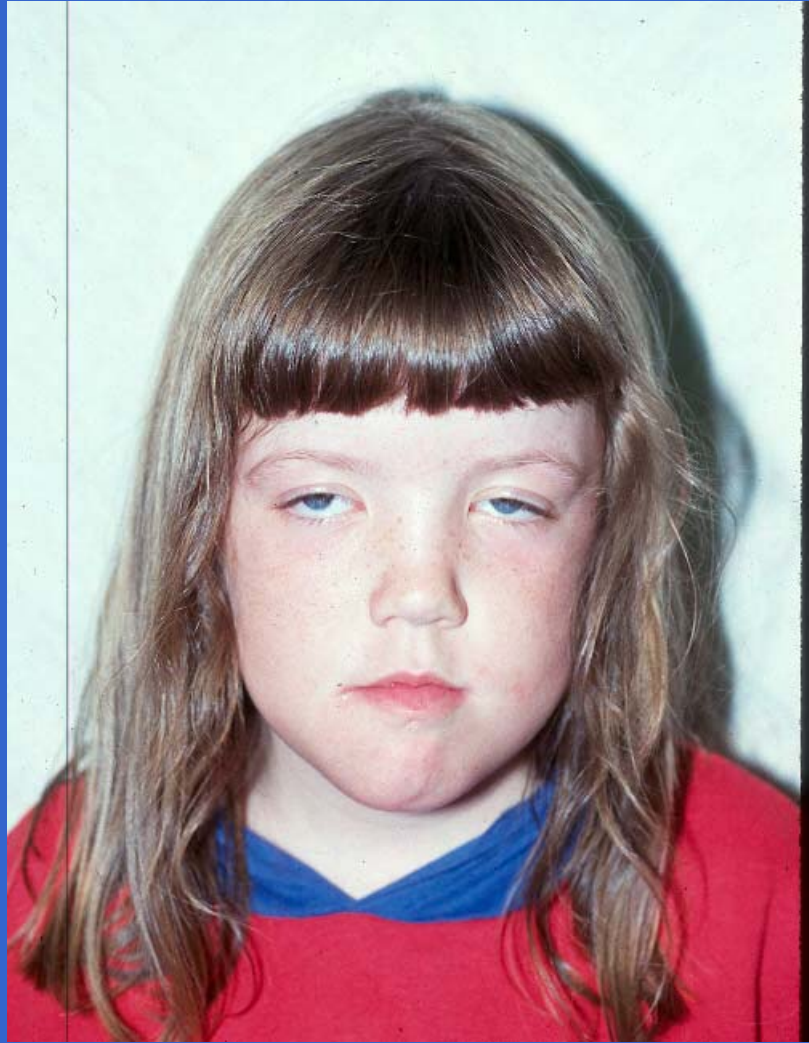
# Sotos syndrome



Macrocephaly (+4 SD)  
with high broad  
forehead, pointed chin  
macrocephaly.  
developmental delay,  
neurologic impairment

Low incidence of  
neuroblastoma, Wilms  
tumor, hepatoblastoma

# Basal cell nevus syndrome



Autosomal dominant  
Macrocephaly, broad forehead, widely spaced eyes, odontogenic keratocyst, cardiac fibroma, bifid ribs, palmar pits, learning disabilities

Medulloblastoma (5%),  
basal cell carcinoma (10 yo here, usually > 20 yo)  
X-ray sensitivity: BCCs

# Basal cell nevus syndrome with medulloblastoma

~10 % of medulloblastoma pts  
2 yo or younger have syndrome



Macrocephaly with broad face and forehead,  
mild increase in eye spacing

# Cranium: Microcephaly

- Fanconi anemia syndrome



- Bloom syndrome



- Xeroderma pigmentosum (acquired)



# Skin

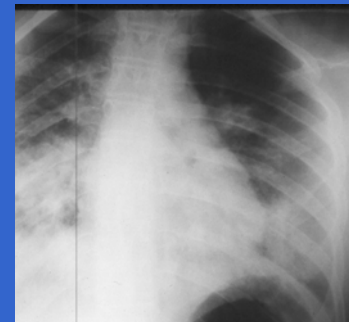
- Telangiectasia (pinnae, conjunctivae)
- Ataxia telangiectasia
- Lymphoreticular, leukemia
  
- Epidermal (sebaceous) cysts
- Gardner syndrome (familial adenomatous polyposis with extracolonic manifestations)
- Colon cancer, hepatoblastoma (<4 yo)

# Ataxia telangiectasia



Autosomal recessive  
Progressive cerebellar ataxia,  
oculocutaneous  
telangiectases, immune  
deficiency, postnatal growth  
deficiency

Lab: elevated AFP >90%  
Non-Hodgkin lymphoma,  
leukemia, increased breast  
cancer risk in carriers  
X-ray sensitivity: cautious  
radiotherapy



16 yo with non-Hodgkin lymphoma

# Skin: Hyperpigmentation

- Neurofibromatosis-1
- Café au lait patches, axillary freckling
- Optic glioma, astrocytoma
- Malignant peripheral nerve sheath tumor
  
- Fanconi anemia



# Neurofibromatosis, type 1



Autosomal dominant  
Tumor suppressor gene  
1/3000 individuals, 50% new  
mutations

Café au lait patches, axillary  
freckling, dermal neurofibromas

Optic glioma (15%), astrocytoma,  
malignant peripheral nerve  
sheath tumor arising from  
plexiform neurofibroma, leukemia

Fatal MPNST arising from diffuse plexiform  
neurofibroma. Note generalized hyper-  
pigmentation/hair growth in addition to CAL  
spots

# Skin: Photosensitivity/Hyperpigmentation

- Bloom syndrome
- Leukemia, lymphoma  
Wilms tumor
  
- Xeroderma pigmentosum
- UV-induced skin cancers



# Xeroderma pigmentosum



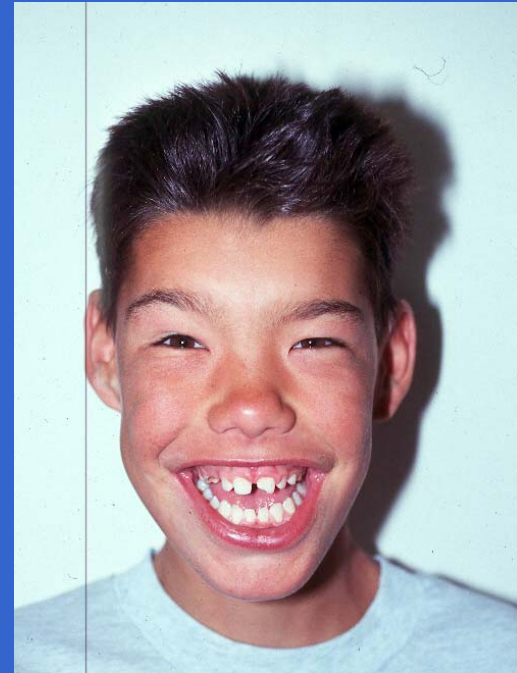
Autosomal recessive heterogeneous group of disorders with similar clinical features. Defective nucleotide excision repair after UV damage

Skin and ocular photosensitivity with freckles in exposed areas. 30% with progressive neurologic deterioration

2000X increase in skin and ocular cancers: basal cell, squamous cell and malignant melanoma (~8 yo)

# Face & Orbits

- Ocular hypertelorism
- Basal cell nevus syndrome
- Simpson-Golabi-Behmel syndrome



# Eyes

- Aniridia
- WAGR syndrome (del 11p13)
  - Wilms tumor, aniridia, genital anomalies, mental retardation
- Bulbar telangiectasia
- Ataxia telangiectasia



# WAGR syndrome

- Multiple malformation syndrome with:
- **Wilms tumor** in ~40%: led to the localization of the WT1 gene at 11p13
- **Aniridia** (sporadic: 2/3 of aniridia is AD due to PAX6 gene mutations/deletions)  
**Readily diagnosed in a neonate**
- **Genital anomalies**
- **Retardation of growth and development**

# Phenotype of WAGR syndrome



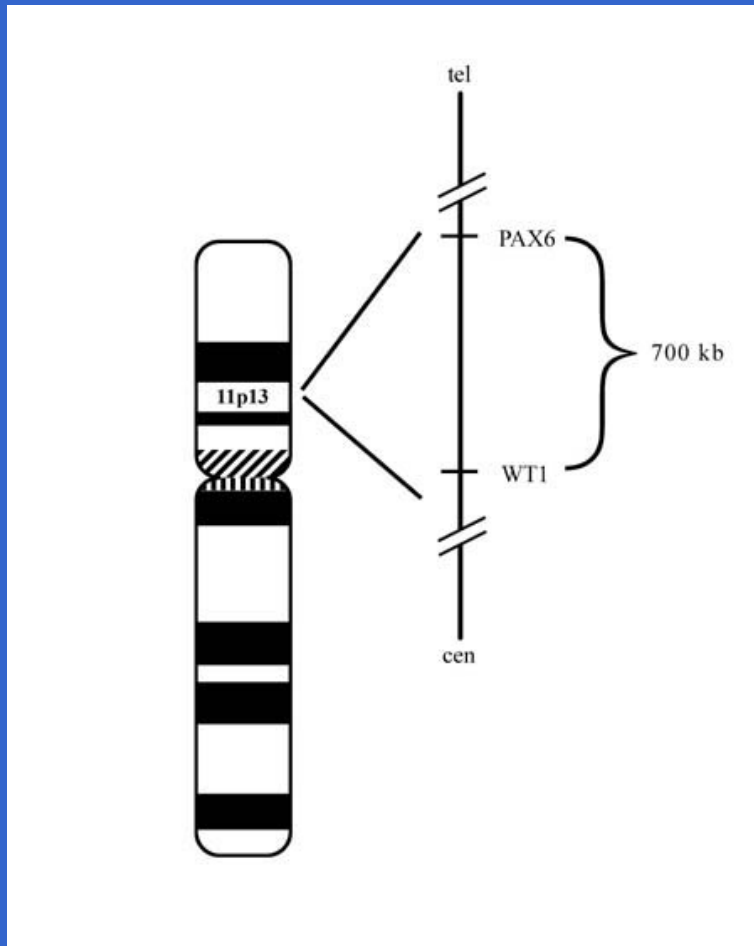
Aniridia



Retarded boy with WAGR syndrome and blindness due to congenital glaucoma caused by aniridia. No Wilms tumor, but has late-onset kidney dysfunction.

Mild genital anomaly in the boy: undescended R testis and small phallus

# WAGR syndrome



Due to deletion of the distal band 11p13, a small region which includes the PAX6 gene (regulates iris/eye development) and WT1 gene (regulates kidney and male genital development and also a *tumor suppressor gene*)

# Mouth/Lips

- Prominent fleshy lips, mucosal neuromas
- Multiple endocrine neoplasia 2B
- Medullary thyroid carcinoma, pheochromocytoma
  
- Mucocutaneous hyperpigmentation
- Peutz-Jeghers syndrome
- Hamartomatous GI polyps; colorectal, esophageal, gastric, breast, ovarian and pancreatic cancers

# Multiple endocrine neoplasia 2B



Autosomal dominant  
Mucosal neuromas of the lips and tongue, enlarged lips, ganglioneuromatosis of the GI tract (diarrhea), asthenic “Marfanoid” build

Medullary thyroid carcinoma in early childhood, bilateral pheochromocytoma

Pt’s diagnosis suggested by a pathologist after biopsy of tongue lesions: led to presymptomatic diagnosis of **medullary thyroid carcinoma**

# Peutz-Jeghers syndrome



Autosomal dominant

Mucocutaneous  
pigmentation

GI hamartomatous polyposis  
Intestinal and extraintestinal  
malignancies, including  
breast, pancreatic

5 yo girl with hx of rectal  
“juvenile polyp” @ 1 yo;  
pigmented spots noted at  
4.5 years; now has gastric  
polyps. Pathology: + PJS

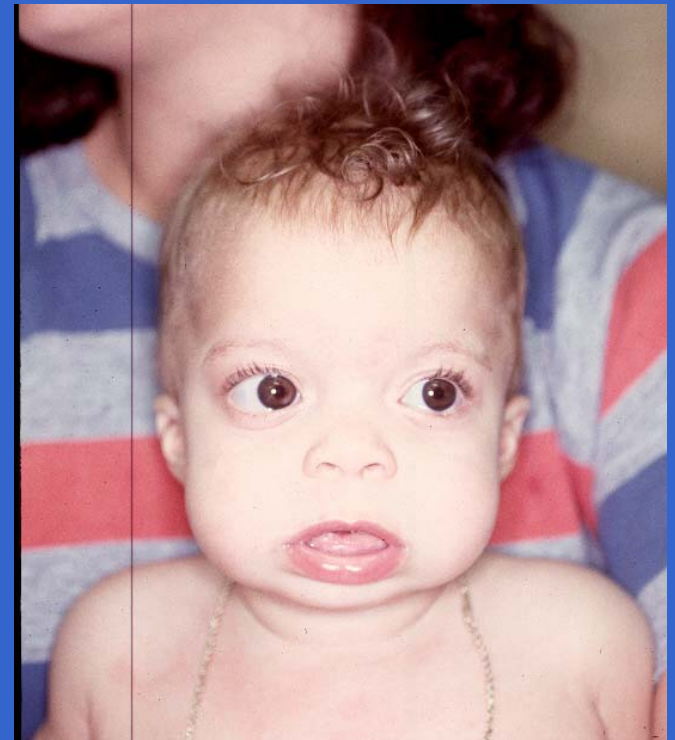
**DNA study: + for mutation in  
LKB1 gene. This will allow  
testing of her parents.**

# Tongue & Jaw

- **Macroglossia**
- Beckwith-Wiedemann syndrome
- Simpson-Golabi-Behmel syndrome
  
- **Odontogenic keratocysts of jaw**
- Basal cell nevus syndrome

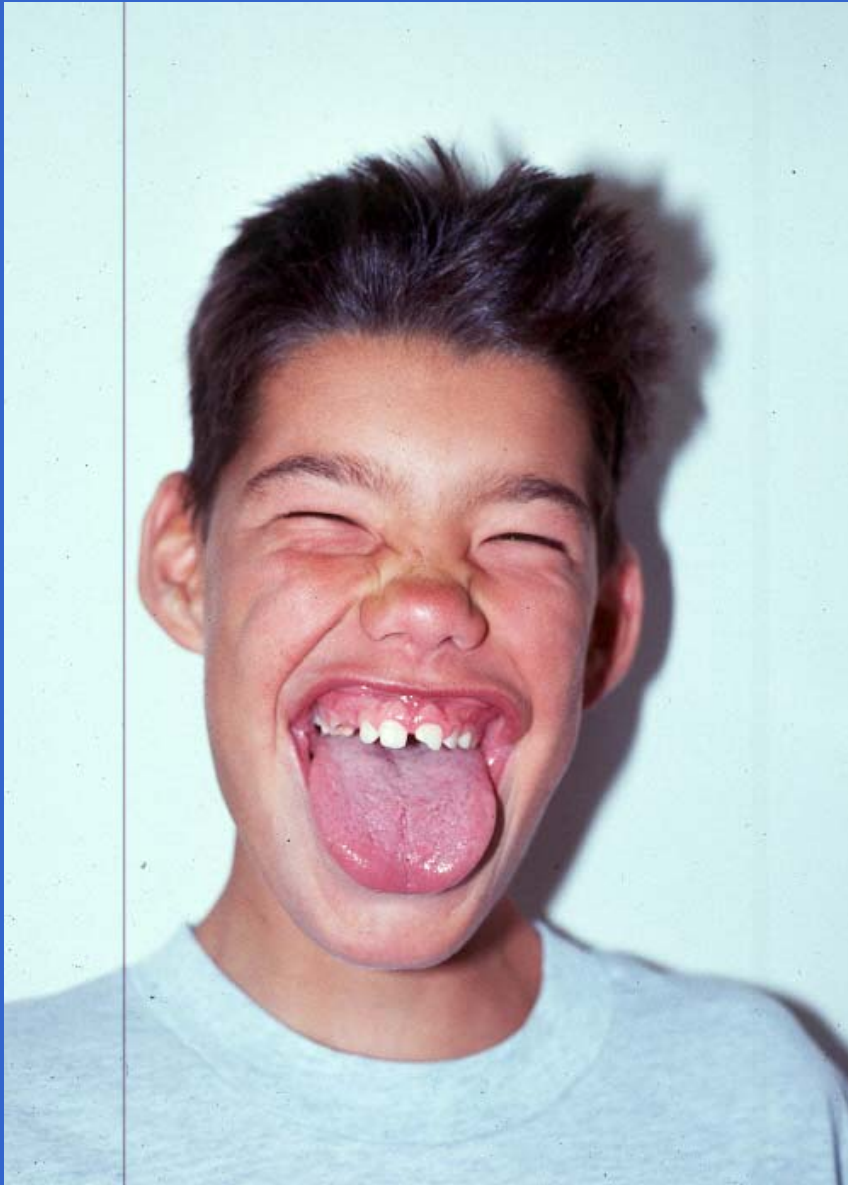
# Beckwith-Wiedemann syndrome

**Macroglossia:** usually managed without tongue reduction surgery



**Macroglossia and cleft palate**

# Simpson-Golabi-Behmel syndrome



X-linked recessive

Mild overgrowth

Nephromegaly

Macroglossia

Congenital heart disease

Differentiate from

Beckwith-Wiedemann  
syndrome

Increased risk for

Wilms tumor

# Basal cell nevus syndrome (Gorlin)



Autosomal dominant  
Odontogenic keratocyst,  
macrocephaly, broad  
forehead, widely spaced  
eyes, cardiac fibroma,  
bifid ribs, palmar pits,  
learning disabilities  
Medulloblastoma (5%),  
basal cell carcinoma (10  
yo here, usually > 20 yo)

Pt diagnosed after evaluation  
for odontogenic keratocyst

# Heart Defects

- Fanconi anemia



- Down syndrome

- AML 30X population risk (~1%)



# Gastrointestinal Anomalies

- Omphalocele, umbilical hernia
- Beckwith-Wiedemann syndrome
- Tracheoesophageal fistula, atresias, anorectal malformations
- Fanconi anemia syndrome
- Enteric neuroma (diarrheal syndrome)
- Multiple endocrine neoplasia 2B



# Renal Anomalies

- Ectopic, horseshoe, dysplastic, absent
- Fanconi anemia
- Hyperplasia, cysts, hydronephrosis
- Beckwith-Wiedemann syndrome
- Simpson-Golabi-Behmel syndrome
- Normal 46,XX females with unexplained glomerulosclerosis, proteinuria
- Denys-Drash syndrome due to WT1 mutation



# Male Genital Anomalies

- Severe hypospadias, ambiguous genitalia
- Denys-Drash syndrome
  - Renal failure due to diffuse mesangial sclerosis, **Wilms tumor**
- Asymmetric ambiguous genitalia
- X0/XY mixed gonadal dysgenesis
- **Gonadoblastoma**
- Milder genital anomalies: undescended testes, hypospadias
- WAGR syndrome: **Wilms tumor**
- Fanconi anemia: **leukemia**

# Denys-Drash syndrome

Autosomal dominant due to  
WT1 mutation (de novo)

Genital anomalies, renal failure  
(diffuse mesangial sclerosis)

>90% Wilms tumor



Perineal hypospadias,  
UDT, penoscrotal  
transposition



18 mo boy with  
bilateral WT and  
severe genital  
anomalies

# Ambiguous genitalia: 45,X/46,XY mosaicism

## Mixed gonadal dysgenesis



Term newborn with **ambiguous genitalia**. Small gonad (testis) palpable in right labioscrotal fold. Urethral opening on perineum. No vaginal opening. Has unicornuate uterus/tube associated with streak gonad on left. Streak gonad removed due to risk for **gonadoblastoma**. Sex of rearing a complex decision = male here.

# Genital phenotype for 45,X/46,XY depends on mode of ascertainment

- Newborn with ambiguous genitalia
  - Incidental prenatal amnio: male
  - Short girl evaluated for Turner syndrome: female
  - Intra-abdominal gonads must be removed because of risk for gonadoblastoma – 50% of which have coexistent malignant dysgerminoma.
- Girls with Turner syndrome should have 200 additional cells screened for Y chromosome (FISH) ~6 % mosaic for XY.

# Male Hypogonadism

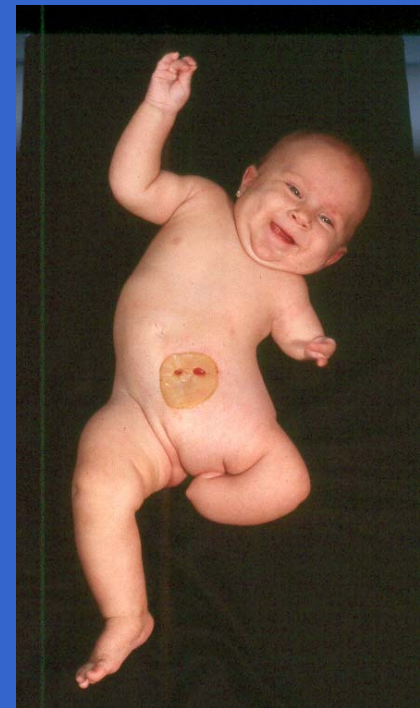
- Small firm testes - postpubertal
- Klinefelter syndrome - 47,XXY; 48,XXXY
- Germ cell tumor, breast cancer (female risk)



47,XXY boy with pineal germ cell tumor

# Skeletal Anomalies

- Radial ray defects
  - Clinodactyly
  - Abnormal toes
  - Vertebral anomalies
  - See below!
  - Fanconi anemia
- 
- If you think it's VACTERL association - consider Fanconi anemia
- Vertebral, Anal, cardiac, TEF, Renal, Radial, Limb



VACTERL association

# Genetic Testing, Cancer Screening and Genetic Counseling

*12 Childhood Cancer Syndromes*

# Sporadic aniridia/ WAGR syndrome

- Chromosomal deletion of 11p13
- FISH now available for del WT1
- Wilms tumor (40%), aniridia, genital anomaly, mental retardation
- Renal u/s and q 3 mos until 6 yo
- Daily caretaker abdominal exam

# Multiple endocrine neoplasia 2B

- AD due to RET gene mutation at 10q11
- Proto-oncogene
- Multiple mucosal neuromas, intestinal ganglioneuromatosis, large corneal nerves, marfanoid habitus, thyroid carcinoma (100%), pheochromocytoma
- DNA diagnostic test available (95% detection) – prophylactic thyroidectomy

# Denys-Drash syndrome

- Sporadic AD due to WT1 mutation at 11p13
- DNA testing of WT1 now available
- Tumor suppressor gene, also a transcription factor for genitourinary morphogenesis
- Genital anomaly, nephropathy and WT (>90%)
- Renal u/s q 3 mos until 6 years
- Daily caretaker abdominal exam

# Beckwith-Wiedemann syndrome

- Due to over expression of IGF-2 at 11p15
- 15% cases familial
- High resolution chromosome study, IGF2 expression studies
- Abdominal u/s q 3 mos until 7 yo.
- Serum AFP q 3 mos until 4 yo.
- Daily caretaker abdominal exam

# Neurofibromatosis, type 1

- AD due to NF1 mutation at 17q11.2
- Tumor suppressor gene
- 1/3000 individuals, 50% new mutations
- CAL patches, axillary/inguinal freckling, dermal neurofibromas, optic glioma and other neural tumors, leukemia, MPNST from plexiform neuroma
- Annual eye and physical exam

# Fanconi anemia

- AR chromosomal breakage syndrome
- Pancytopenia and anomalies; 1/4 of patients have no physical stigmata
- Progressive marrow failure: elevated MCV
- Bone marrow transplant if progressive
- Leukemia, hepatocellular carcinoma
- Consider CBC q3-6 mos

# Xeroderma pigmentosum

- AR with multiple loci
- DNA excision repair disorder: UV damage
- Normal skin at birth, progressing to freckling and skin cancers, survival to 10-20 yo
- DeSanctis-Cacchione variant: progressive microcephaly and dementia
- Frequent dermatologic assessment; minimize sun exposure and protect eyes

# Basal cell nevus syndrome (Gorlin)

- AD due to PTCH gene mutation at 9q
- Broad facies, odontogenic cysts, bifid ribs, palmar pits, ovarian fibromas, calcified falx, cardiac fibromas
- Medulloblastoma, basal cell carcinoma beginning in childhood
- Biannual neurologic exam and annual MRI until 7 yo for medulloblastoma, frequent dermatologic exams starting age 10 yo

# Ataxia telangiectasia

- AR due to ATM gene mutation at 11q22.3
- DNA repair disorder
- Progressive ataxia, oculocutaneous telangiectasia, high serum AFP, immunodeficiency
- Carriers with increased breast cancer risk
- Lymphoma, lymphoid leukemia, breast cancer
- Monitor health status closely
- Question of screening female carriers for breast cancer: mutation analysis available

# Bloom syndrome

- AR due to BLM mutation at 15q26.1
- DNA repair disorder due to a helicase mutation
- Increased sister chromatid exchange
- Pre- and postnatal growth retardation, telangiectatic facial rash, acquired hyperpigmentation
- Leukemia, lymphoma, Wilms tumor; stomach, colon, breast carcinoma
- Some have recommended u/s screening of children for WT; close health monitoring of older individuals

# Gardner syndrome

- AD, familial adenomatous polyposis (FAP) with extra-colonic manifestations
- Due to APC mutation at 5q21-22
- Tumor suppressor gene
- Jaw and skull osteomas, sebaceous/epidermoid cysts, congenital hypertrophy of retinal pigment epithelium,
- Hepatoblastoma; colon/GI, thyroid, other cancers
- Diagnostic DNA test detects 95%; screening for hepatoblastoma until age 4 years; sigmoidoscopy @ 10 yo then colonoscopy when polyps detected; colectomy when adenomas emerge

# XO/XY mixed gonadal dysgenesis

- Sporadic chromosomal disorder
- If prenatally ascertained, often have normal male genitalia
- Postnatal ascertainment of ambiguous genitalia, often with asymmetry
- Turner syndrome females may have XY mosaicism (~ 6 %)
- Gonadoblastoma prevented by gonadectomy

# Dysmorphology of Cancer Syndromes

- Clericuzio CL (1999): Recognition and management of childhood cancer syndromes: a systems approach. *Am J Med Genet.* 89(2):81-90.
- Nichols KE, Li FP, Haber DA, Diller L (1998): Childhood cancer predisposition: Applications of molecular testing and future applications. *J Ped* 132:389-97.
- Hodgson SV, Maher ER. *A Practical Guide to Human Cancer Genetics.* Cambridge University Press, UK. 2<sup>nd</sup> Ed. 1999