GENETIC DISORDERS

IN THE GENERAL PEDIATRIC SETTING

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OBJECTIVES

- Explain clinical risk factors for a given genetic disorder.
- Discuss the morphological changes and clinical manifestations of a given genetic disorder.
- Describe the role of genetic testing and counseling for genetic disorders and when a genetics referral should be made.

“GENETIC DISORDERS ARE COMPLEX, MULTIORGAN, SYSTEMIC CONDITIONS, AND THE CARE OF PERSONS WITH THESE DISORDERS CAN ALSO INVOLVE MULTIPLE MEDICAL SPECIALTIES.” -MEDICAL GENETICS, 5TH EDITION, JORDE, 2016, CHAPTER 15

TERATOGEN

- A **teratogen** is an agent that can cause malformations of an embryo or fetus. This can be a chemical substance, a virus or ionizing radiation.
- Contact in the first trimester of pregnancy has the greatest effects on the fetus.
- Agent is not problematic for adults.
- Crosses the placenta
- Affected by maternal metabolism of agent

COMMON TERATOGENS

CHEMICAL AGENTS

- Alcohol
- Tobacco
- Opioids
- Illicit drugs- marijuana, cocaine, ecstasy, amphetamines, heroin
- Ionizing agents
- Organic mercury componds
- Herbicides
- Prescription and OTC drugs

INFECTIOUS AGENTS

- Rubella
- Cytomegalovirus
- Varicella
- Herpes Simplex
- Toxoplasma
- Syphilis

GOVERNMENT WARNING: (1) According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects. (2) Consumption of alcoholic beverages impairs your ability to drive a car or operate machinery, and may cause health problems.

PATHOGENESIS OF DEVELOPMENTAL DISORDERS

- **Hereditability**-statistic used in the fields of breeding and genetics that estimates the degree of variation in a phenotypic trait in a population that is due to genetic variation between individuals in that population

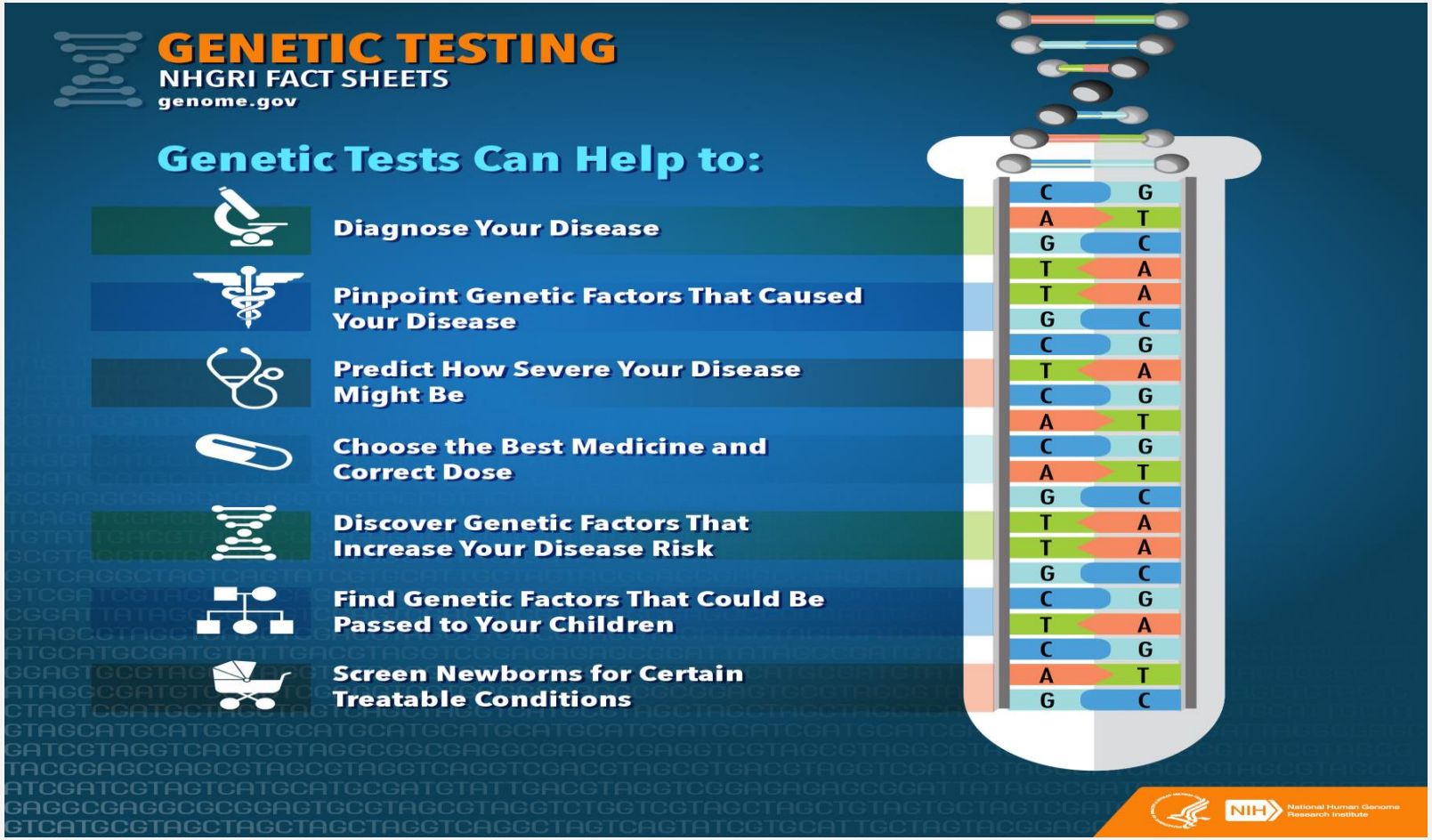
- **Deficiencies**-a shortage of substances necessary to health

- **Physiologic Defects-** a defect in the way a person's body functions

- **Genetic Mutations-** permanent alteration/change in the DNA sequence that makes up a gene

GENETIC TESTING

- **Genetic Testing-** a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder.



GENETIC COUNSELING

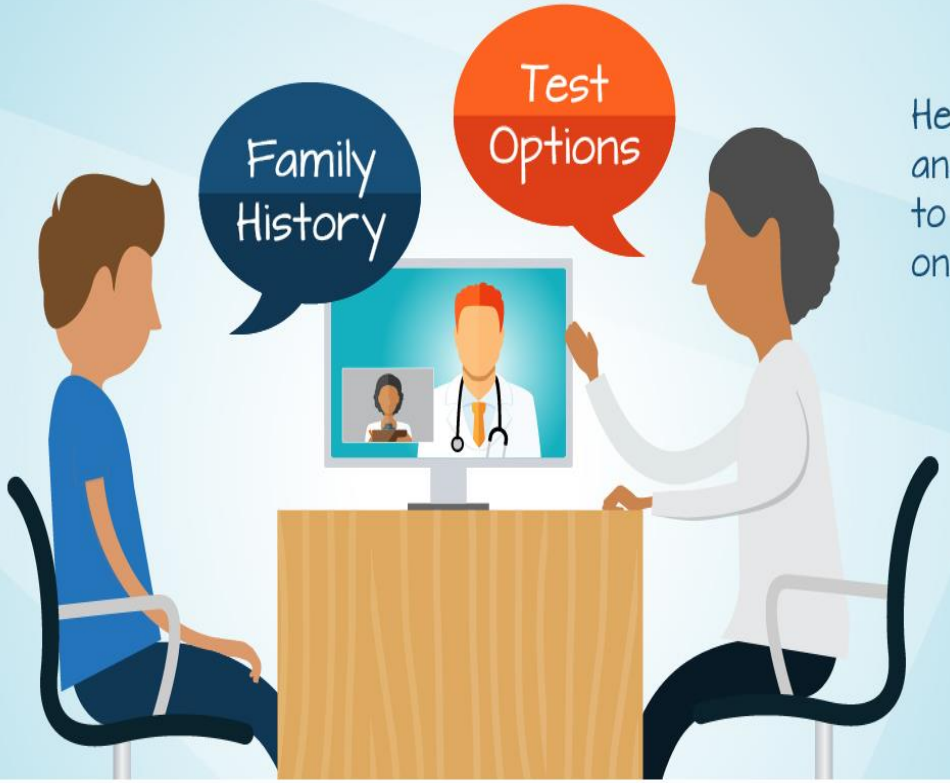
- **Genetic Counseling-** a process to evaluate and understand a family's risk of an inherited medical condition.
- G**enetic counselor -** a healthcare professional with specialized training in medical genetics and counseling.

Your Experience with a Genetic Counselor

Appointment with Your Genetic Counselor

What test results may or may not tell you and how results may be used

Review medical history and understand inherited risks



Health care and support options to consider based on possible results

Identify testing options and decide whether to proceed

www.FindAGeneticCounselor.com

“ALL DISCUSSIONS OF NATURAL HISTORY, PROGNOSIS, MANAGEMENT, RISK DETERMINATION, OPTIONS FOR PRENATAL DIAGNOSIS, AND REFERRAL TO GENETIC SUPPORT GROUPS (ALSO TERMED *GENETIC ADVOCACY GROUPS*) DEPEND ON AN ACCURATE DIAGNOSIS OF THE PATIENT'S CONDITION.” -MEDICAL GENETICS, 5TH EDITION, JORDE, 2016, CHAPTER 15

ANGELMAN SYNDROME

- **Etiology-**single gene disorders
- **Pathogenesis-** Imprinting involves transcriptional silencing of the maternal copies certain genes during gametogenesis. Only one functional copy exists. Loss of functional allele by deletion gives rise to disease.
- **Morphological Changes-** deletion of band q 12 on long arm of maternal chromosome 15, prominent chin, deep set eyes, wide mouth protruding tongue, wide spaced teeth
- **Clinical Manifestations-** ataxic gait, seizures, intellectual disability, speech impairment and inappropriate laughter
  - **"Happy Puppet Syndrome"**

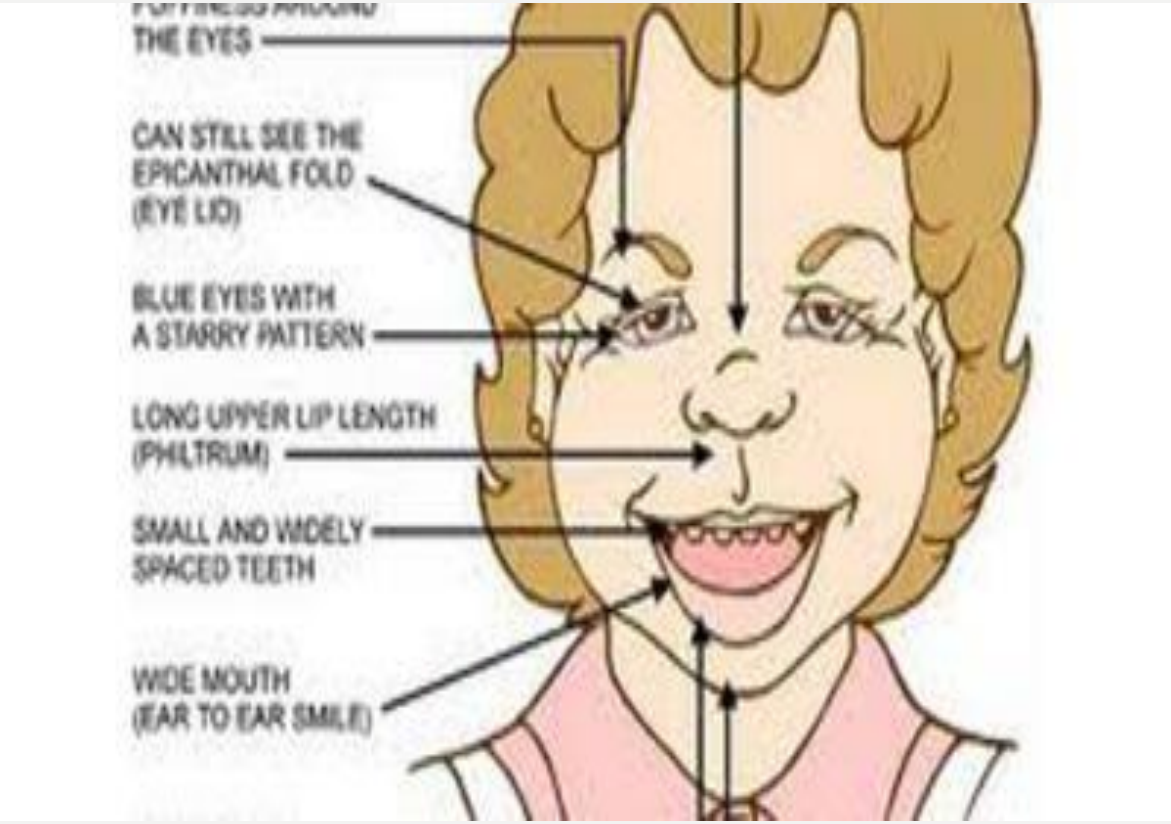
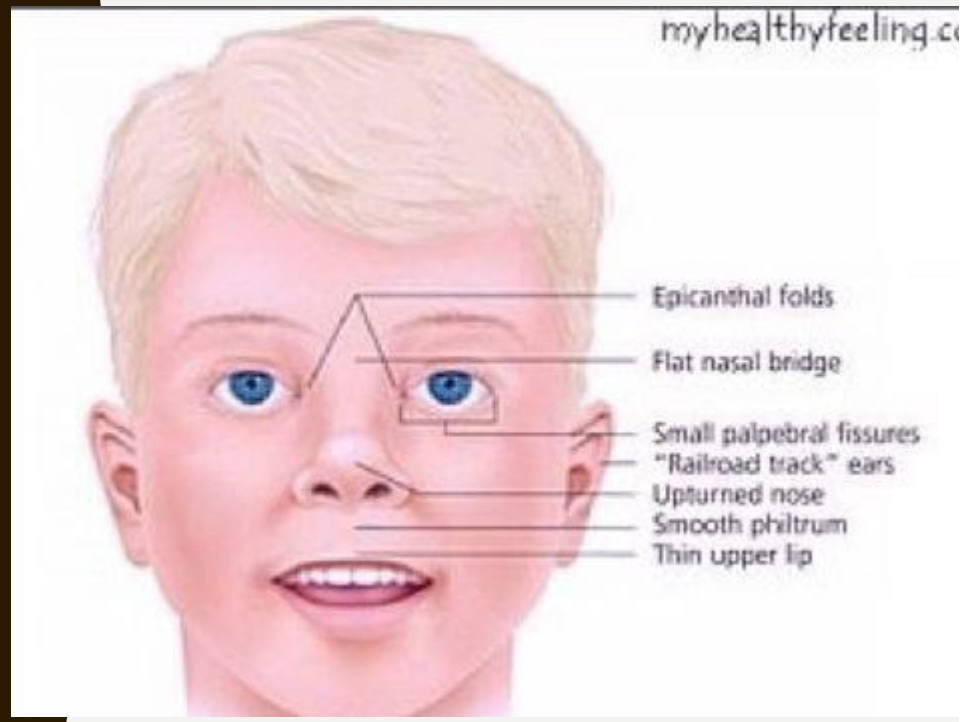


Photo: Achievement Center of Texas

Photo: Angelman Syndrome Foundation

PRADER- WILLI SYNDROME

- **Etiology-** single gene disorder
- **Pathogenesis-**Imprinting involves transcriptional silencing of the paternal copies certain genes during gametogenesis. Only one functional copy exists. Loss of functional allele by deletion gives rise to disease.
- **Morphological Changes-** deletion of band q12 on long arm of paternal chromosome 15, short stature, small hands and feet, hypogonadism, thin lip, broad flat nasal bridge
- **Clinical Manifestations-** mental retardation, hypotonia, obesity



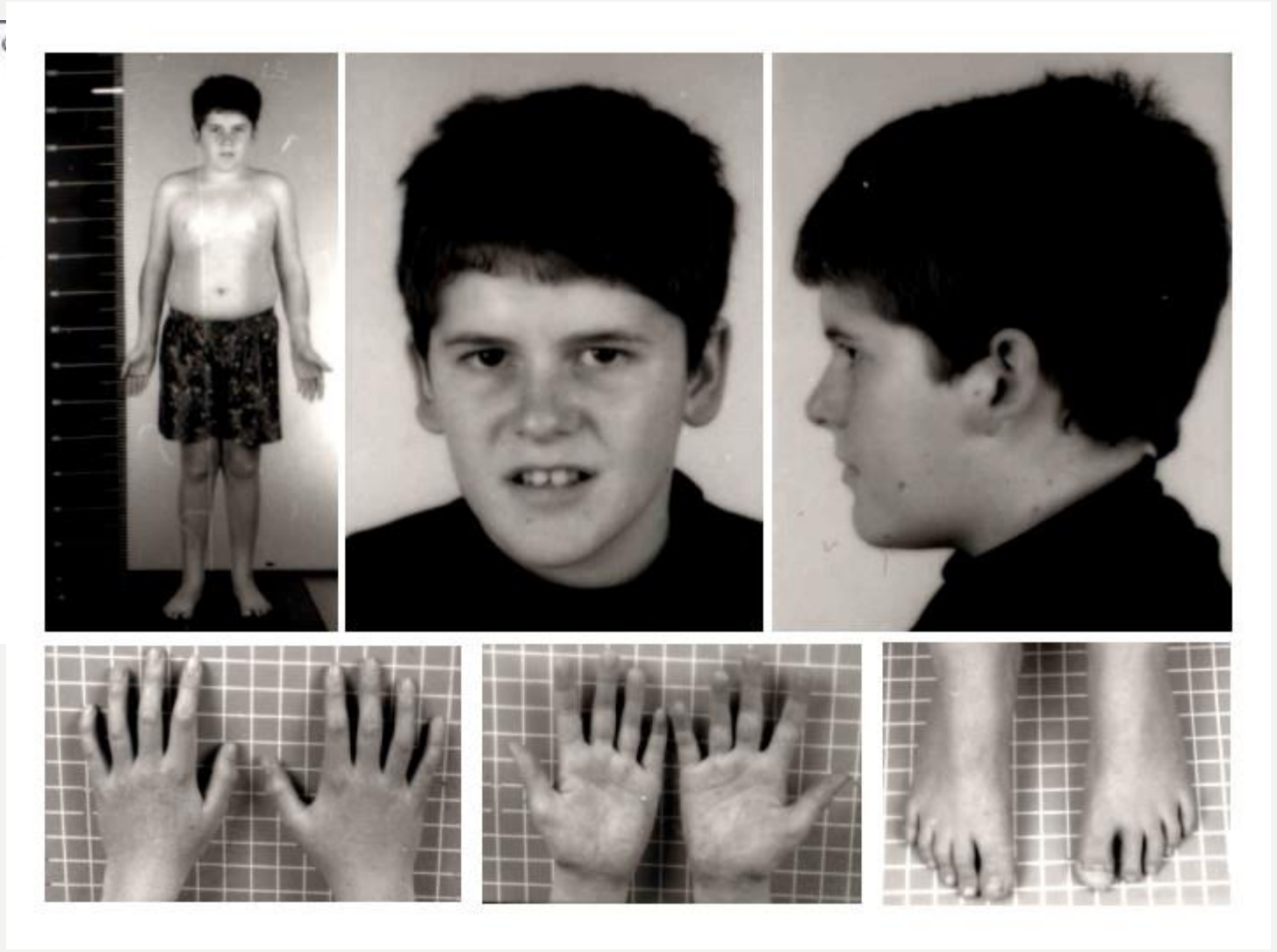
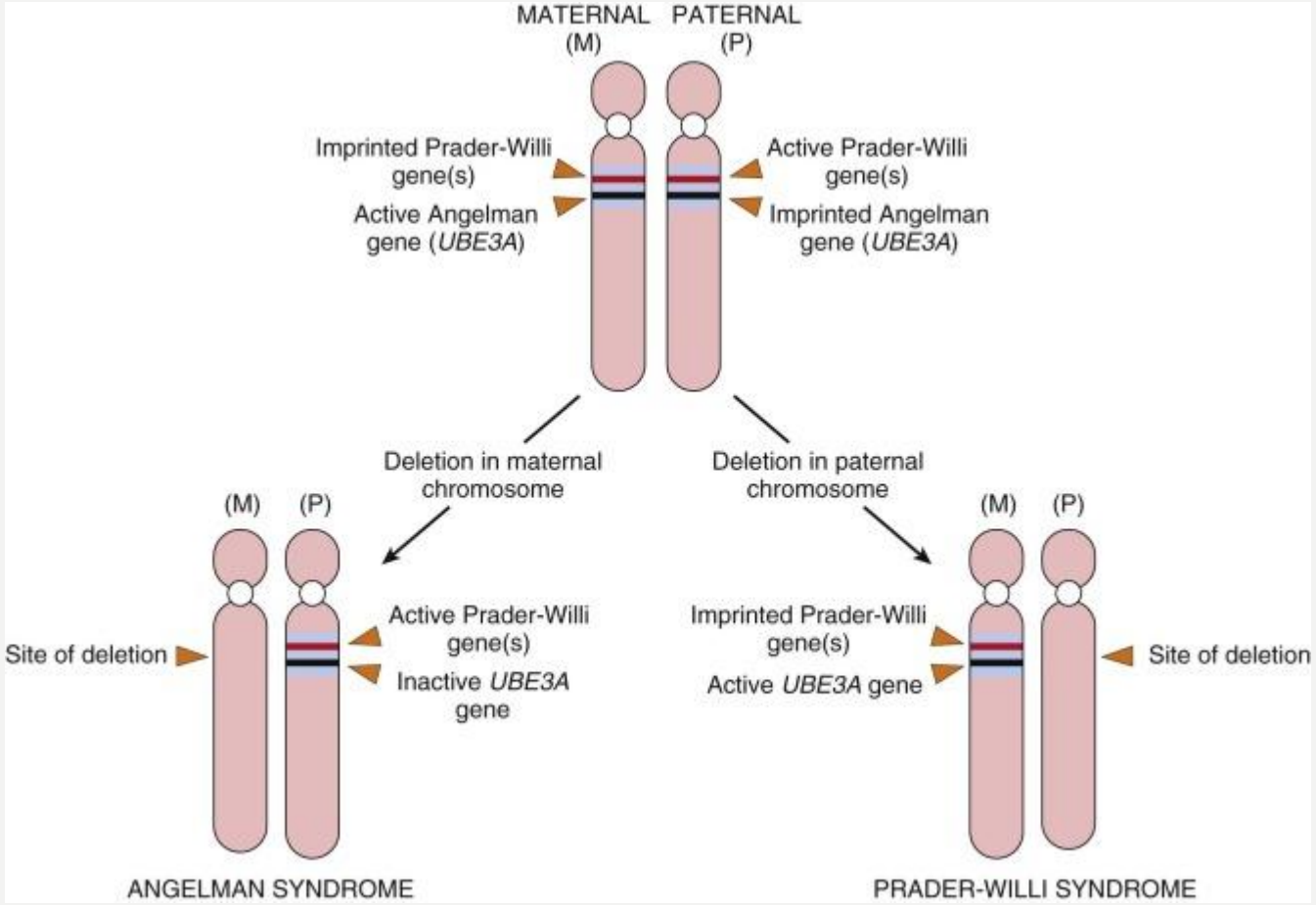


Photo: BMC Medical Genetics. 6



Genetic Disorders
Kumar, Vinay, MBBS, MD, FRCPath, Robbins and Cotran Pathologic Basis of Disease, Chapter 5, 137-183

BIOTINIDASE DEFICIENCY

- **Etiology-** genetic mutation in the BTD gene
- **Pathogenesis-**mutations in the BTD gene reduces or eliminates the activity of biotinidase which removes biotin, when biotin builds up it impairs the activity of biotin dependent carboxylases that lead to toxic compounds in the body
- **Morphological Changes-** BTD gene 3p25 mutation, cannot recycle endogenous biotin and develops a secondary dietary deficiency
- **Clinical Manifestations-** develops at 3 to 6 months of age, seizures, hypotonia, breathing problems, vision loss, ataxia, skin rashes, hair loss, fungal infections, developmental delay, poor feeding, lethargy

Photo: The University of Iowa, Iowa Now

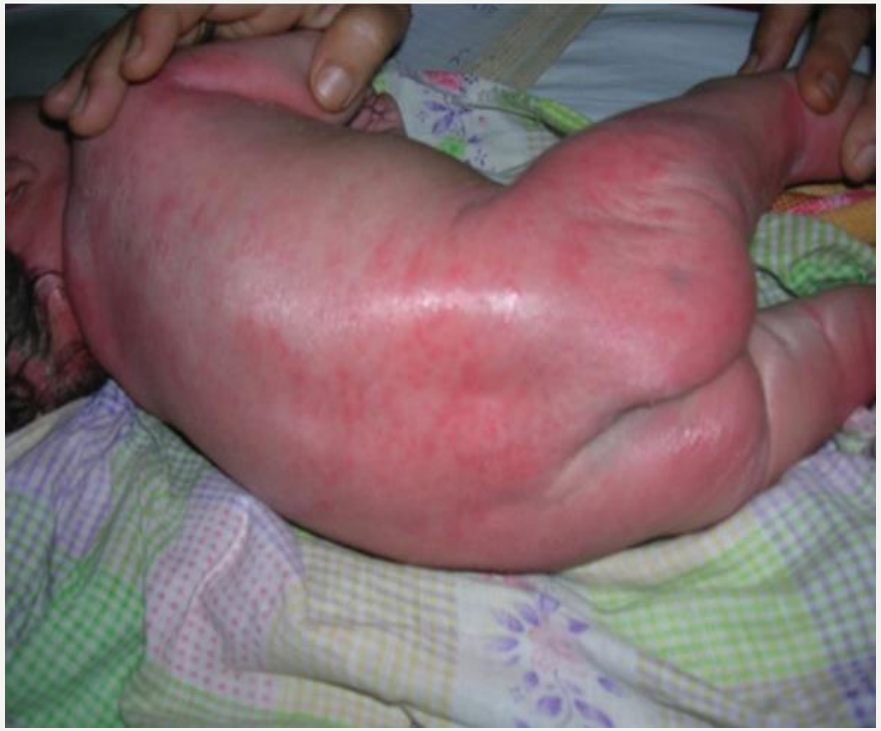


Photo: Semantic scholar

CONGENITAL ADRENAL HYPERPLASIA

- **Etiology**
  - Approximately 95% of cases of CAH are caused by mutations in *CYP21A2*
- **Pathogenesis**
  - Genetic mutation
  - 21-hydroxylase characterized by cortisol deficiency, variable deficiency of aldosterone, and an excess of androgens
  - More than 75% of mutant *CYP21A2* alleles are caused by gene conversion ‡ in which deleterious mutations are transferred to *CYP1A2*. These mutations result in a protein product that lacks normal 21-hydroxylase activity.
- **Morphological Changes**
  - ambiguous genitalia in females, adrenal cortex is thickened and nodular
- **Clinical Manifestations**
  - hypernatremia, hyperkalemia,

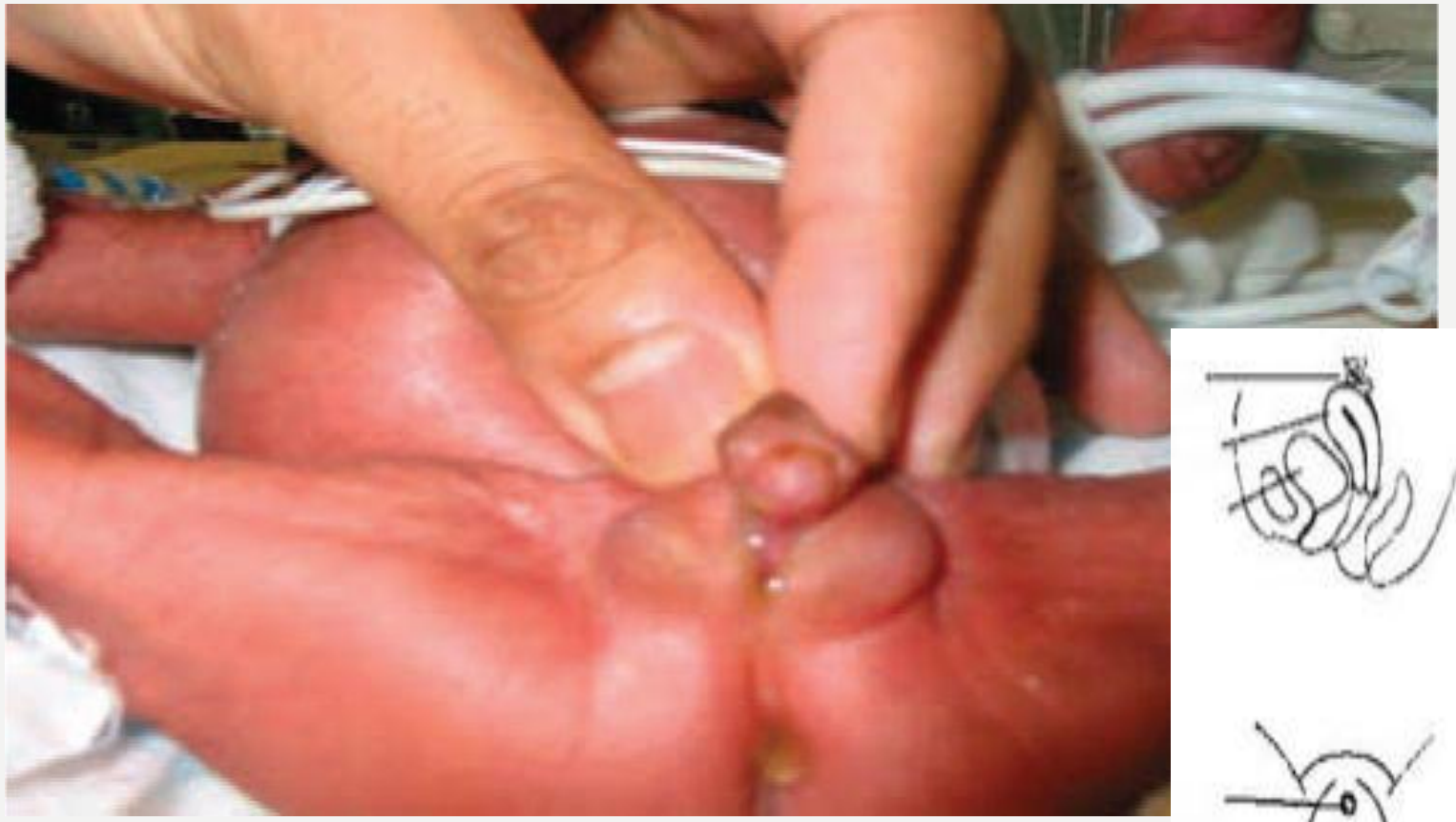


Photo: Obgyn Key

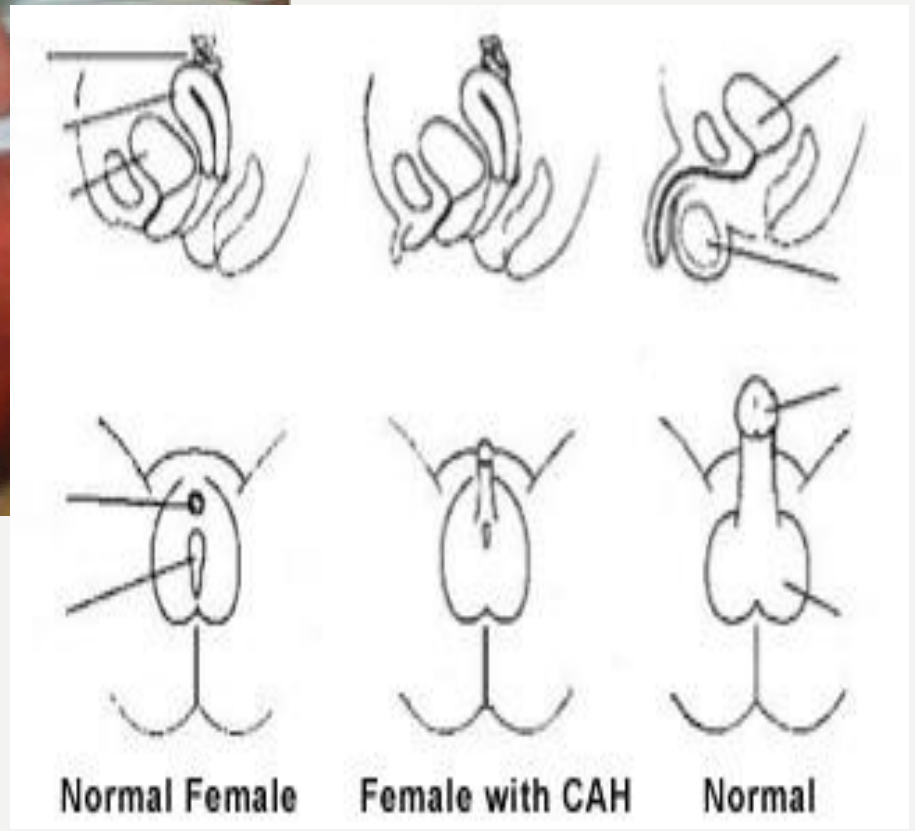
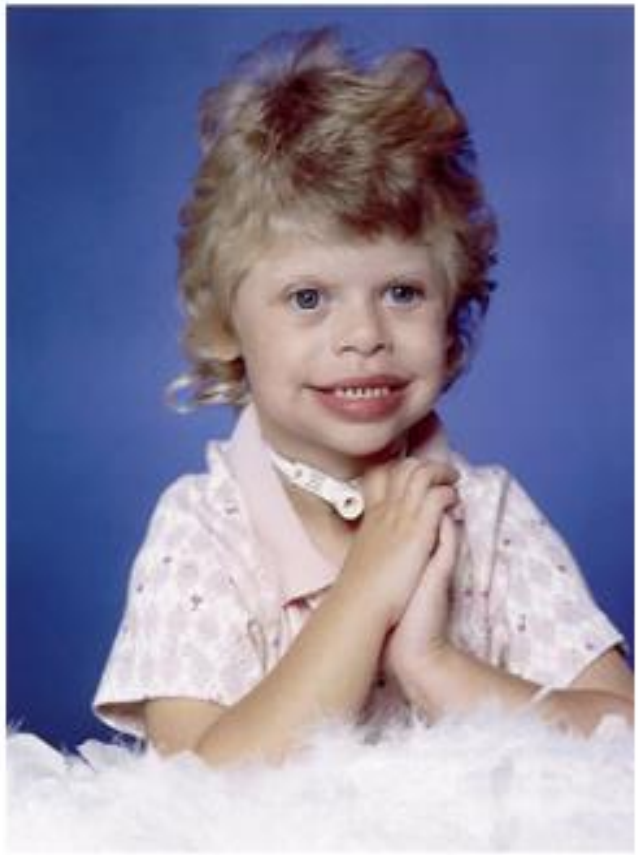


Photo: The ZB Foundation

CRI DU CHAT SYNDROME

- **Etiology-** genetic deletion
- **Pathogenesis-** deletion of the short arm of chromosome 5
- **Morphological Changes-** tracheal hypoplasia, microcephaly, craniofacial dysmorphism (hypertelorism, epicanthic folds, low set malformed ears), cleft lips and palate, congenital heart disease
- **Clinical Manifestations-** catlike cry during infancy which is the result of tracheal hypoplasia, low birth weight, failure to thrive, hypotonia, developmental disability



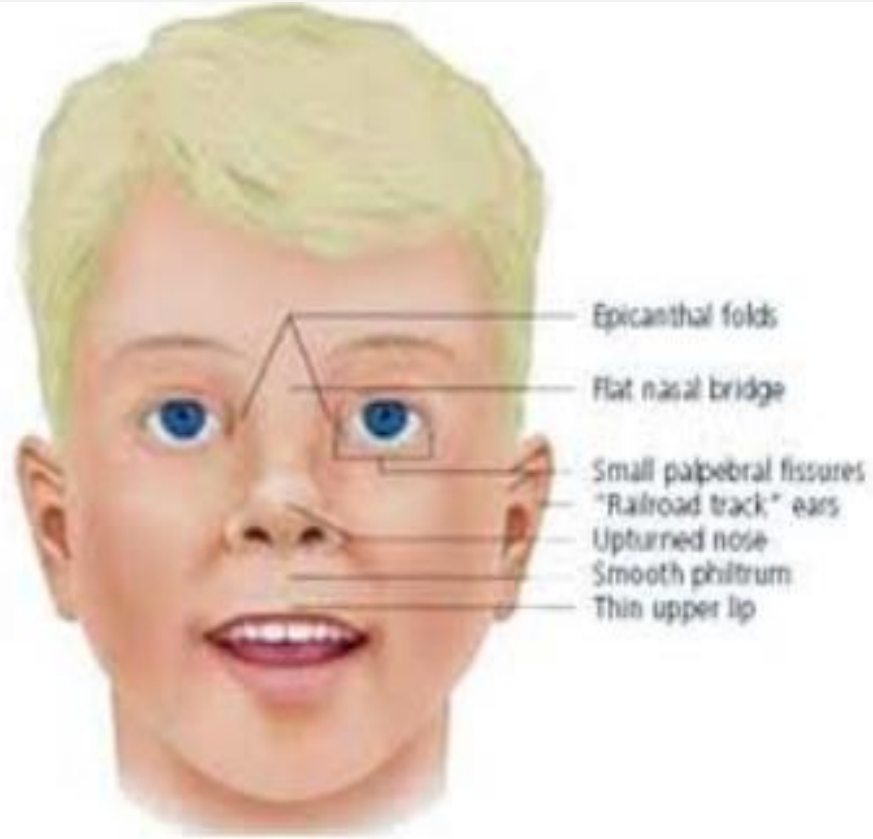


Photo: Simplebooklet, Tokyo Medical University

CYSTIC FIBROSIS

- **Etiology-**
  - mutations in a gene, *CFTR*
  - 2,000 different mutations at the *CFTR* locus
  - Cystic fibrosis (CF) is one of the most common single-gene disorders in North America, affecting approximately 1 in 2000 to 1 in 4000 European American newborns. The prevalence among African Americans is about 1 in 15,000 births, and it is less than 1 in 30,000 among Asian Americans. Approximately 30,000 Americans have this disease.
- **Pathogenesis**
  - Class I mutations result in no synthesis of the gene product.
  - Class II mutations produce a defective protein product that is destroyed in proteasomes.
  - Class III mutations produce a protein that gets to the cell surface but is abnormally regulated.
  - Class IV mutations result in defective chloride ion conductance.
  - Class V mutations are typically promoter or intron–exon splicing mutations that reduce the number of mRNA transcripts, allowing some normal protein products.
  - Class VI mutations result in increased rates of turnover of the chloride channel at the cell surface.
- **Morphological Changes-**
  - **Varies**
  - Absence to malfunctioning sweat glands (complete lack of chloride ion channels)
  - Varying degrees of pancreatic function
  - Varying digress of lung function
- **Clinical Manifestations**
  - Defective ion transport results in salt imbalances, depleting the airway of water and producing the thick, obstructive secretions seen in the lungs. The pancreas is also obstructed by thick secretions, leading to fibrosis and pancreatic insufficiency. The chloride ion transport defect explains the abnormally high concentration of chloride in the sweat secretions of CF patients: chloride cannot be reabsorbed from the lumen of the sweat duct.
  - pancreas is unable to secrete digestive enzymes, contributing to chronic mal-absorption of nutrients

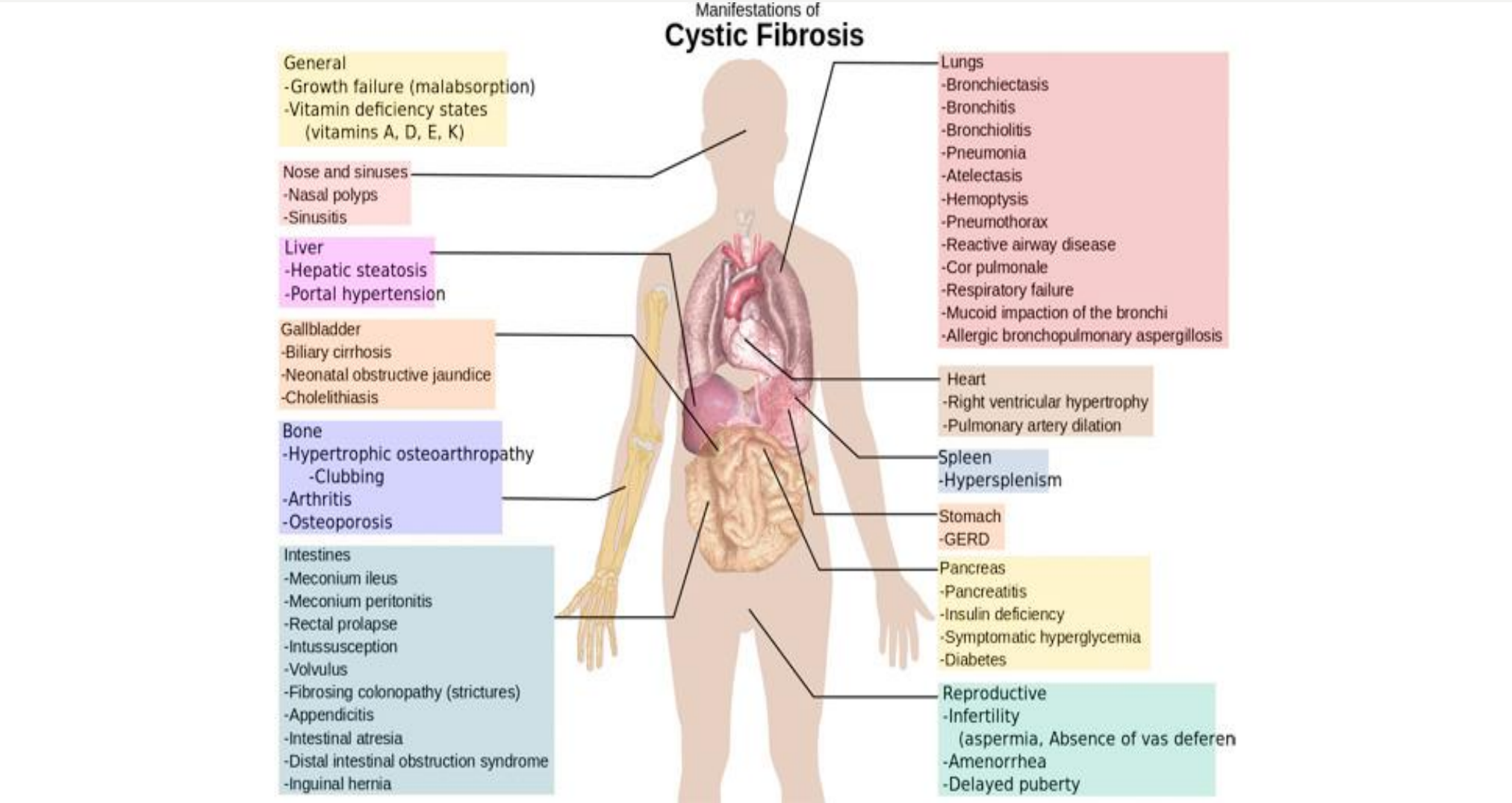
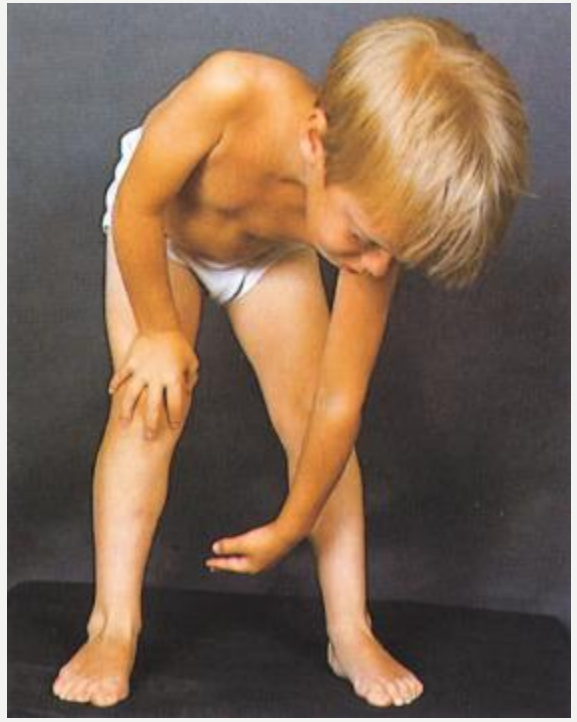
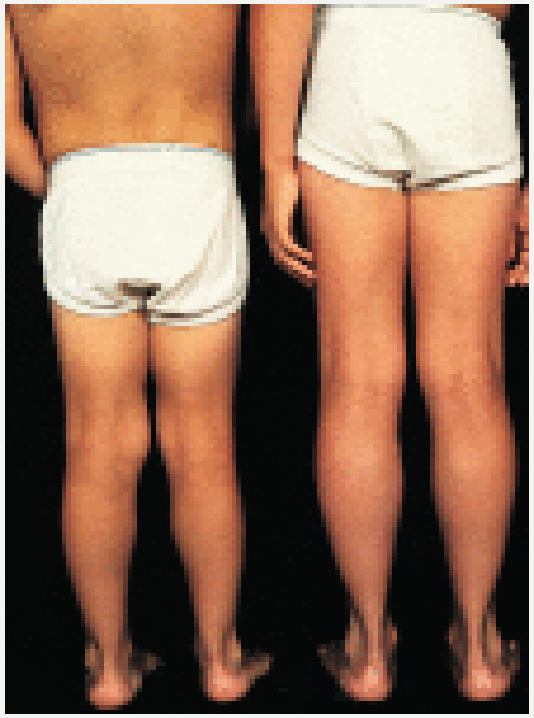


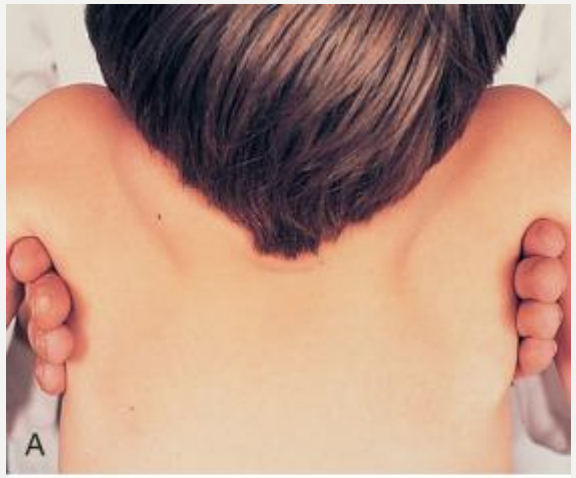
Photo: Baylor College of Medicine

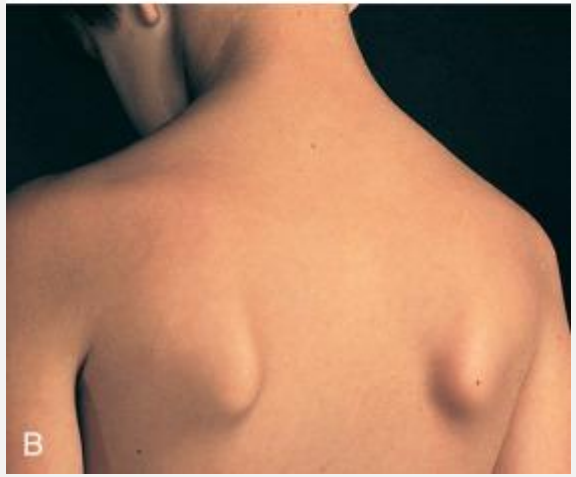
DUCHENNE MUSCULAR DYSTROPHY

- **Etiology-** x linked recessive, deletion mutation
- **Pathogenesis-** germline mosaicism, deletion mutation affecting Xp21 region on the short arm of the X chromosome, dystrophin (large cytoskeletal protein) is absent from muscular fibers
- **Morphological Changes-** progressive degeneration of skeletal muscle starting at the 2nd year of life or later
- **Clinical Manifestations-** mental retardation, cardiomyopathy, pseudohypertrophy of calves, weakness of pelvic and shoulder girdle









Photos: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis
Photo 1: Child age 5 has difficulty rising from floor. Unilateral hand support on the knee is required to get erect. Photo 2: Pseudophyertrophy- note enlargement of calves in brothers ages 5 and 8. Photo 3: Shoulder girdle weakness. Child age 5 demonstrates weakness and hypotonia of the shoulder girdle musculature. Upward displacement of shoulders and abnormal rotation of scapulae are seen.

EDWARD'S SYNDROME

- **Etiology-** partial or complete trisomy 18
- **Pathogenesis-** **depends on etiology of trisomy 18**
- **Morphological Changes-** small for gestational age, frail appearance, petite face in relation to the rest of the craniofacial contour, clenched hands with overlapping fingers, short sternum, "low arch" fingerprint patterns, congenital heart disease, prominent occiput, low-set and structurally abnormal ears, micrognathia and rocker bottom feet
- **Clinical Manifestations-** significant developmental and cognitive impairments

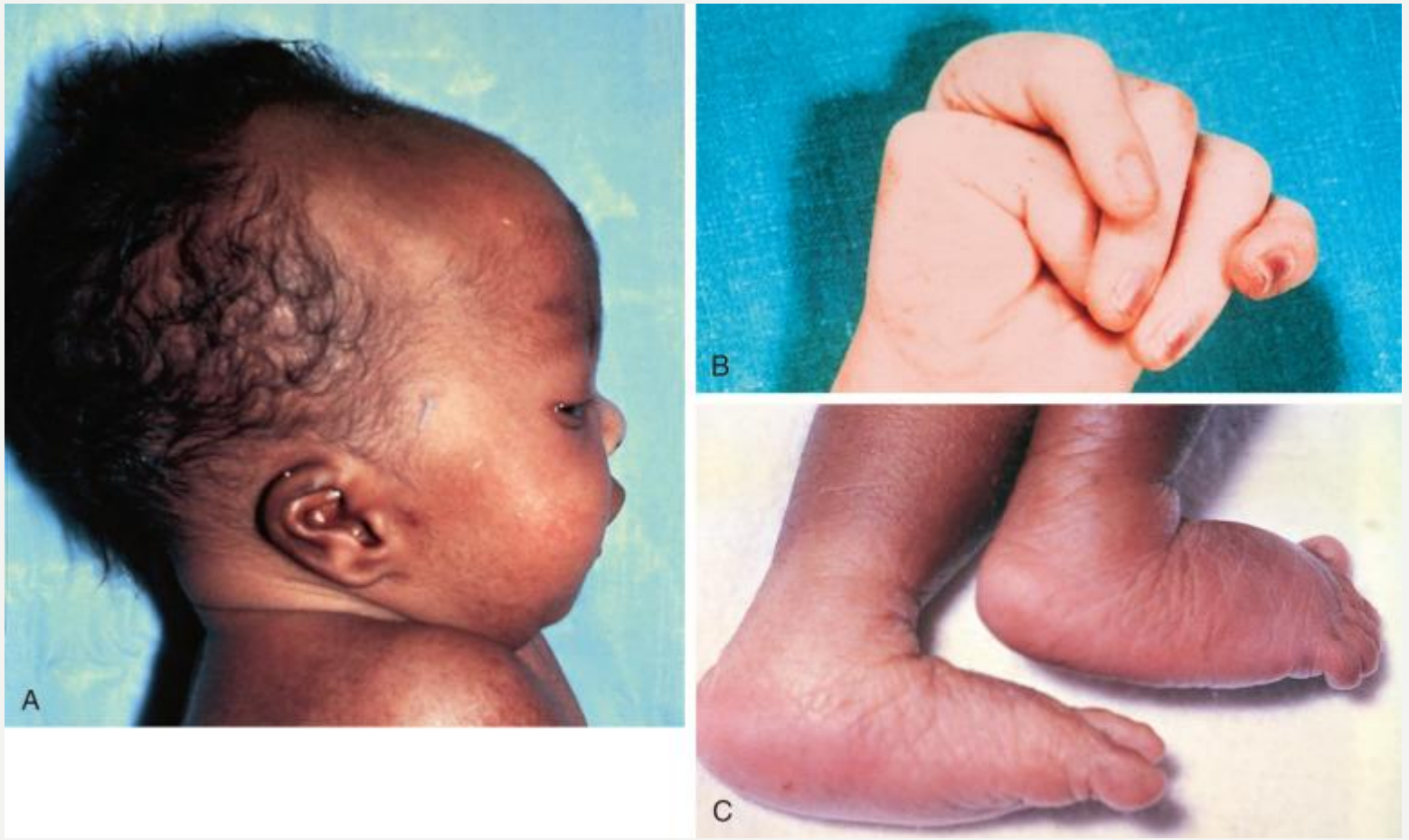
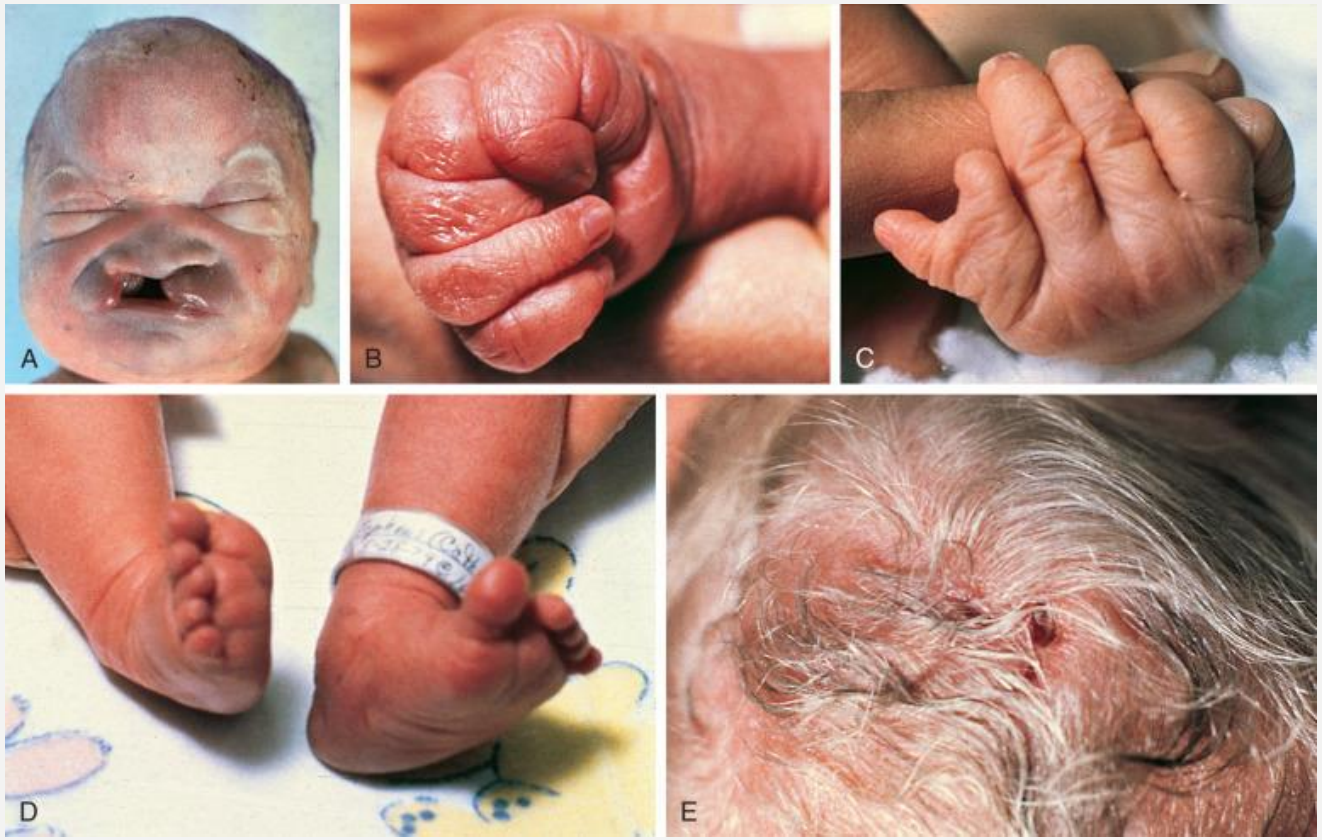


Photo: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, 2018. Several physical manifestations of trisomy 18. **A,** Typical profile reveals prominent occiput and low-set, posteriorly rotated malformed auricles. **B,** Clenched hand showing typical pattern of overlapping fingers. **C,** Rocker-bottom feet.
(Courtesy Kenneth Garver, MD, Pittsburgh, PA.)

PATAU SYNDROME

- **Etiology-** chromosomal abnormality
- **Pathogenesis-** trisomy 13 (part or all of the 13th chromosome)
- **Morphological Changes -** The hallmark features are defects of forebrain development related to those seen in holoprosencephaly, aplasia cutis congenita, polydactyly (most frequently of the postaxial type), and narrow hyperconvex nails
- **Clinical Manifestations- spontaneous abortion of fetus,**



Several physical manifestations of trisomy 13. **A,** Facies showing midline defect. **B,** Clenched hand with overlapping fingers. **C,** Postaxial polydactyly. **D,** Equinovarus deformity. **E,** Typical punched-out scalp lesions of aplasia cutis congenita.
(**A,** Courtesy T. Kelly, MD, University of Virginia Medical Center, Charlottesville. **B** to **E,** Courtesy Kenneth Garver, MD, Pittsburgh, PA.)
Table 1.5

Abnormality	Trisomy 13	Trisomy 18
Severe developmental retardation	††††	††††
Approximately 90% die within first year	††††	††††
Cryptorchidism in males	††††	††††
Low-set, malformed ears	††††	††††
Multiple major congenital anomalies	††††	††††
Prominent occiput	†	††††
Cleft lip and/or palate	†††	†
Micrognathia	††	†††
Microphthalmos	†††	††
Coloboma of iris	†††	†
Short sternum	†	†††
Rocker-bottom feet	††	†††
Congenital heart disease	††	††††
Scalp defects	†††	†
Flexion deformities of fingers	††	††††
Polydactyly	†††	†
Hypoplasia of nails	††	†††
Hypertonia in infancy	†	†††
Apneic spells in infancy	†††	†
Midline brain defects	†††	†
Horseshoe kidneys	†	†††

MARFAN SYNDROME

- **Etiology-**mutations in genes that encode structural proteins

- **Pathogenesis-**mutations in a gene, *FBN1*.
  - *FBN1* encodes a connective tissue protein, fibrillin, mutations of this gene alter the structure of connective tissue. This helps to explain some of the cardiovascular and ocular features of this disorder. Hundreds of different *FBN1* mutations have been identified in Marfan syndrome patient

- **Morphological Changes-**unusually stretchable connective tissue.

- **Clinical Manifestations-** eye, skeletal system and cardiovascular system abnormalities: arachnodactyly, joint hyperflexia, tall stature with thin extremities, arm span that exceeds height, pectus excavatum or carinatum, pes planus, thoracolumbar kyphoscoliosis, subluxation of the lenses, retinal detachment

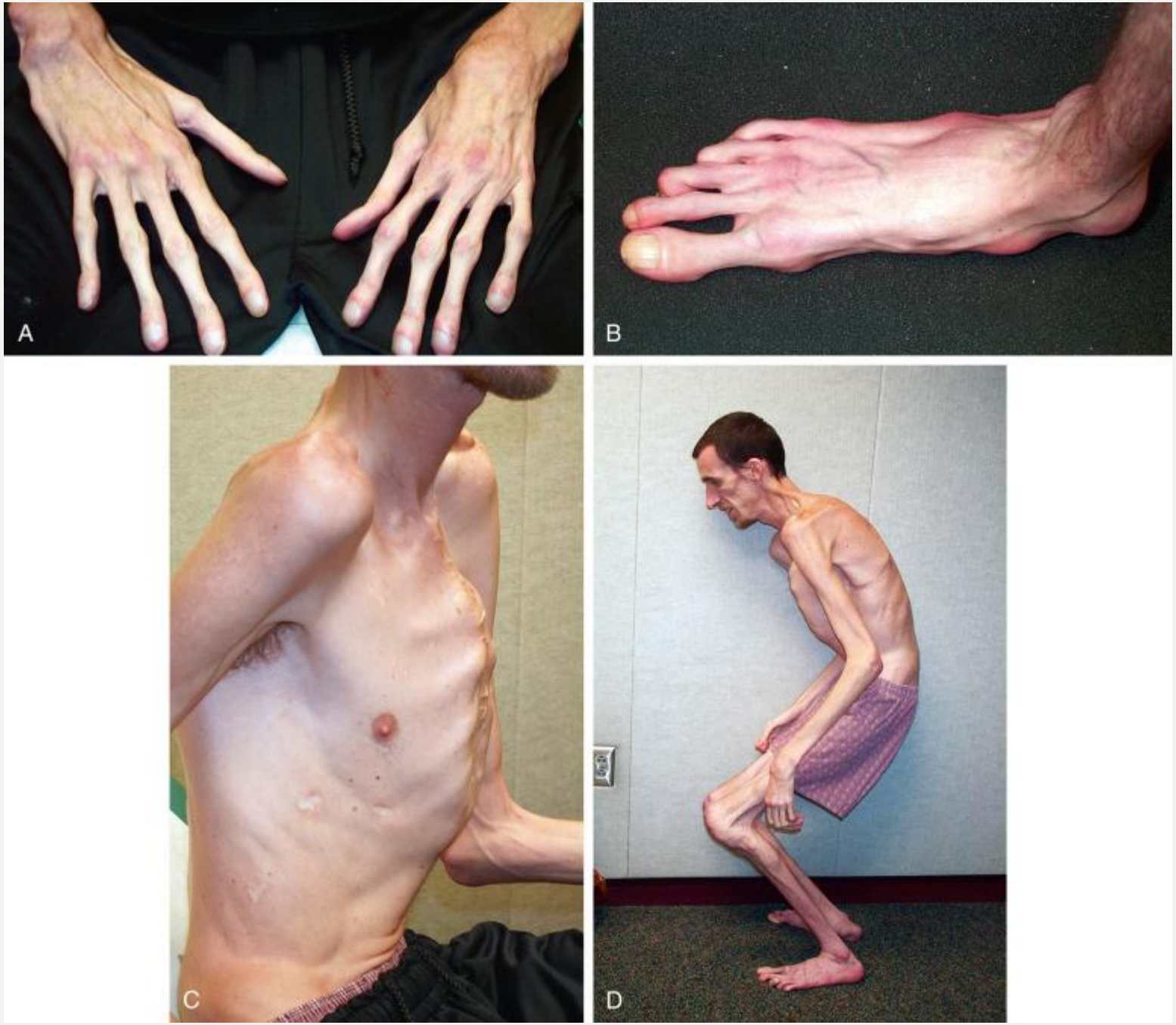


Photo: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis. A and B- arachnodactyly with clubbing due to cardiopulmonary problems, flattening of the arch of his foot, severe, pectus carinatum C-kyphosis and joint contractures D- long arms

EHLERS- DANLOS SYNDROME

- **Etiology –** genetic mutation that is autosomal dominant or autosomal recessive
- **Pathogenesis –**inherited connective tissue disorder
- **Morphological Changes –**defect in syntheses of type I, III, or V collagen resulting in decreased tensile strength of connective tissue
- **Clinical Manifestations-** hyper-extensibility and fragility of skin, ligamentous laxity, secondary joint hypermobility, vascular form has fragility of vasculature and visceral tissue components

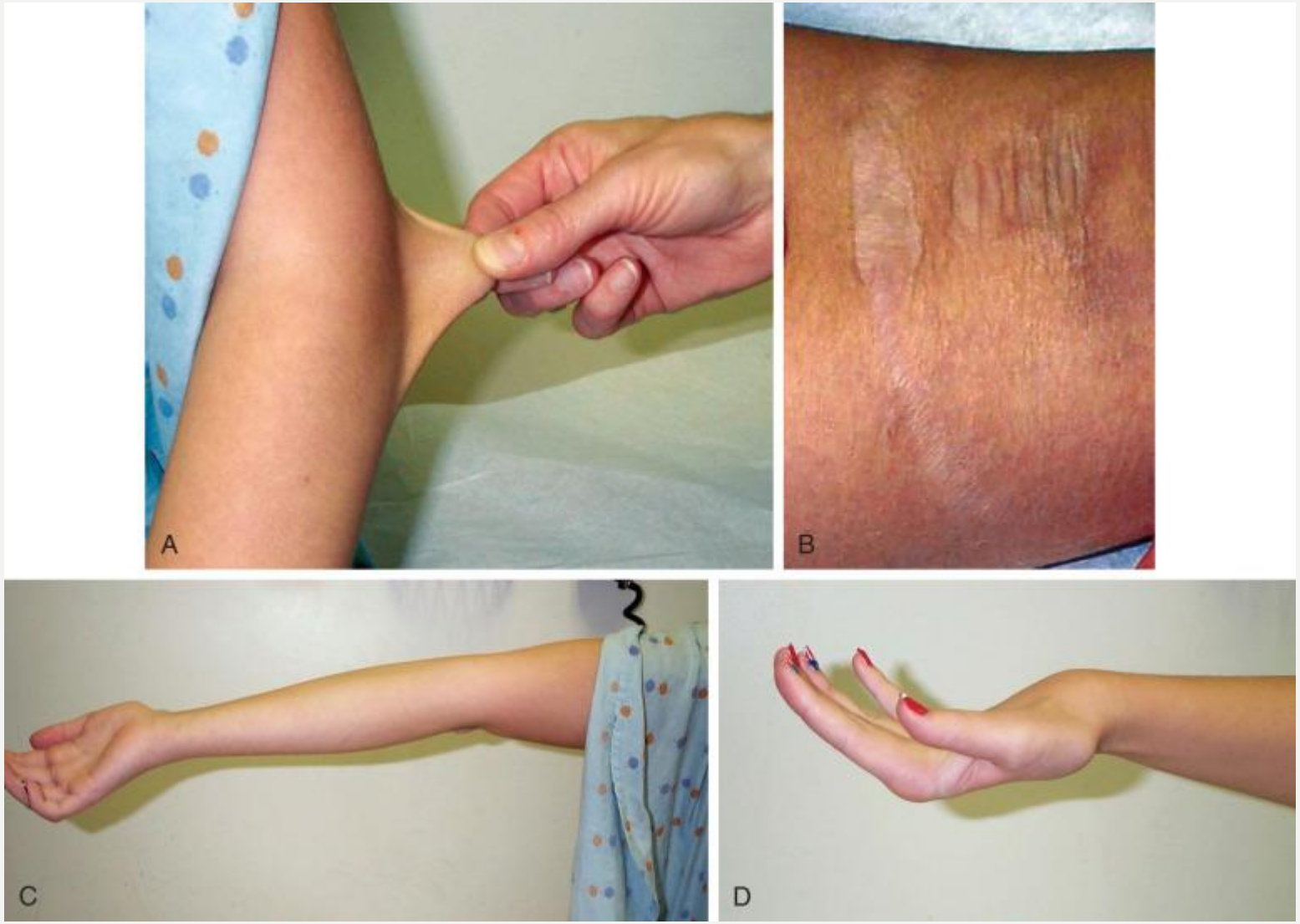
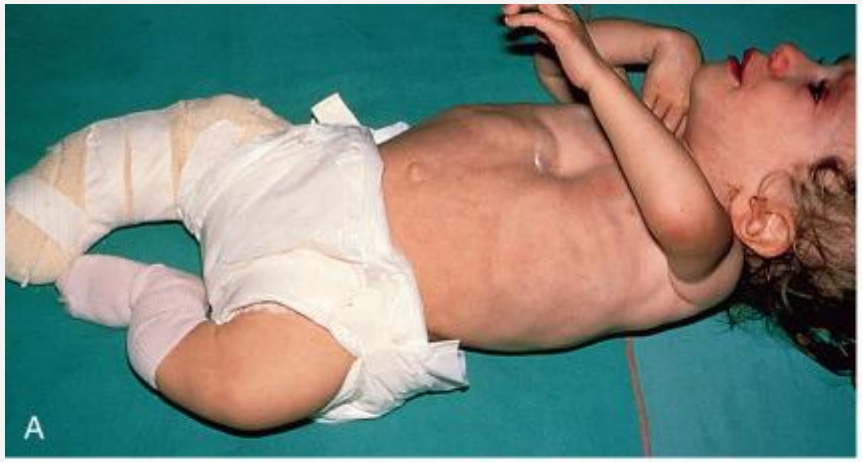
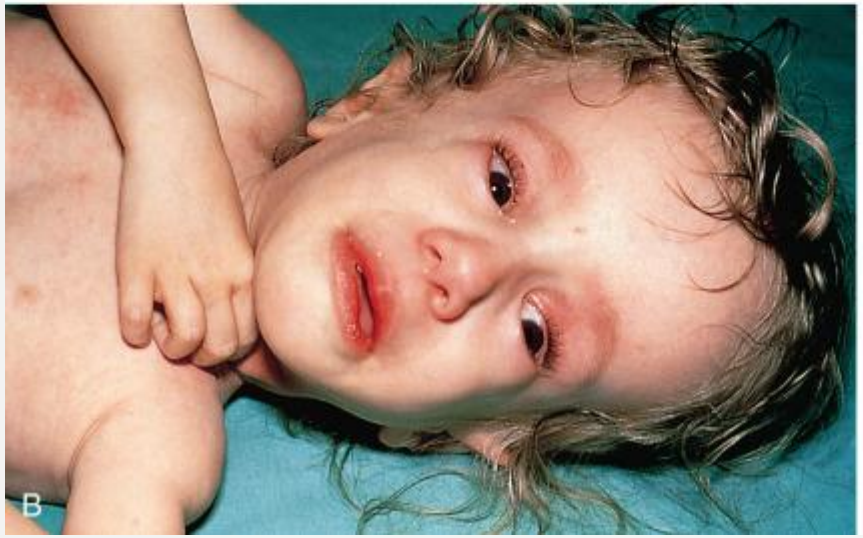


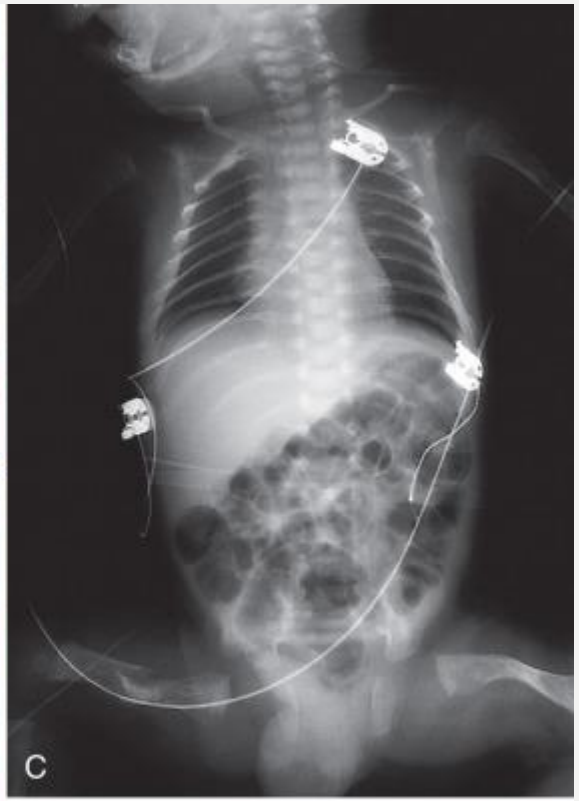
Photo: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, A-hyperextensibility of skin, B-widened atrophic scars with thin papery texture, C and D- hyperextensibility of the joint

OSTEOGENESIS IMPERFECTA

- **Etiology-** genetic mutation of COL1A1 or COL1A2 genes, hundreds of different mutations
- **Pathogenesis-**genes encode production of pro-a1 and pro-a2 polypeptide chains which assemble the triple helix to form type I collagen which is a major structural protein of bone and other connective tissues
- **Morphological Changes-** varies with type I-IV, fragile bones and connective tissues, triangular facies, broad nose, frontal and temporal bossing, sclerae may be normal color to light blue or gray, small stature, thin sternum
- **Clinical Manifestations-**varies with type I-IV, mild to severe fractures, limb deformities, abnormal dentition, ligament laxity



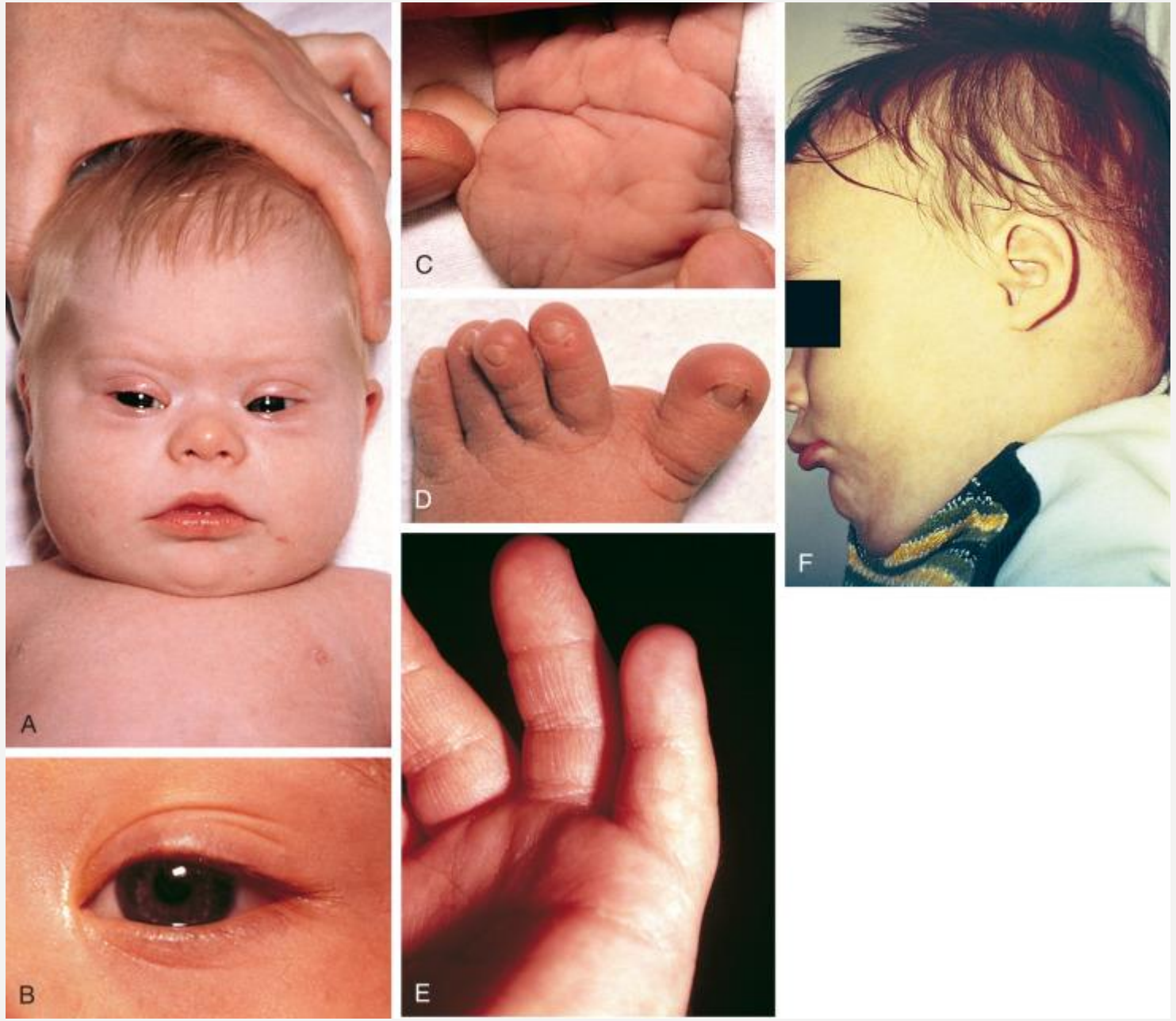


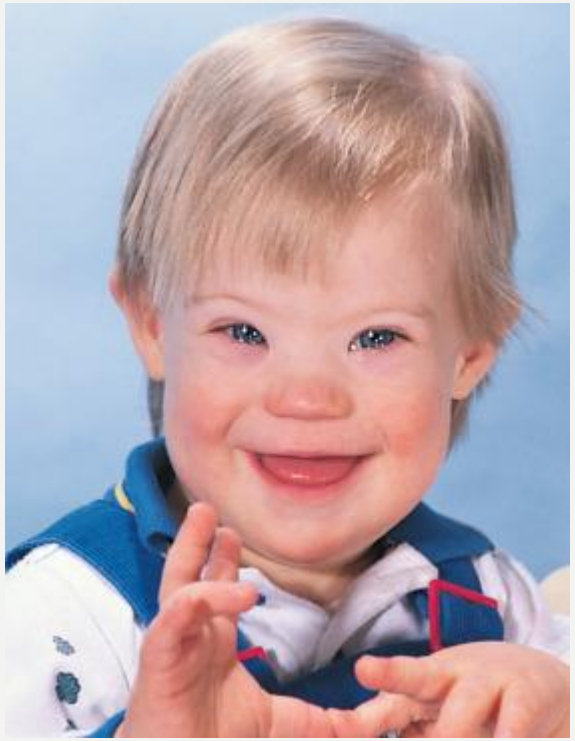


Zitelli and Davis' Atlas of Pediatric Physical Diagnosis. OI type III. A- extremely small stature of 5 year old with deformities of rib cage and lower extremities. B- craniofacial features with triangular facies, broad nose and frontal and temporal bossing, sclerae may be normal in color, C- radiograph of infant shows dwarfed deformed femurs with new fracture in the mid shaft of the right femur. Note thin peculiarly, shaped ribs.

INTELLECTUAL DEVELOPMENT DISORDERS

- **Etiology-** old language was "mental retardation", mentally retarded individual, multiple genetic abnormalities, trisomy 21 for down syndrome
- **Pathogenesis –** depends on the disease state
- **Morphological Changes-** short stature
- **Clinical Manifestations-** *Limitations in intellectual functioning* is generally defined as scores on standardized intelligence quotient (IQ) tests that are two or more standard deviations below age-group norms; *adaptive behaviors* refers to the broad areas of conceptual, social, and practical functioning, such as learning, communication, self-care, community participation (e.g., riding public transportation, engaging in recreation, voting), and social interactions.

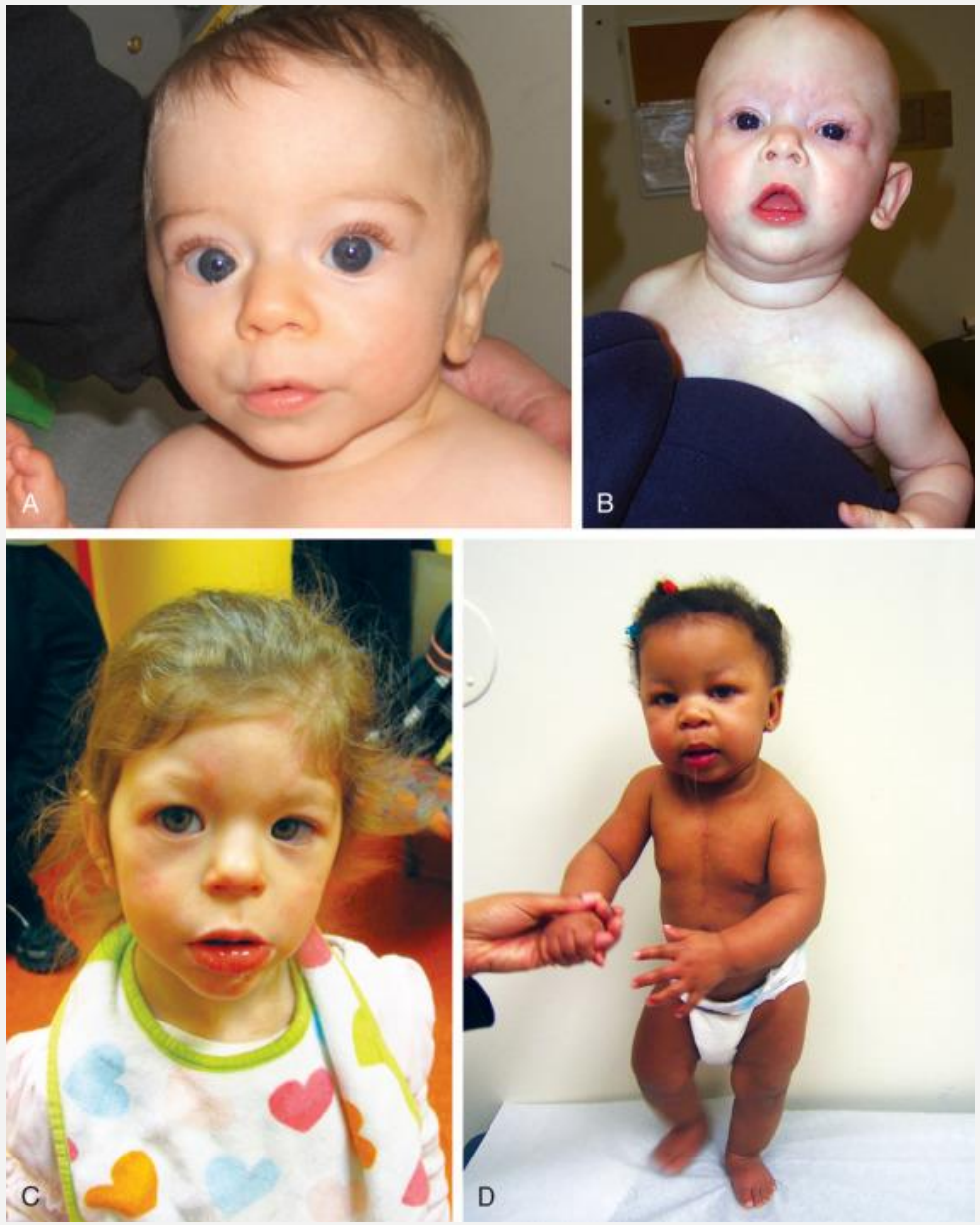




Photos: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis. Down Syndrome: A- upslanting palpebral fissures, epicanthal folds, and flat nasal bridges B- brushfield spots C-bridged palmar crease D- wide space between first and second toes E- short fifth finger F-small ears and flat occiput

WILLIAM- BEUREN SYNDROME OR WILLIAMS SYNDROME

- **Etiology-** chromosomal microdeletion
- **Pathogenesis-** microdeletion of the elastin gene at chromosome 7q11.13 or 7q11.23
- **Morphological Changes-** elfin facies- wide mouth, small upturned nose, widely spaced teeth and full lips, inward bend of 5th finger, short stature, cardiac abnormalities
- **Clinical Manifestations-** mild to moderate intellectual disability, speech delay, kidney abnormalities, far sightedness, overly friendly, sensitive to loud noises, aversion to physical contact, hypercalcemia, impaired glucose tolerance, subclinical hypothyroidism, early menarche

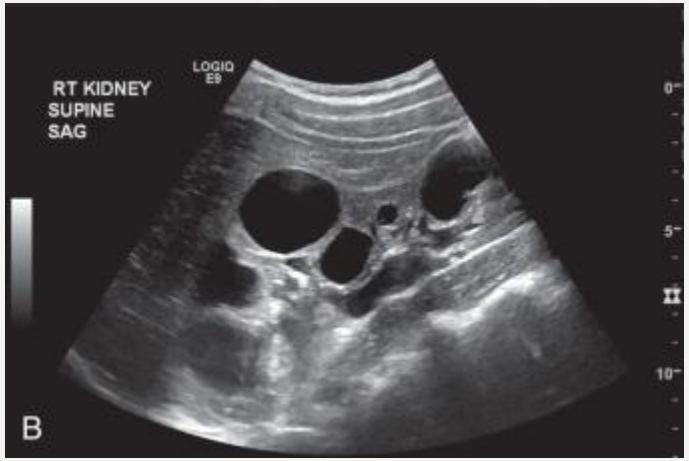


Photos: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis

A to D, Williams syndrome in four different patients. Hallmark features include supravalvular aortic stenosis, hypercalcemia, friendly personality, connective tissue abnormalities, and characteristic facies. Note the periorbital fullness, epicanthal folds, prominent lips, long philtrum and stellate lacy iris pattern.

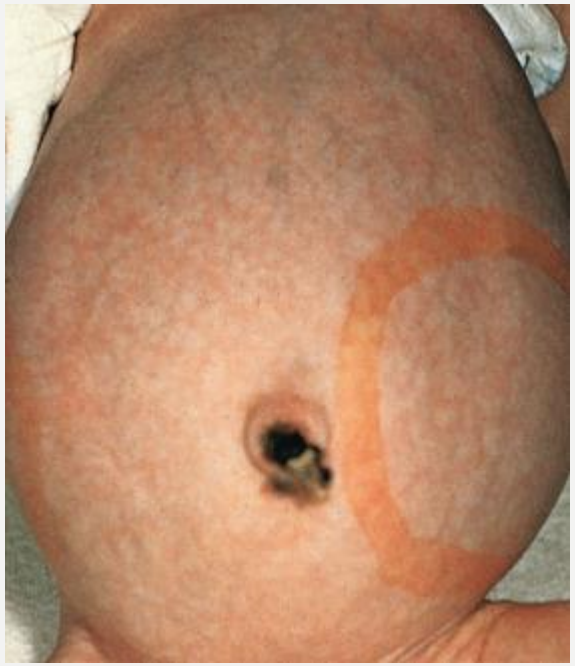
MULTI-CYSTIC DYSPLASTIC KIDNEY

- **Etiology-** genetic mutations, teratogens- mothers with diabetes, medications, anti-seizure drugs, lacked certain vitamins or minerals during pregnancy such as folic acid
- **Pathogenesis-** kidney development in urtero is altered and tubules fail to compete development, urine collects in kidney and forms fluid filled cysts
- **Morphological Changes-** Multicystic dysplasia, usually unilateral, unaffected contralateral kidney is usually hypertrophied and has normal corticomedullary differentiation and no evidence of obstruction, complete loss of the normal renal architecture
- **Clinical Manifestations-** usually found on prenatal ultrasound, abnormal kidney usually regresses with time so individual only has one kidney, manifestations depend on if 1 or 2 kidneys are affected
- **Note: Different from hereditary polycystic kidney disease**



Macrocysts in varying sizes with distortion of normal

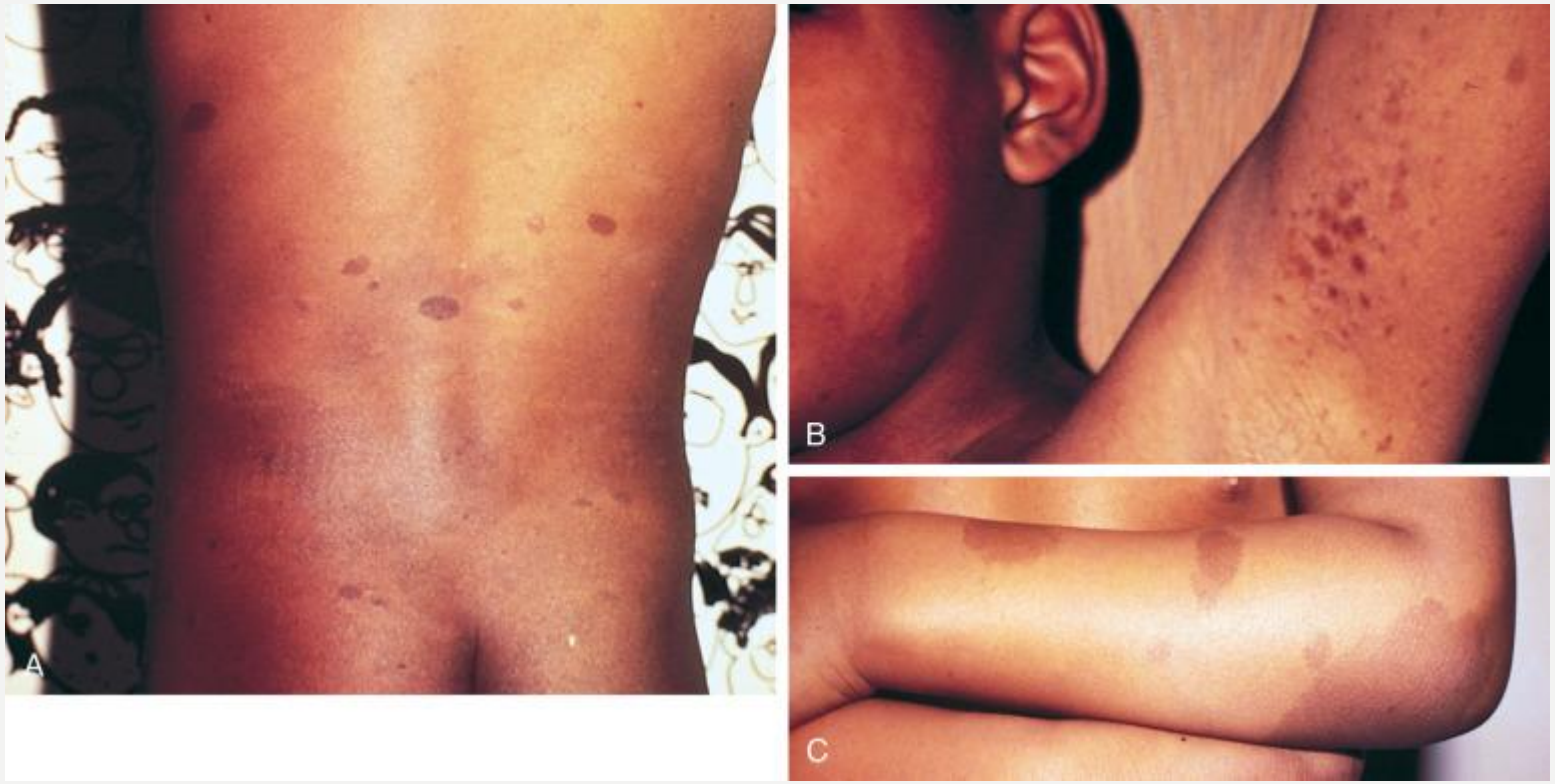
Zitellil and Davis' Atlas of Pediatric Physical Diagnosis



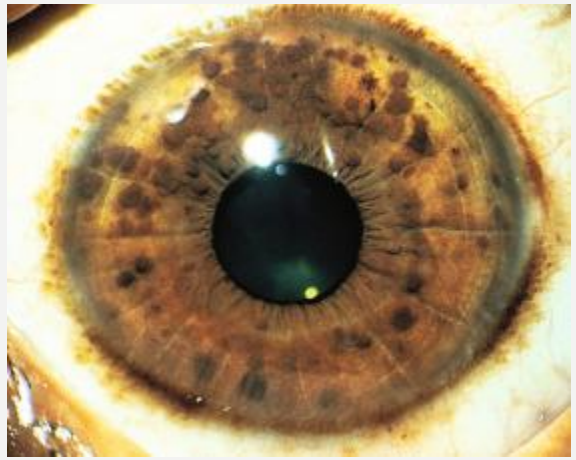
Autosomal recessive polycystic kidney disease

NEUROFIBROMATOSIS

- **Etiology- type I and type II**
- **Pathogenesis-**germline mosaicism, autosomal dominant
- **Morphological Changes**
  - **Type I-**neurofibromas, plexiform neurofibromas, optic pathway gliomas (benign tumors of the optic nerve), learning disabilities, hypertension, scoliosis (lateral curvature of the spine), and malignancies.
  - **Type II-**vestibular schwannomas (tumors that arise in Schwann cells and affect the eighth cranial nerve) and, occasionally, *café-au-lait* spots. Patients who have NF2 do not, however, have true neurofibromas, so the term "neurofibromatosis type 2" is a misnomer. The *NF2* gene encodes a tumor suppressor protein called merlin or schwannomin.
- **Clinical Manifestations-** multiple hyperpigmented skin macules (café-au-lait spots), axillary or inguinal freckling, multiple skin neurofibromas, and iris hamartomas (Lisch nodules). Associated abnormalities may include optic gliomas; other CNS tumors of glial or meningeal origin; neurofibromas of spinal or peripheral nerves; pheochromocytoma, macrocephaly, and cognitive impairment; and bony abnormalities.



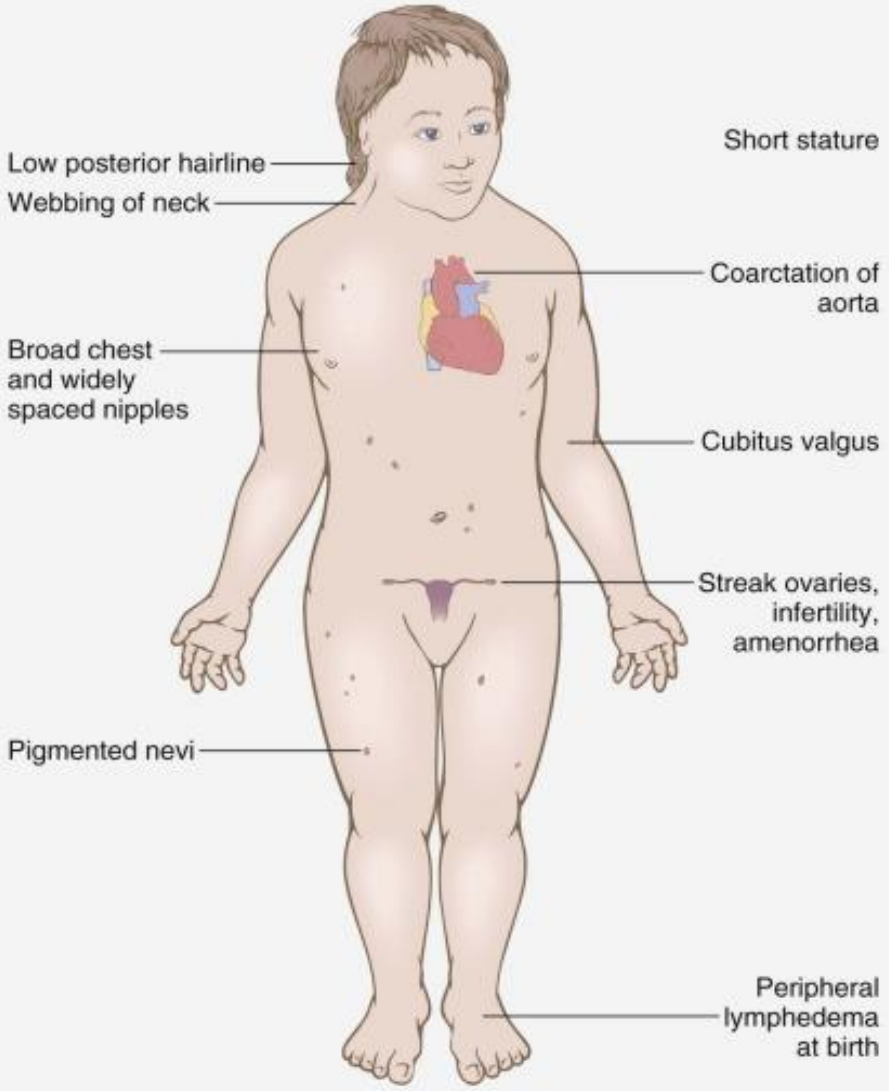
Multiple café’ au lait spots over trunk, axillary freckling and extensive hyperpgmentation



Pigmented hamartomas of the iris, Lisch nodules

TURNER SYNDROME

- **Etiology-** 45X, missing sex chromosome is paternally derived, female phenotype
- **Pathogenesis-**loss of the short arm of an X chromosome results in full blown symptoms, deletion of long arm results in fibrous gonads with sterility and amenorrhea
- **Morphological Changes-** sparse pubic and axillary hair, underdeveloped breasts, short stature, webbing of neck, shield chest with widely spaced nipples, malformed protruding ears, renal abnormalities, congenital heart disease, lymphedema in newborns and at times adolescents
- **Clinical Manifestations-** amenorrhea, sterility

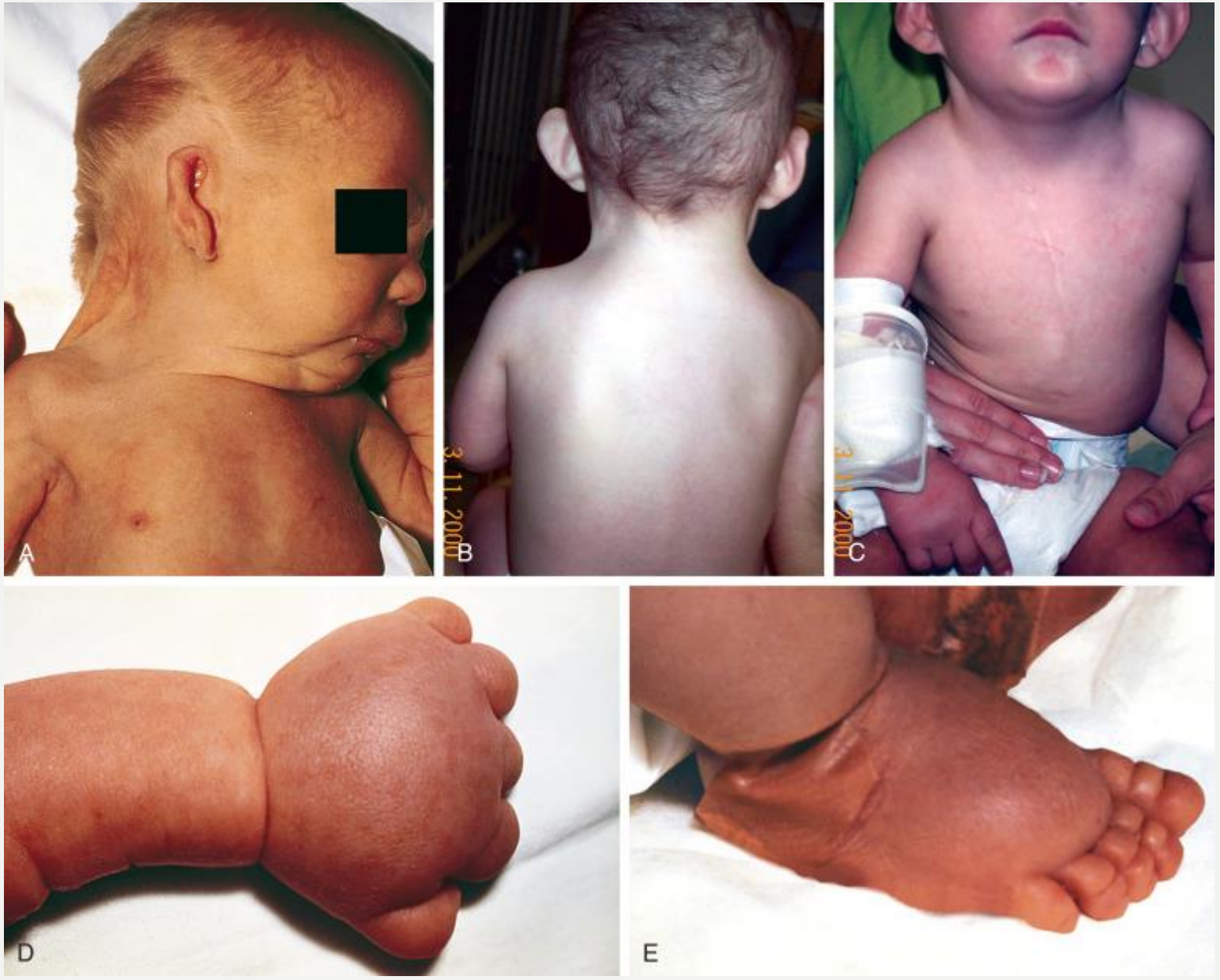


TURNER SYNDROME

Incidence: 1 in 3000 female births

Karyotypes:	
Classic:	45,X
Defective second X chromosome:	46,X,i(Xq) 46,X,del(Xq) 46,X,del(Xp) 46,X, r(X)
Mosaic type:	45,X/46,XX 45,X/46,XY 45,X/47,XXX 45,X/46,X,i(X)(q10)

Genetic Disorders
Kumar, Vinay, MBBS, MD, FRCPath, Robbins and Cotran Pathologic Basis of Disease, Chapter 5, 137-183



Photos: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis

A-webbed neck, low hair line, shield chest, abnormal ears, micrognathia

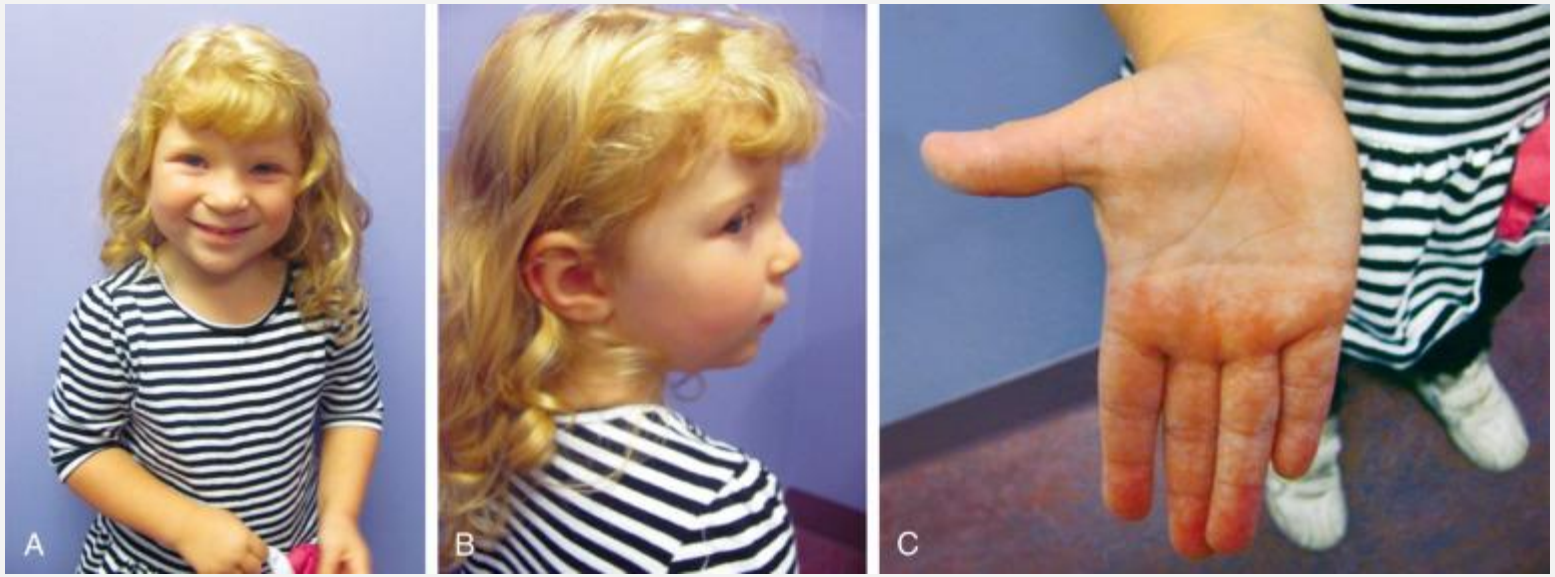
B-low set posterior hair line and protruding ears

C-mild webbing of neck, widely spaced nipples

D and E-lymphedema

XXX SYNDROME

- **Etiology-** 47 chromosomes, female
- **Pathogenesis-** error in chromosomal division during meiosis
- **Morphological Changes-** none to little, fertile
- **Clinical Manifestations-**usually normal range of intelligence, delays in developmental motor skills and coordination



Zitelli and Davis' Atlas of Pediatric Physical Diagnosis

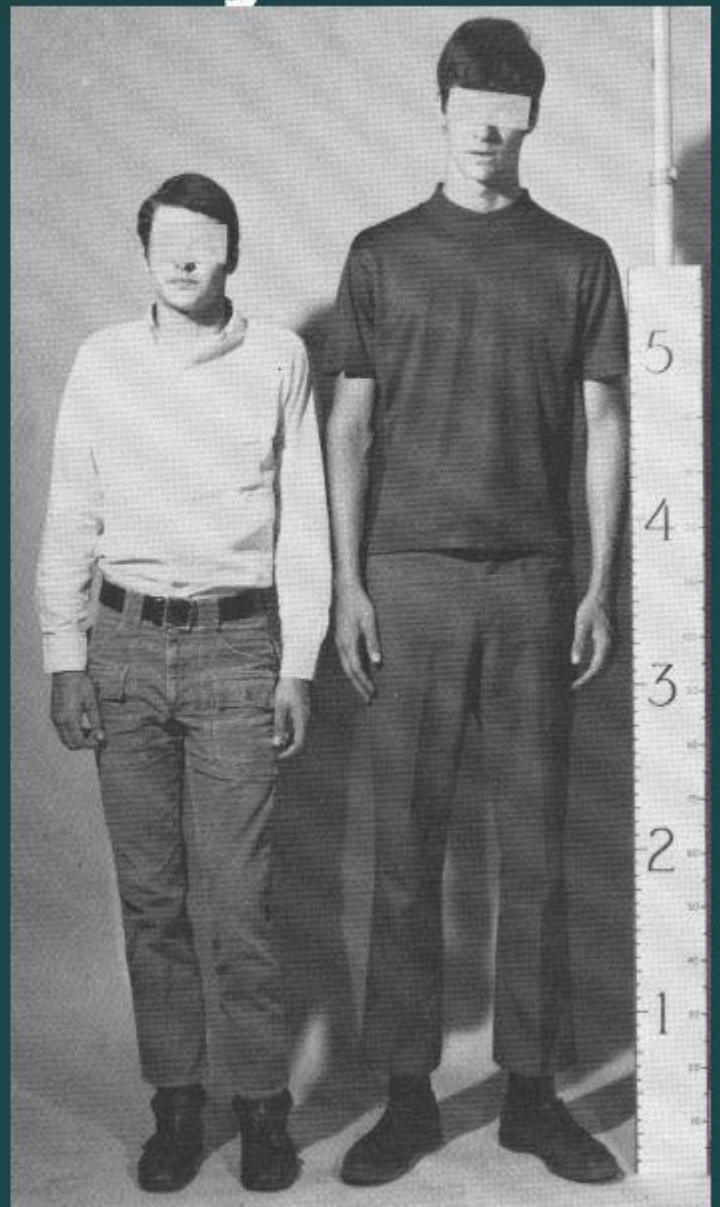
A female, 3 years and 8 months old, with double aneuploidy: Aneuploidy depicted by cytogenetic studies. Karyotype and fluorescence in situ hybridization (FISH) studies show predominantly 47XXX; some 47XXX also have an extra 21 (48XXX+21). The patient has some features of Down syndrome. Note the up-slanted palpebral fissures **(A),** low-set ears**(B),** and unilateral simian crease **(C).** An echocardiogram showed a patent foramen ovale. The patient is receiving behavioral and speech therapy; she is not toilet trained and has an individualized education program (IEP) in preschool. Triple X females are tall, and mosaic Down syndrome is similar to full Down syndrome but with a much milder phenotype. Her weight was in the 95th percentile, her height in the 80th, and occipital-frontal circumference (OFC) in the 20th.

XYY SYNDROME

- **Etiology-** 47 chromosomes, males
- **Pathogenesis-** error in chromosomal division
- **Morphological Changes-** tall, otherwise normal
- **Clinical Manifestations-** fine motor coordination, speech disorder, learning disabilities, "Super male" and misconceptions

Metamale – XYY Syndrome

These are twin brothers. The brother on the left is “normal” the brother on the right has two Y chromosomes.



CLUB FOOT

- **Etiology-** multifactorial
- **Pathogenesis-** teratogenic deformity of the foot, underlying predisposing conditions, abnormal intrauterine positioning and pressure at critical points of development, male, familial incidence
- **Morphological Changes-** foot positioned in plantar flexion, hindfoot position in fixed inversion (varus), forefoot exhibits adductus deformity which may be combined with supination
- **Clinical Manifestations-** contractures of the Achilles and posterior tibial tendons and of the medial ankle

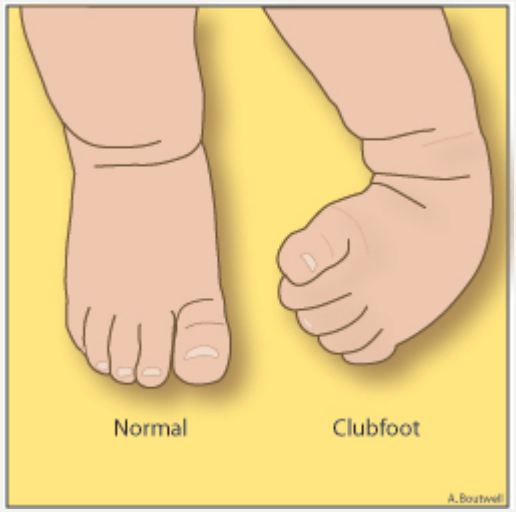


Photo: Children's Hospital of Chicago

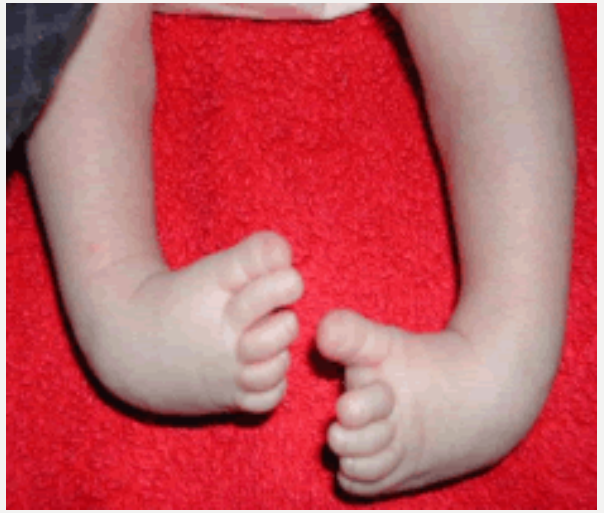


Photo: Club foot club

ACHONDROPLASIA

- **Etiology-** spontaneous mutation
- **Pathogenesis-**mutation in the fibroblast growth factor receptor 3 gene found on the short arm
- **Morphological Changes-** disproportionate short stature, flattened nasal bridge, upturned nose, protruding jaw, deep set eyes, frontal bossing, midface hypoplasia, macrocephaly
- **Clinical Manifestations-** hydrocephalus, normal intelligence and development with the exception of delayed motor milestones

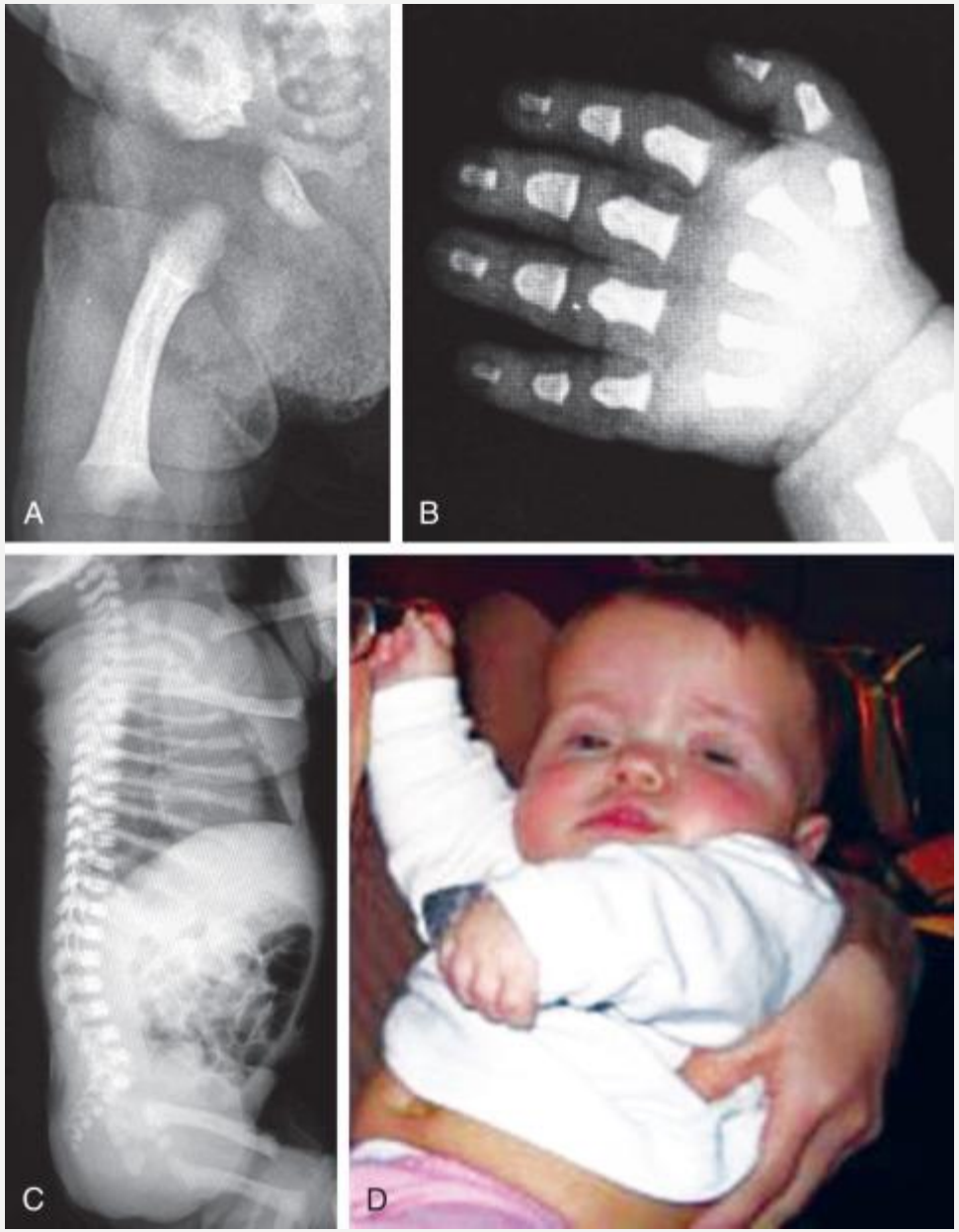


Photo: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis
A- radiograph of femur in infant with achondroplasia, proximal ends club like with metaphyseal flaring

B-shortened metacarpals and phalanges

C-thoracic lumbar kyphoscoliosis

D- upturned nose, flat nasal bridge and large forehead

CRANIOSYNOSTOSIS SYNDROMES

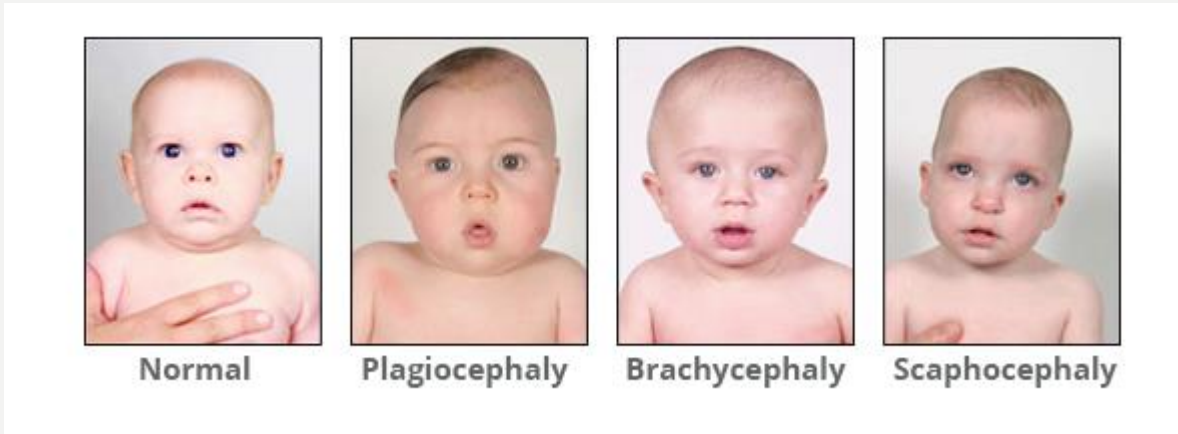
- **Etiology-** genetic and fetal environment play a role, breech positions
- **Pathogenesis-**premature closing of sutures between cranial bones during development
- **Morphological Changes-** deformities of skull
- **Clinical Manifestations-** increased intracranial pressure, intracranial hypertension, developmental delays, blindness

TABLE

Table 23.2

Skull Shape Nomenclature

Name	Suture(s) Involved	Shape
Acrocephaly	Bilateral coronal	Skull height greater anteriorly, slanting downward posteriorly
Brachycephaly	Bilateral coronal	Wide, taller skull shortened in anteroposterior dimension
Oxycephaly	Bilateral coronal	Taller skull, shortened width and anteroposterior dimension
Turricephaly	Bilateral coronal	Tall skull
Plagiocephaly	Unilateral coronal or unilateral lambdoidal	Asymmetrical skull
Scaphocephaly	Sagittal	Anteroposterior elongation with bitemporal narrowing
Trigonocephaly	Metopic	Narrow, triangular, ridged forehead
Kleeblattschädel	Bilateral coronal, lambdoidal, and metopic	Cloverleaf deformity



Photos: Cranialtech.com

NOONAN SYNDROME

- **Etiology-** autosomal dominant simple mendelian genetic disorder, mutations in multiple genes
- **Pathogenesis-** gene mutations alter protein development and cell division
- **Morphological Changes-** webbing of the neck, sternal abnormalities, pulmonic stenosis and cryptorchidism in males, widely spaced eyes, down-slanting palpebral fissures, ptosis, short stature
- **Clinical Manifestations-** normal intelligence, developmental delays
- **LEOPARD –L**entigines**, E**lectrocardiographic conduction abnormalities**, O**cular hyper-telorism**, P**ulmonic stenosis**, A**bnormal genitalia**, R**etardation of growth**, S**ensorineural deafness

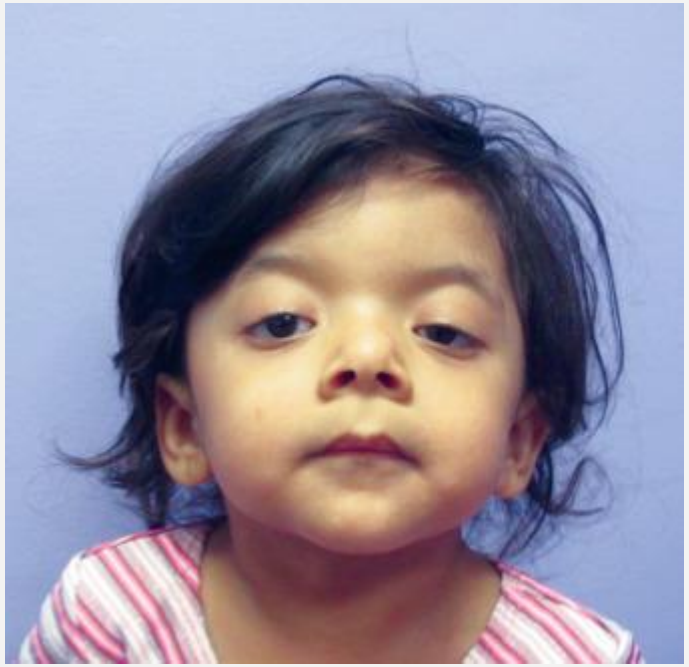


Photo: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis

Note: Down slanting palpebral fissures, ptosis, and low set posteriorly rotated ears. Bilateral simian creases and underwent cardiac surgeries for severe pulmonic stenosis and atrial septal defect. She has short stature.

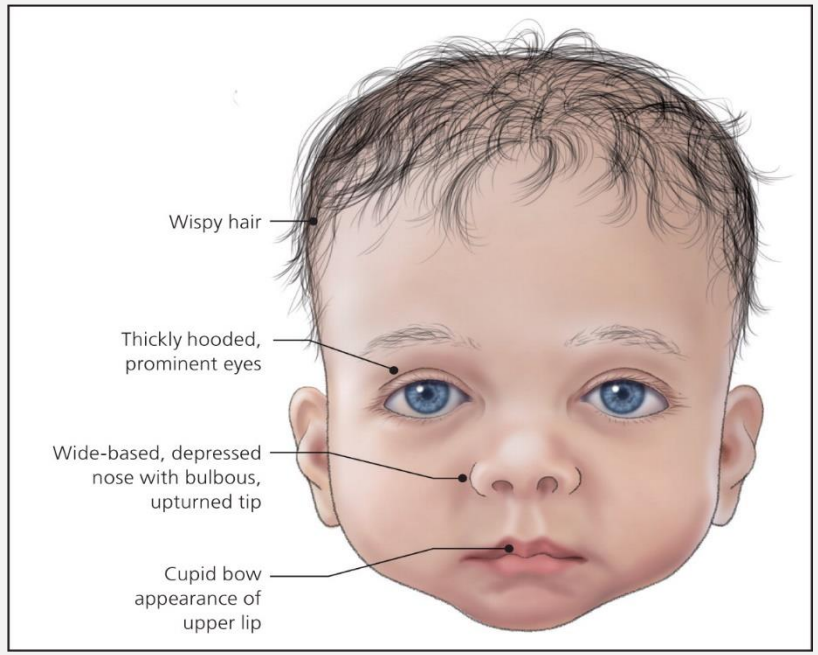
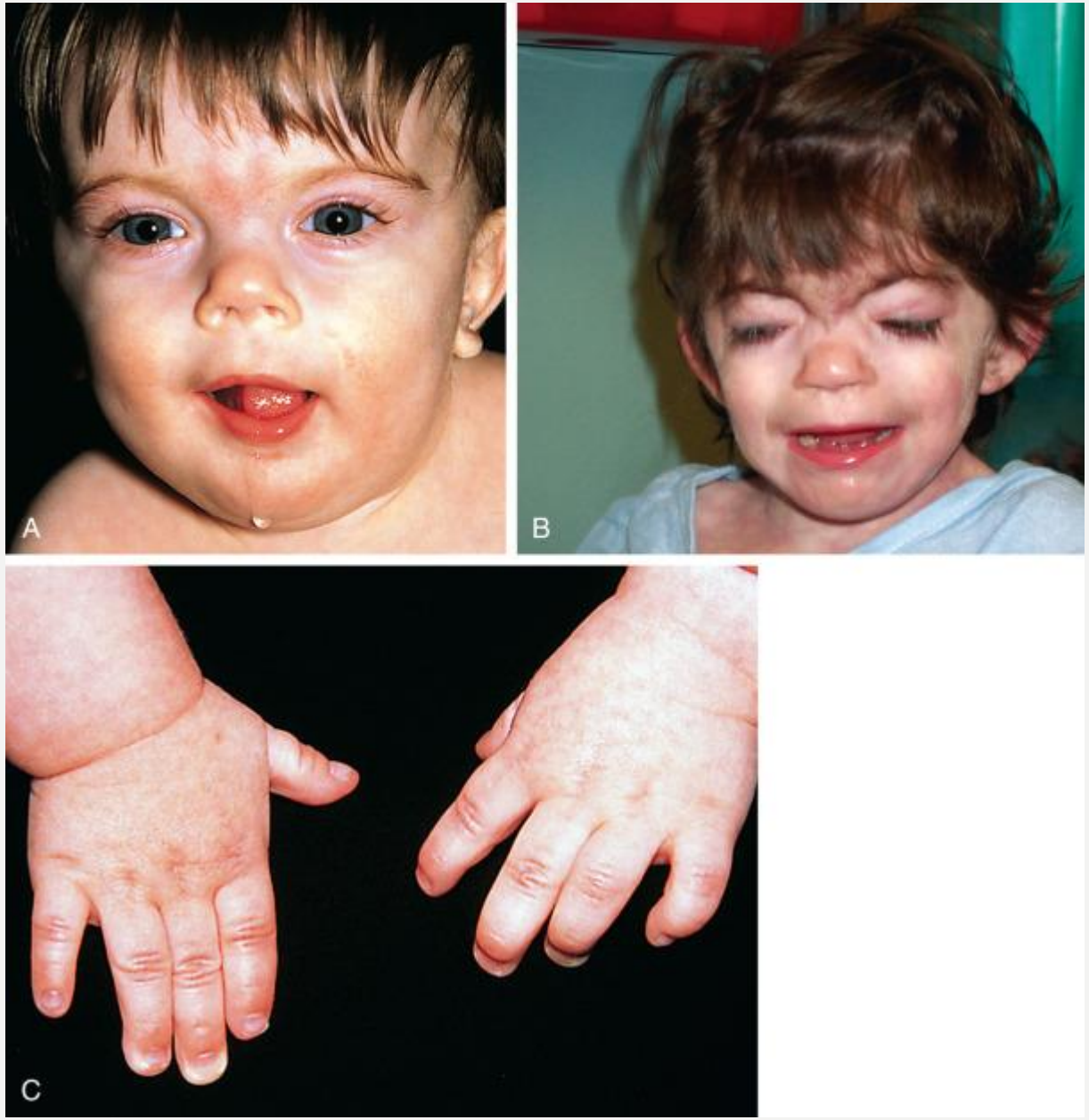


Photo: NHGRI, NIH

CORNELIA DE LANGE SYNDROME

- **Etiology-** autosomal dominant mutations, abnormalities of short arm of chromosome 3, can result in mutations of 5 different genes
- **Pathogenesis-** the proteins produced in all five genes contribute to the structure or function of the cohesion complex which plays an important role in development before birth
- **Morphological Changes-** affects many body parts: microcephaly, low hairline, long eyelashes, downturned upper lip, small hands and feet, proximally placed thumbs, in males-hypospadias with cryptorchidism, females-bicornuate uterus, short stature,
- **Clinical Manifestations-** moderate to severe cognitive impairment, failure to thrive, intrauterine growth retardation

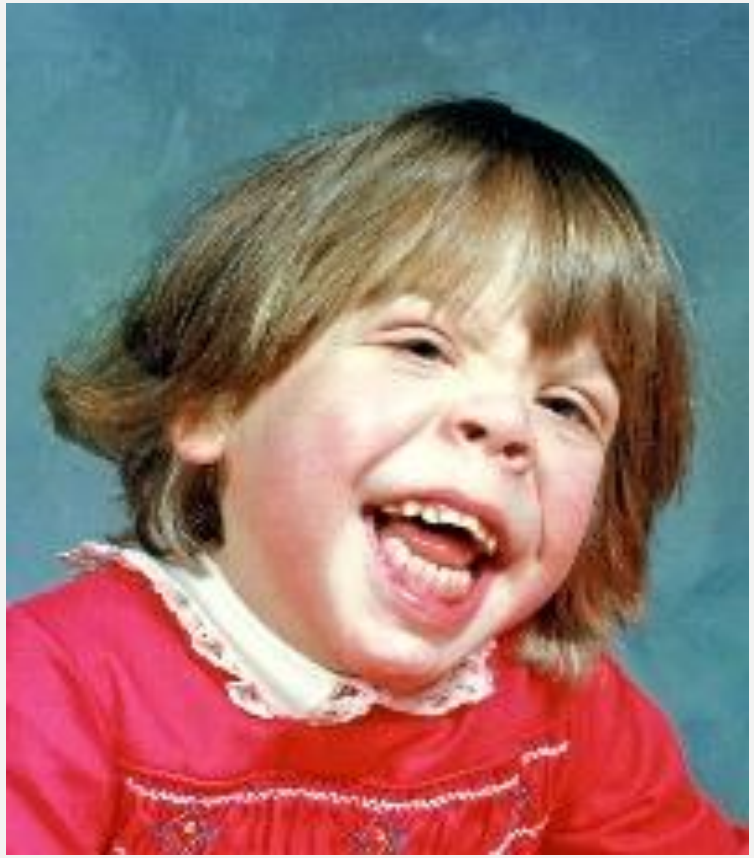


Photos: Zitelli and Davis' Atlas of Pediatric Physical Diagnosis

A and B-facial features- arched heavy eyebrows, long lashes, small upturned nose, long smooth philtrum, cupid's bow mouth C- small hands, hypoplastic proximally placed thumb and short fifth finger

OPITZ SYNDROME
SMITH-LEMLI OPTIZ SYNDROME

- **Etiology-** autosomal recessive, mutation in DHCR7 gene
- **Pathogenesis-** gene provides instructions for enzyme that is responsible for final step in the production of cholesterol which plays a role in embryonic development, structural components of cell membranes and myelin, production in hormones and digestive acids
- **Morphological Changes-** microcephaly, malformations of heart, lungs, kidneys, GI tract, and genitals, webbed toes, abnormal fingerprints and dental shape, nasal tip upturned
- **Clinical Manifestations-** intellectual disability, learning and behavioral problems, communication and social interaction



Photos: Smith-Lemli Opitz /RSH Foundation

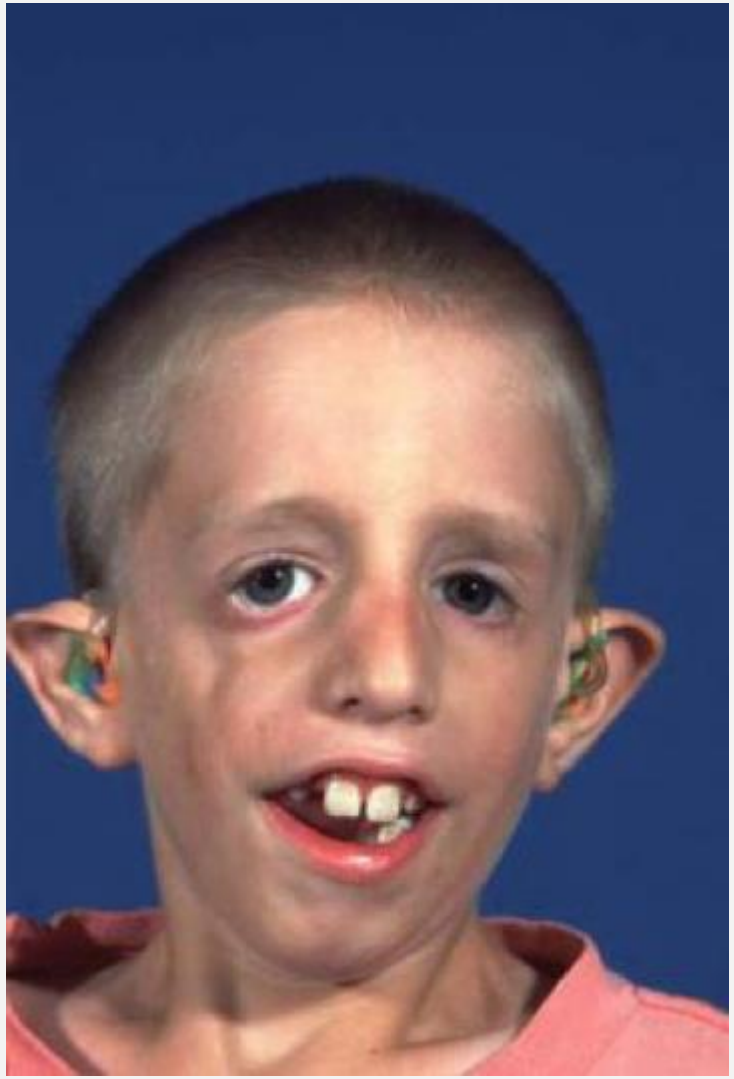
RETT SYNDROME

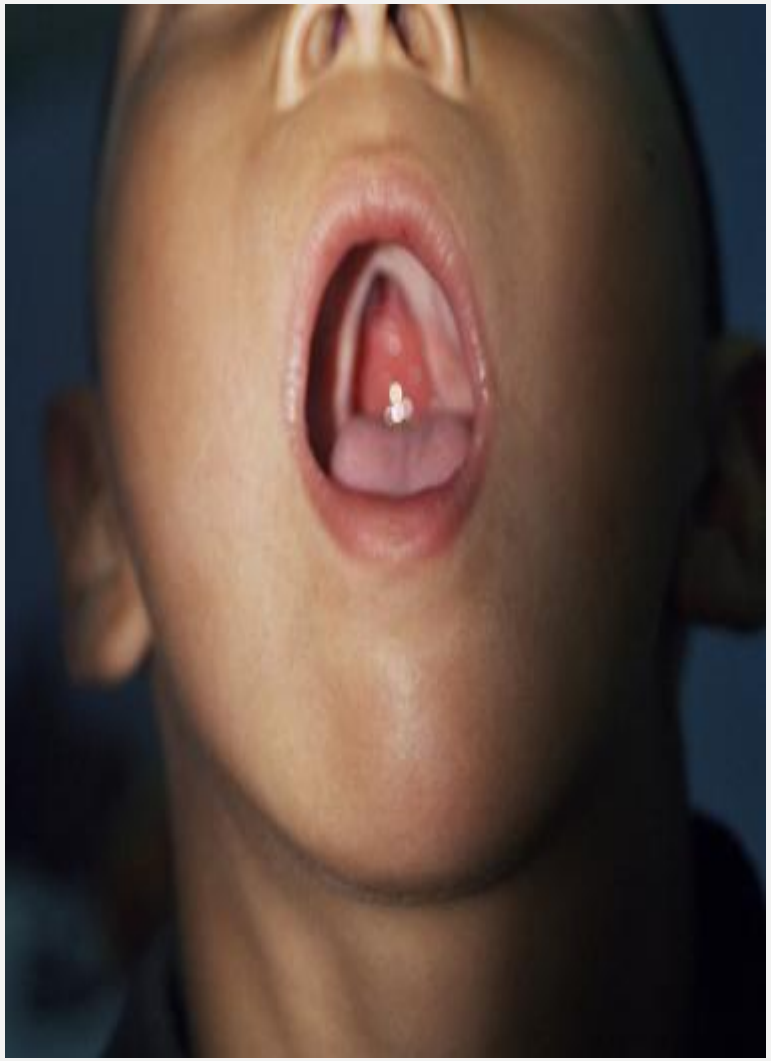
- **Etiology-** mutations in MECP2 gene inherited in x linked manner (girls only), new mutation- not inherited from parent
- **Pathogenesis-** progressive neuro-developmental condition due to mutation in gene that makes proteins needed for development of nervous system
- **Morphological Changes-** normal gross morphology
- **Clinical Manifestations-** developmental plateau, rapid regression of language and motor skills at 18 months of age, repetitive hand movements, fits of screaming and inconsolable crying
- **Other names: autism, ataxia**


Hi I'm Edie
and I love listening to rap music
I can pick notes on a musical instrument
I laugh really hard when I hear the word 'pit'
I hate it when strangers think I'm naughty just because I'm loud
but I have Rett Syndrome
so screaming is the only way I can express myself
cure rett
.org.uk

PIERRE ROBIN

- **Etiology-** mutations, exact cause unknown
- **Pathogenesis-**Possibly mutations near the SOX9 gene
- **Morphological Changes-** small mandible, glossoptosis, U shaped cleft palate, abnormal ear shapes and small ears
- **Clinical Manifestations-** airway obstruction, substernal breathing, stridor, feeding difficulties, reflux





Photos: University of Chicago and Emedicine

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