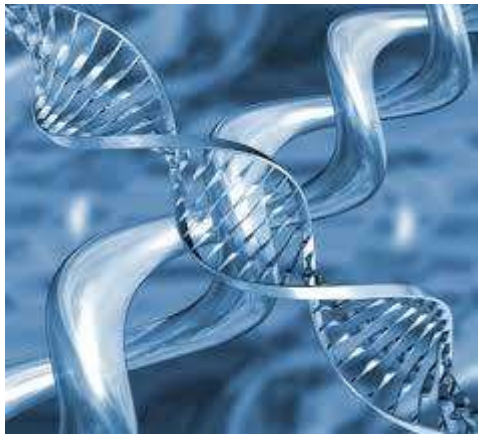


Genetics
Chromosomal Abnormalities

Background

- Human cells contain a multiple of 23 chromosomes (n = 23).
- **Haploid** cell (n) has 23 chromosomes (typically in the ovum or sperm).
- Diploid cell has a normal **diploid** number of 46 (2n) chromosomes
- Abnormal cells that do not contain a multiple of haploid number of chromosomes are termed **aneuploid** cells.
- Aneuploidy is the most common and clinically significant type of human chromosome abnormality, occurring in at least 3-4% of all clinically recognized pregnancies.

- The most common **numerical abnormalities** in live born children include:
  - Trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), trisomy 13 (Patau syndrome)
  - Sex chromosomal aneuploidies: Turner syndrome (usually 45,X), Klinefelter syndrome (47,XXY), 47,XXX, and 47,XYY.

- **Chromosomal disorders**: Chromosome deletions, duplications, and inversions that affect whole chromosomes, or large portions of a chromosome.

Chromosomal Disorders

- The most common cause of aneuploidy is **nondisjunction,** the failure of chromosomes to disjoin normally during meiosis I or II or during mitosis.
- After meiotic nondisjunction, the resulting gamete either lacks a chromosome or has 2 copies instead of 1 normal copy, resulting in a monosomic or trisomic zygote, respectively.

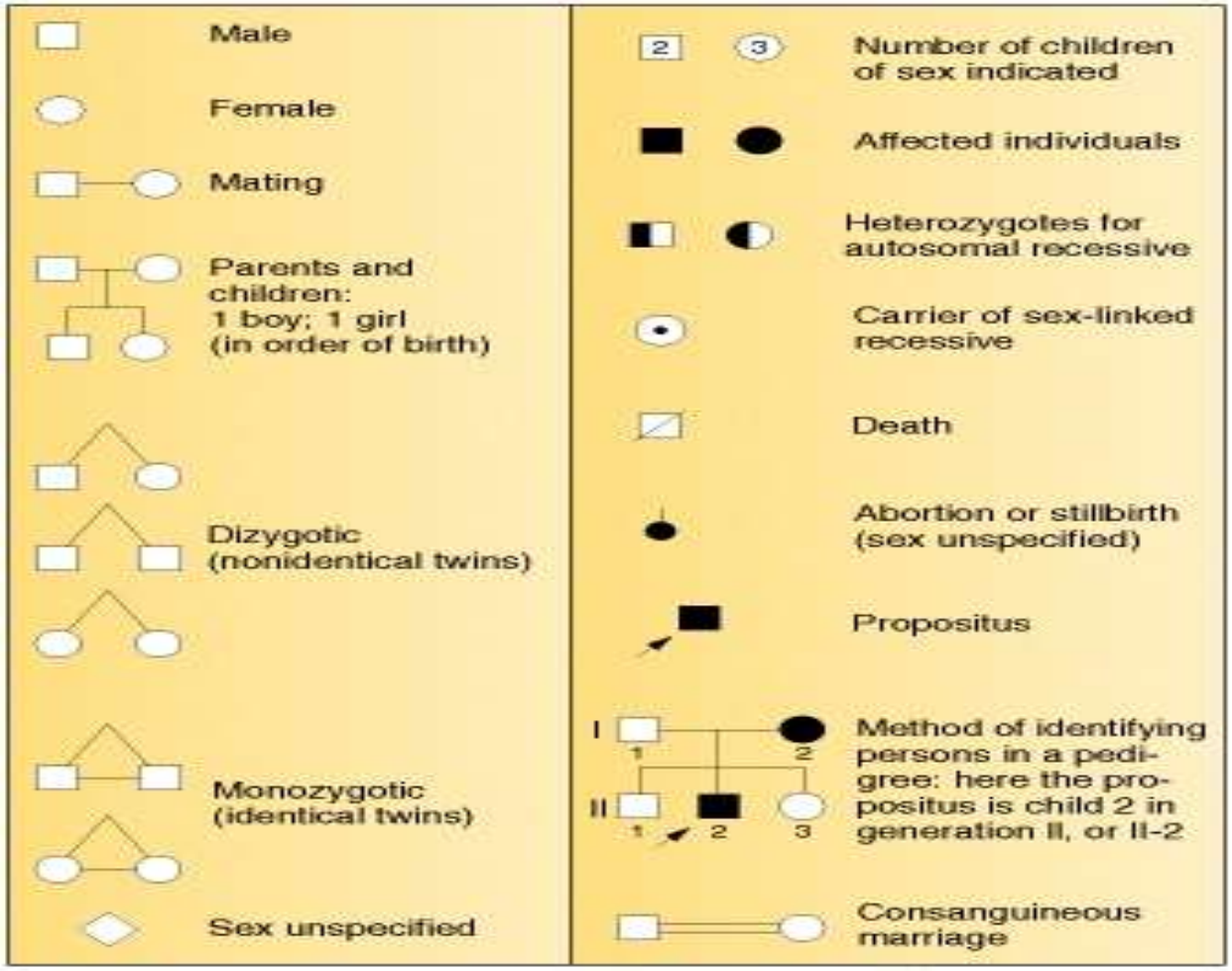
- **Translocations**: common type of chromosomal anomaly, in which a piece of one chromosome breaks off and becomes attached to a different, nonhomologous chromosome.
- **Mosaicism**: when only a portion of cells carry the chromosomal defect and rest of cells are normal.
- Chromosomal disorders are typically identified by chromosomal analysis (**karyotyping**)

- **Genomic disorders** are a group of diseases caused by rearrangements of the genome including deletions (loss of a copy of DNA), duplications (addition of a new copy of DNA), and inversions (altered organization of DNA).
- DiGeorge syndrome {deletions of genes located on chromosome 22q11}
- Genomic disorders are often identified by **fluorescent in situ hybridization (FISH)** or by array comparative genome hybridization (aCGH) technologies

MENDELIAN INHERITANCE

- Human genome: 46 chromosomes (22 pair of **autosomes** and one pair of **sex chromosome**)
- There are 3 classic forms of genetic inheritance:
- **Autosomal dominant**
- **Autosomal recessive**
- **X-linked**

Symbols in family pedigree

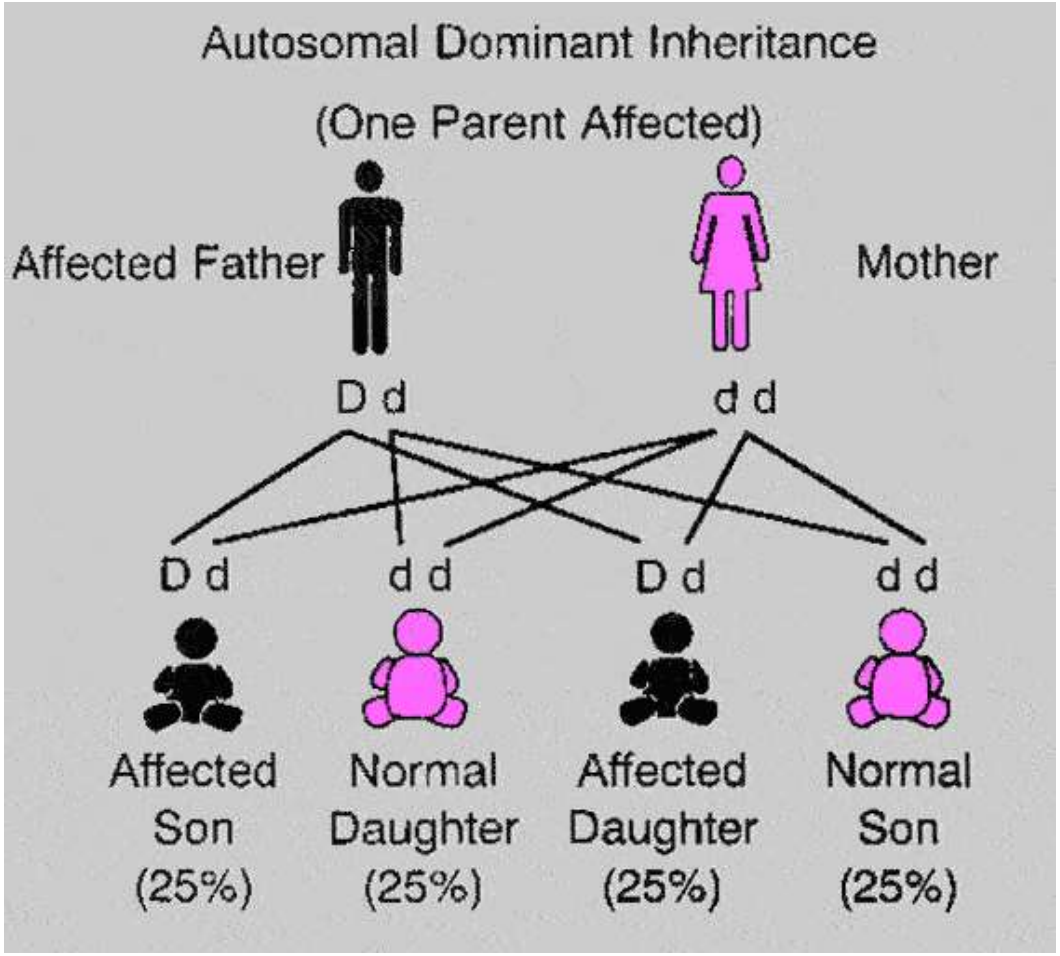


Autosomal Dominant Inheritance

- Determined by the presence of one abnormal gene on one of the autosomes (chromosomes 1 to 22)
- Change in 1 of the paired genes has an effect on the phenotype; (physical manifestations, behavioral characteristics), or differences detectable only through laboratory tests, even though the other copy of the gene is functioning correctly.

Autosomal Dominant Inheritance

- Males and females are equally affected.
- 50% chance of transmission from parent to offspring
- Vertical transmission, all generations.
- Parent to child transmission is a characteristic of autosomal dominant inheritance
- Male to male transmission essentially confirms autosomal dominant inheritance and exclude X linked disorder.


Autosomal Dominant Inheritance
(One Parent Affected)
Affected Father
Mother
D d
d d
D d
d d
D d
d d
Affected Son (25%)
Normal Daughter (25%)
Affected Daughter (25%)
Normal Son (25%)

Autosomal Dominant Inheritance

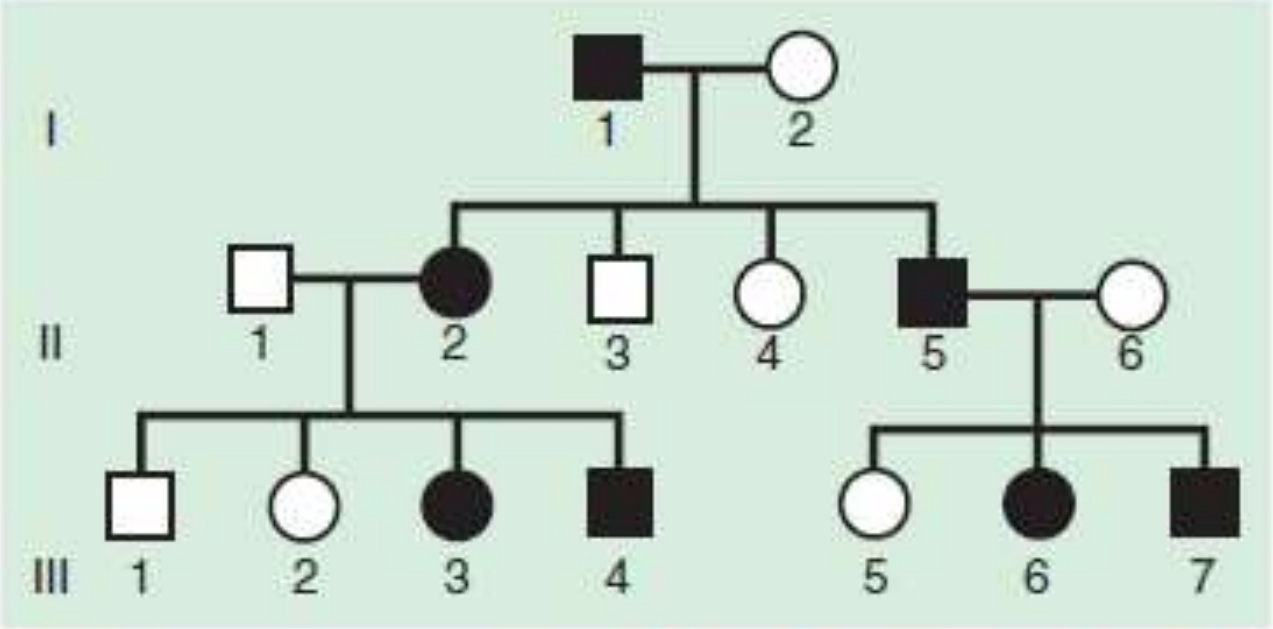


Figure 75-5 Autosomal dominant pedigree. Pedigree showing typical inheritance of a form of achondroplasia *(FGFR3)* inherited as an autosomal dominant trait. *Black*, affected patients.

Mnemonic for **Autosomal Dominant** disorders:

Very Powerful DOMINANT Humans

- Von willebrand disease / Von hippel-lindau
- Pseudo-hypoparathyroidism
- Dystrophia myotonica
- Osteogenesis imperfecta / Osler-weber-rendu
- Marfan syndrome
- Intermittent porphyria
- Neurofibromatosis
- Achondroplasia / Adult polycystic kidney disease
- Noonan syndrome
- Tuberous sclerosis
- Hypercholesterolemia
- Huntington's disease
- Hypertrophic obstructive cardiomyopathy
- Hereditary spherocytosis
- Hereditary non polyposis coli
- Hereditary hemorrhagic telangiectasia

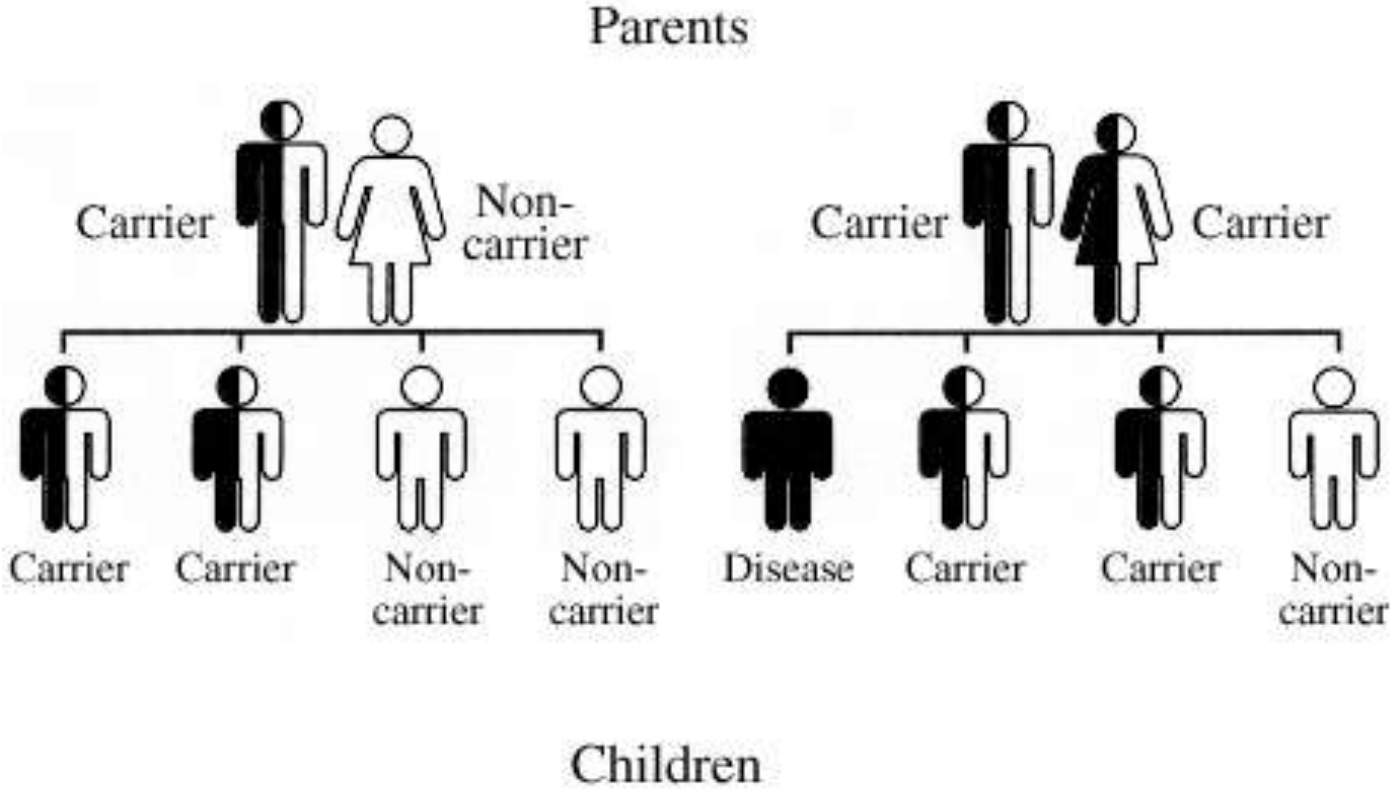
Autosomal Dominant Inheritance

- Many patients with an autosomal dominant disorder have no history of affected family member :
  - **new mutation** occurred in the DNA of the egg or sperm that formed that individual.
  - **Incomplete penetrance,** meaning that not all individuals who carry the mutation have phenotypic manifestations (**skipped generation,** in which an unaffected individual links two affected persons)
  - **variable expression ,**individuals with the same autosomal dominant mutation can manifest the disorder to different degrees.

Autosomal Recessive Inheritance

- Involves mutations in both copies of a gene.
- Examples of autosomal recessive diseases are cystic fibrosis and sickle cell disease.
- Characteristics of autosomal recessive traits include **horizontal transmission,** the observation of multiple affected members of a kindred in the same generation, but no affected family members in other generations;
- recurrence risk of 25% for parents with a previous affected child
- males and females being equally affected

Autosomal Recessive



Autosomal Recessive Inheritance

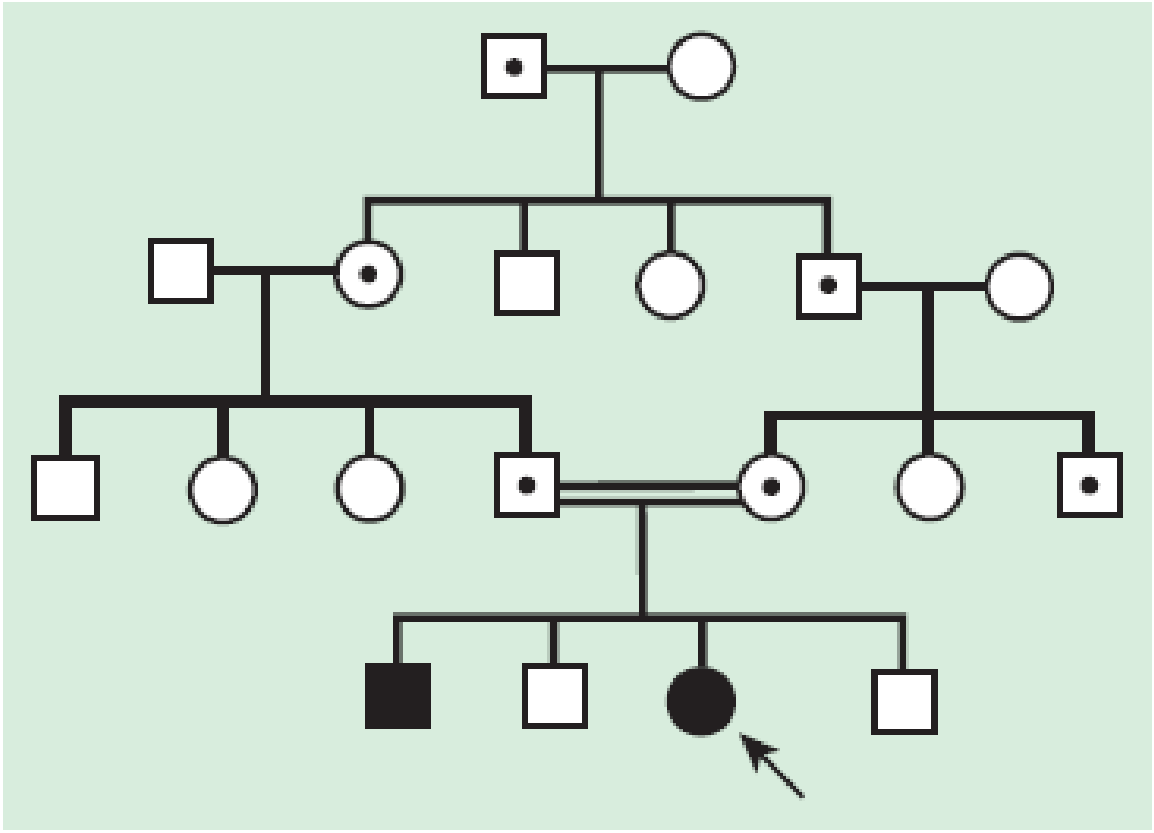


Figure 75-7 Autosomal recessive pedigree with parental consanguinity. *Central dot*, carriers; *black*, affected patients.

AUTOSOMAL RECESSIVE

- CF
- PKU
- GALACTOSEMIA
- HOMOCYSTINURIA
- LYSOSOMAL STORAGE
- A-1 ANTITRYPSIN
- WILSON DISEASE
- HEMOCHROMATOSIS
- GLYCOGEN STORAGE DISEASES

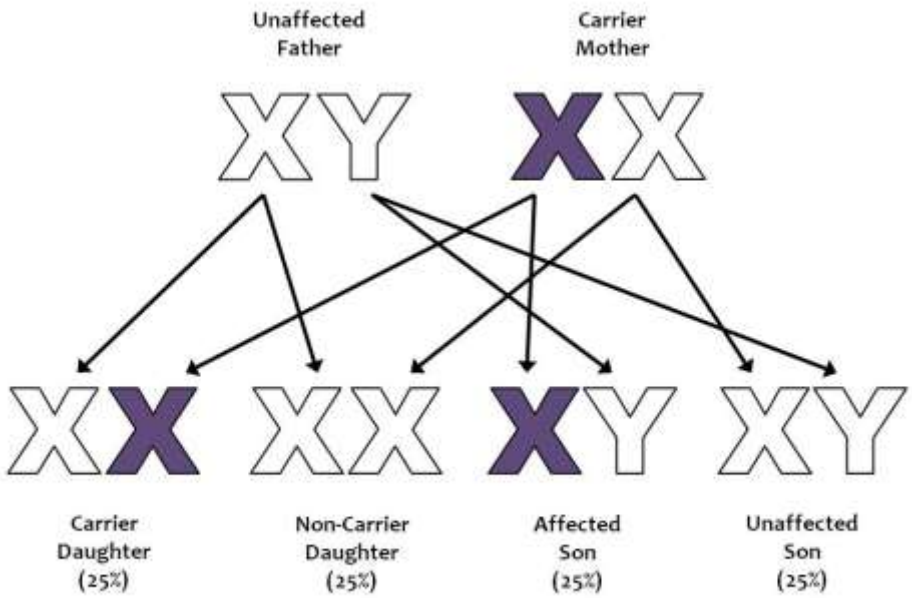
Hgb S
THALASSEMIAS
CONG. ADRENAL HYPERPLASIA
EHLERS-DANLOS (some)
ALKAPTONURIA
NEUROGENIC MUSC. ATROPHIES
FRIEDREICH ATAXIA
SPINAL MUSCULAR ATROPHY

X-Linked Inheritance

- Males are more commonly and more severely affected than females.
- Female carriers are generally unaffected, or if affected, they are affected more mildly than males.

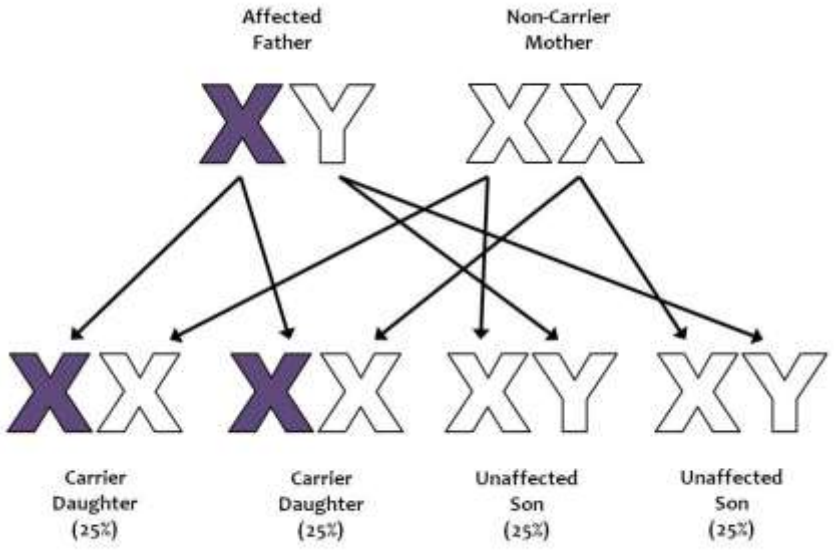
- Male-to-male transmission excludes X-linkage (seen with autosomal dominant and rare disorders of Y-linked inheritance)

X-linked inheritance



Female carriers have a 25% risk for having an affected son, 25% risk for a carrier daughter, and 50% chance of having child that does not inherit the mutated X-linked gene.

X-linked inheritance



- Affected males will have only carrier daughters (all) and have no chance of having an affected son because they will pass the Y chromosome to their sons.

X-Linked Recessive Inheritance

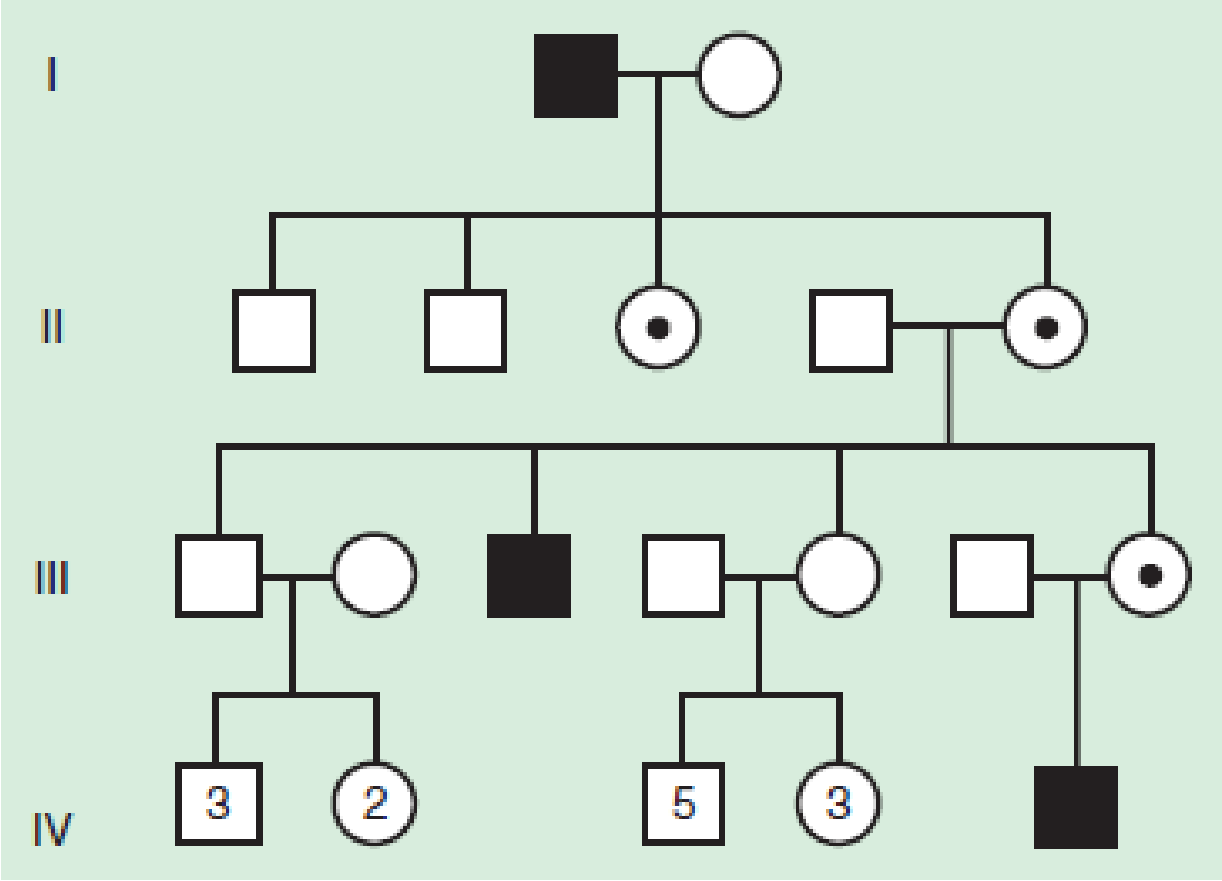


Figure 75-9 Pedigree demonstrating X-linked recessive inheritance.

X linked dominant

- Do not skip generations
- Seen in both males and females
- Females may be more numerous
  - Females can get disease from either parent while males can only get from mother
- Affected male will have 100% daughters affected

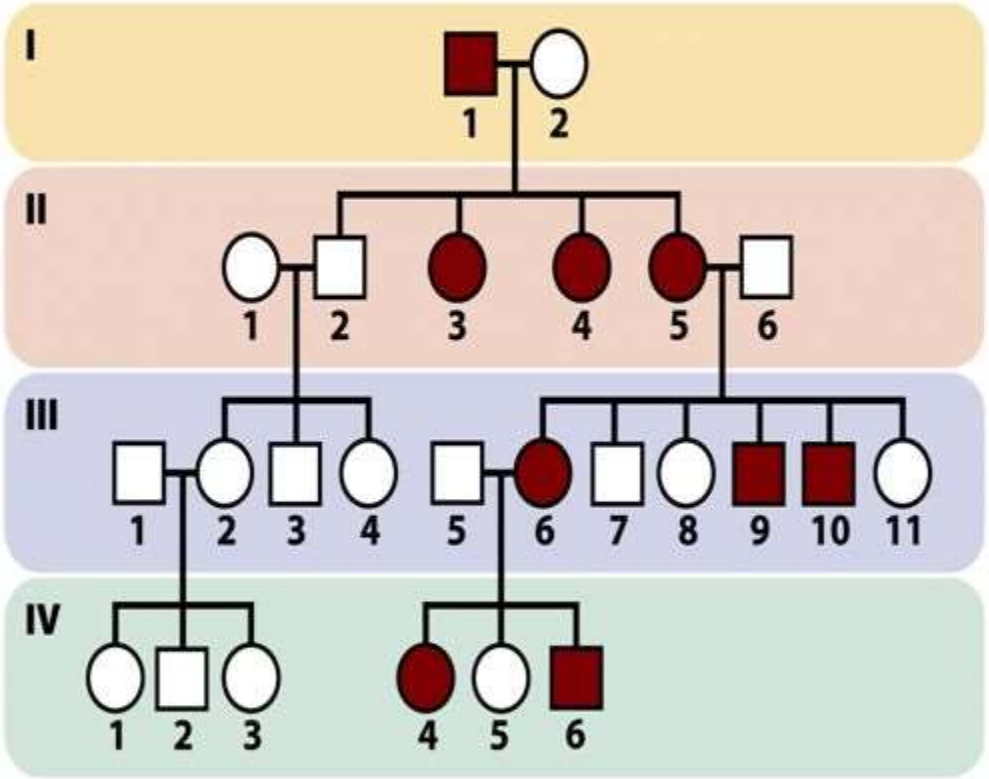


Figure 6-9
Genetics: A Conceptual Approach, Third Edition

Mitochondrial Inheritance

- **Mitochondrial Inheritance**
- An individual's mitochondrial genome is entirely derived from the mother because sperm contain few mitochondria, which are typically shed upon fertilization
- A woman with a mitochondrial genetic disorder can have affected offspring of either sex, but an affected father cannot pass on the disease to his offspring
- e.g mitochondrial myopathy

Clinical cytogenetics

- **Clinical cytogenetics** is the study of chromosomes: their structure, function, inheritance, and abnormalities.
- chromosome abnormalities are very common
- Occur in approximately 1-2% of live births, 5% of stillbirths, and ~50% of early fetal losses in the 1st trimester of pregnancy.
- Chromosome abnormalities are more common among persons with mental retardation and have a significant role in the development of some neoplasms.

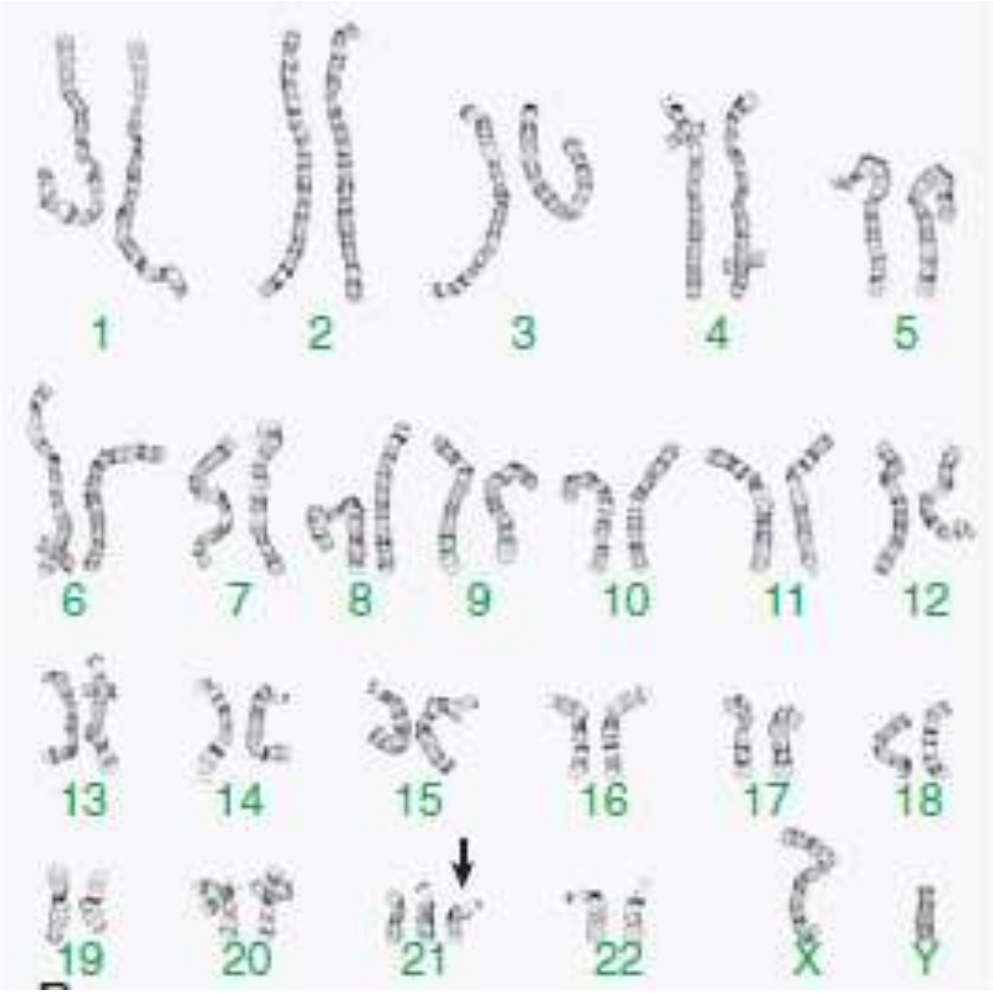
Risks of Chromosomal anomalies

- advanced maternal age
- multiple abnormalities on fetal ultrasound (prenatal testing)
- multiple congenital anomalies
- unexplained growth retardation in the fetus or postnatal growth and development problems
- mental retardation
- ambiguous genitalia
- primary amenorrhea or infertility, recurrent miscarriages (≥3) or prior history of stillbirths and neonatal deaths
- 1st-degree relative with a known or suspected structural chromosome abnormality
- clinical findings consistent with certain chromosomal anomaly
- Certain malignancies, and chromosome breakage syndromes (e.g Fanconi anemia).

Chromosomal disorders

- **Trisomy** is characterized by the presence of 3 chromosomes, instead of the normal 2, of any particular chromosome.
- The occurrence of trisomy 21 and other trisomies increases with advanced maternal age >35yr
- Most individuals with trisomy exhibit a consistent and specific phenotype depending on the chromosome involved:
  - trisomy 21 (Down syndrome)
  - trisomy 18 (Edwards syndrome)
  - trisomy 13 (Patau syndrome)

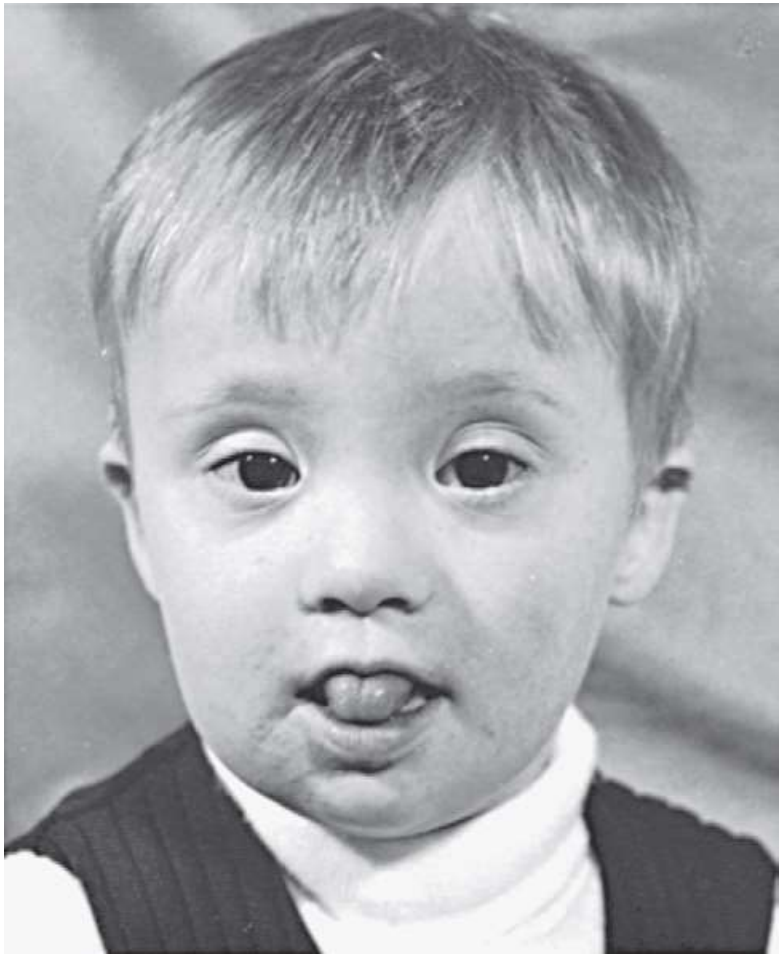
Trisomy 21 (Down Syndrome)



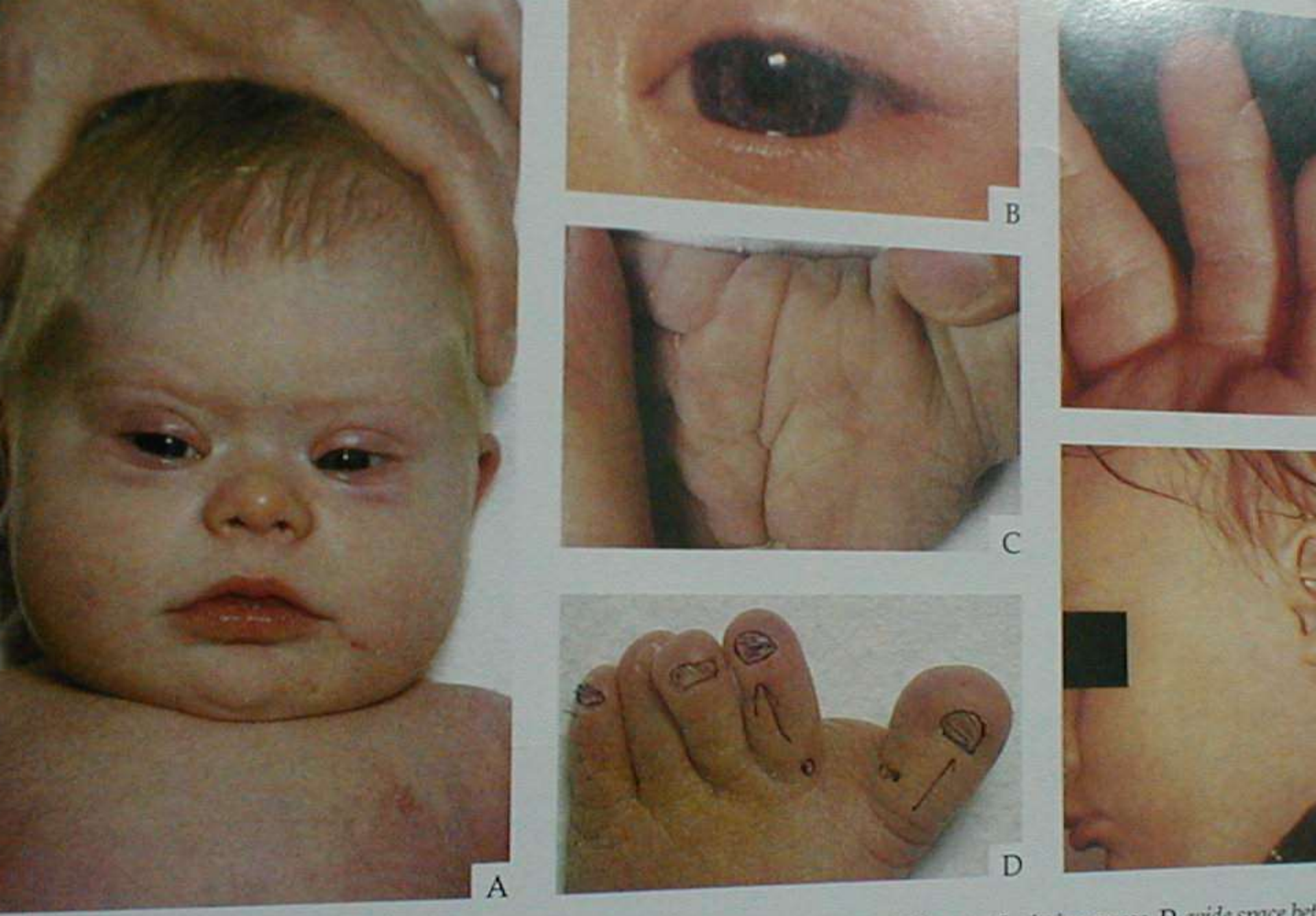
Down Syndrome

- Trisomy 21 is the most common genetic cause of moderate mental retardation.
- The incidence of Down syndrome in live births is approximately 1 in 733
- The life expectancy for children with Down syndrome is reduced (approximately 50-55 yr.)

Down Syndrome



CENTRAL NERVOUS SYSTEM
Hypotonia*
Developmental delay
Poor Moro reflex*
CRANIOFACIAL
Brachycephaly with flat occiput
Flat face*
Upward slanted palpebral fissures*
Epicanthal folds
Speckled irises (Brushfield spots)
Three fontanels
Delayed fontanel closure
Frontal sinus and midfacial hypoplasia
Mild microcephaly
Short hard palate
Small nose, flat nasal bridge
Protruding tongue, open mouth
Small dysplastic ears*
CARDIOVASCULAR
Endocardial Cushing defects
Ventricular septal defect
Atrial septal defect
Patent ductus arteriosus
Aberrant subclavian artery
Pulmonary hypertension
MUSCULOSKELETAL
Joint hyperflexibility*
Short neck, redundant skin*
Short metacarpals and phalanges
Short 5th digit with clinodactyly*
Single transverse palmar creases*
Wide gap between 1st and 2nd toes
Pelvic dysplasia*
Short sternum
Two sternal manubrium ossification centers
GASTROINTESTINAL
Duodenal atresia
Annular pancreas
Tracheoesophageal fistula
Hirschsprung disease
Imperforate anus



G. 1.14 Clinical photographs show several minor anomalies associ-
Brushfield spots. C, simian crease. D, wide space bet
second toes. E, short fifth finger. F, small ears.


Hypotonia
(decreased
muscle tone)
A.D.A.M.


Simian
crease
Normal palm
creases
A.D.A.M.

Down Syndrome

- Neuropsychatric : (autism, disruptive behaviour, depression, alzheimer disease)
- Musculoskeletal : (atlantoaxial instability, hip dysplasia, Slipped capital femoral epiphyses, joints dislocations
- Endocrine : (Congenital or acquired hypothyroidism, DM, infertility, hyperthyroidism)
- Hematology: Transient lymphoproliferative syndrome, acute lymphocytic leukemia, acute myelogenous leukemia
- GI: Celiac disease, obesity

Down Syndrome

- Affected individuals are more prone to congenital heart defects (40-50%) , commonest atrioventricular septal defects
- Developmental delay is universal
- Cognitive impairment does not uniformly affect all areas of development.
- Social development is relatively spared
- Most males with Down syndrome are sterile, but some females have been able to reproduce, with a 50% chance of having trisomy 21 pregnancies

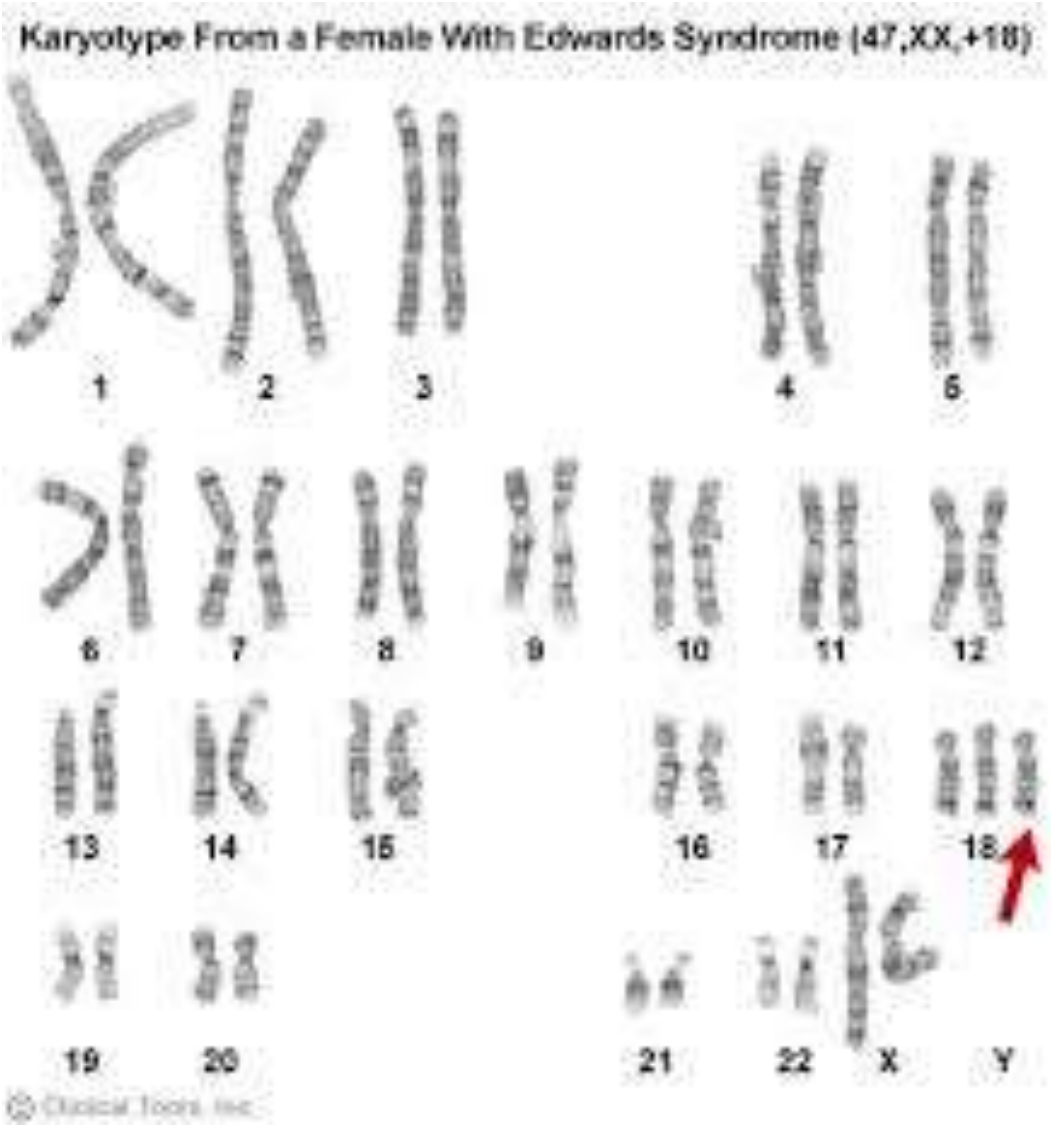
Down Syndrome

- Down syndrome patients are at risk for leukemia (leukemias accounted for 60% of all cancers in people with Down syndrome)

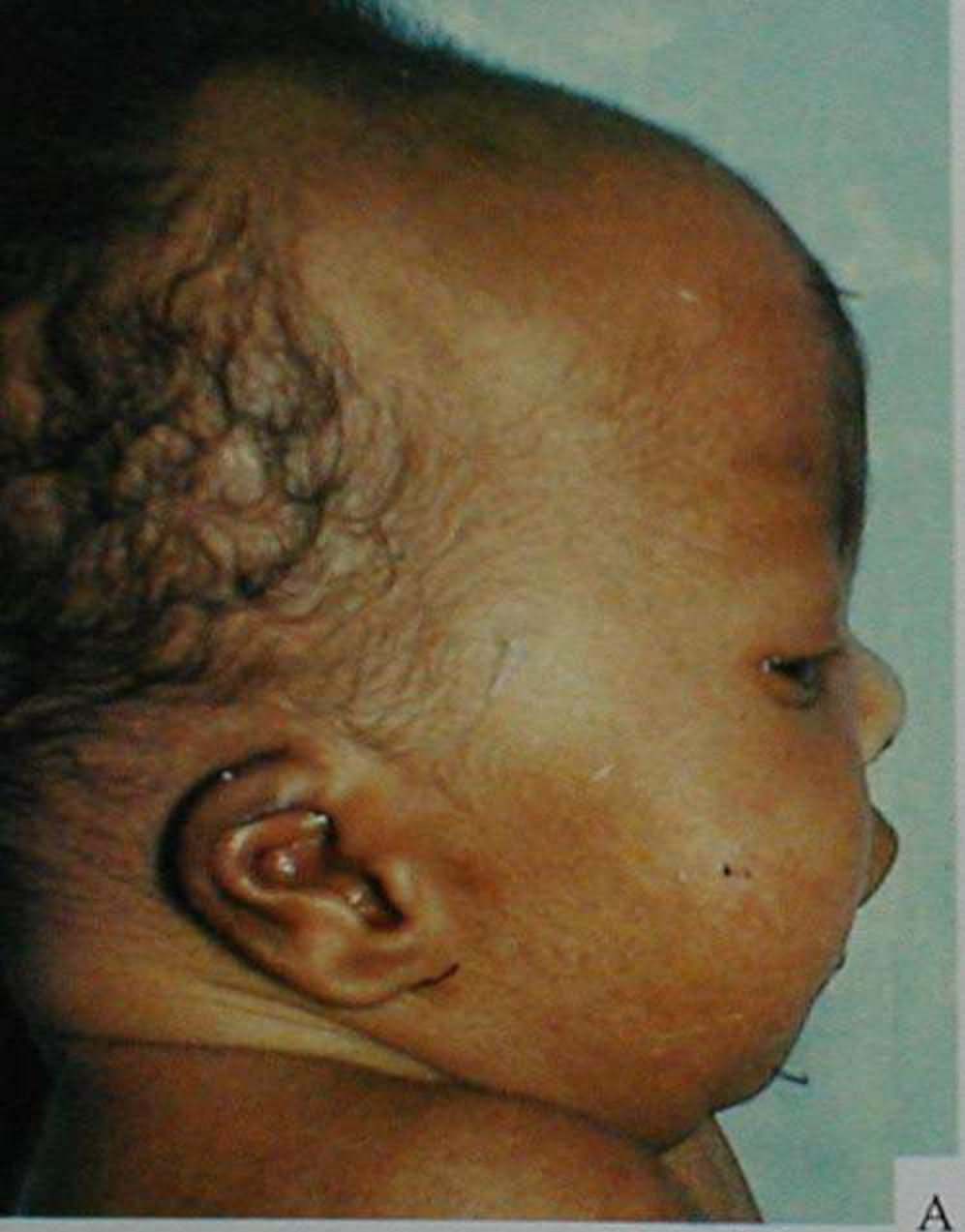
Down Syndrome

- *All women should be offered screening for Down syndrome* in their 2nd trimester by quad screen : 4 maternal serum tests (free β-human chorionic gonadotropin (β-hCG), unconjugated estriol, inhibin, and α-fetoprotein).
- Screening during the 1st trimester by fetal U/S of nuchal translucency thickness

Edward's Syndrome

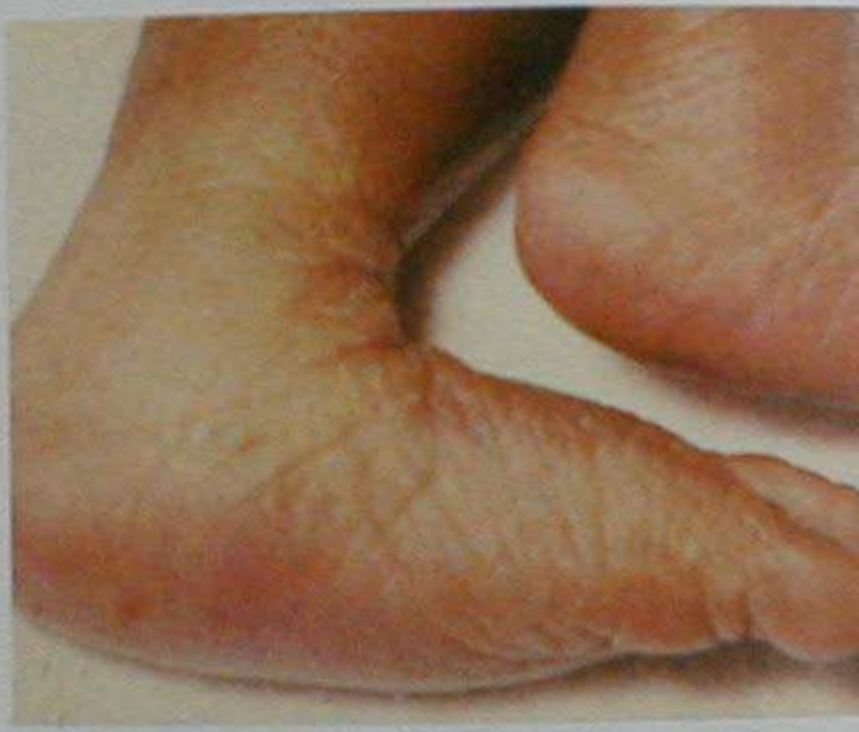


Trisomy 18 (Edward Syndrome)



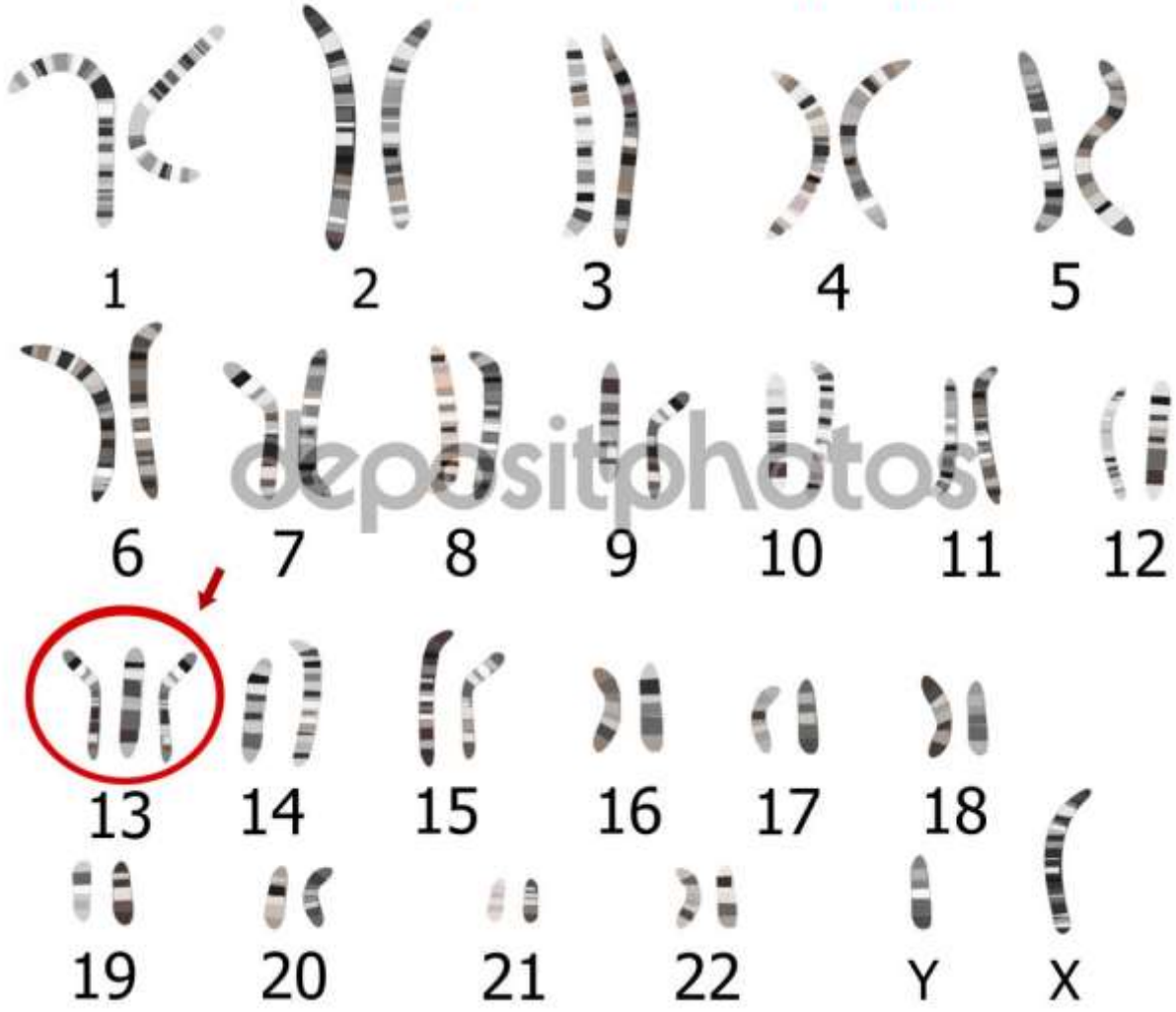
A

l physical manifestations of trisomy 18. A, typical ominent occiput and low-set, posteriorly rotated mal-

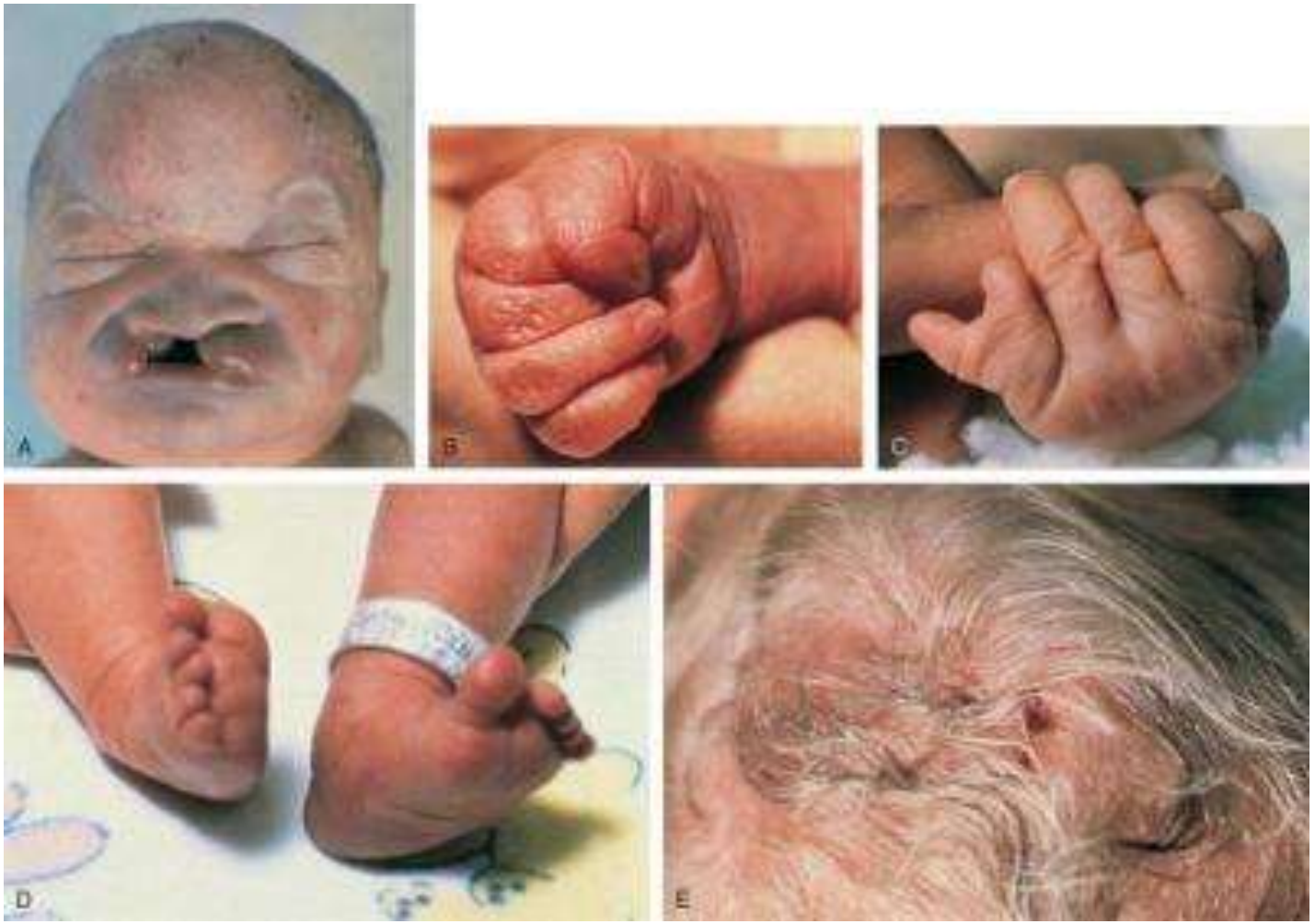


ping fingers. C, rocker-bottom feet. (A, court Garver, West Penn Hospital, Pittsburgh)

Patau syndrome karyotype



Patau Syndrome



Patau Syndrome

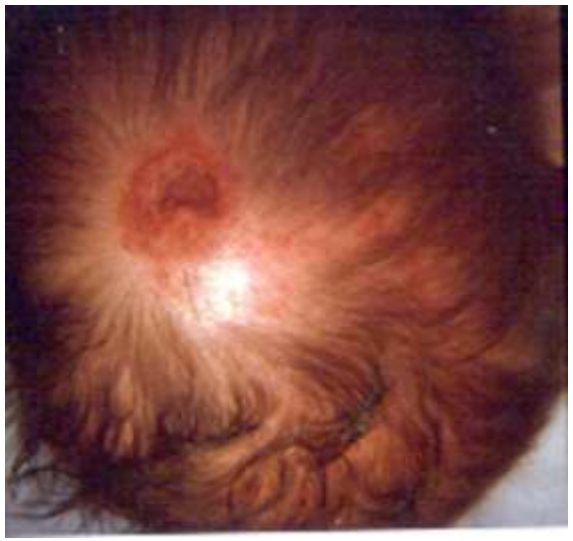
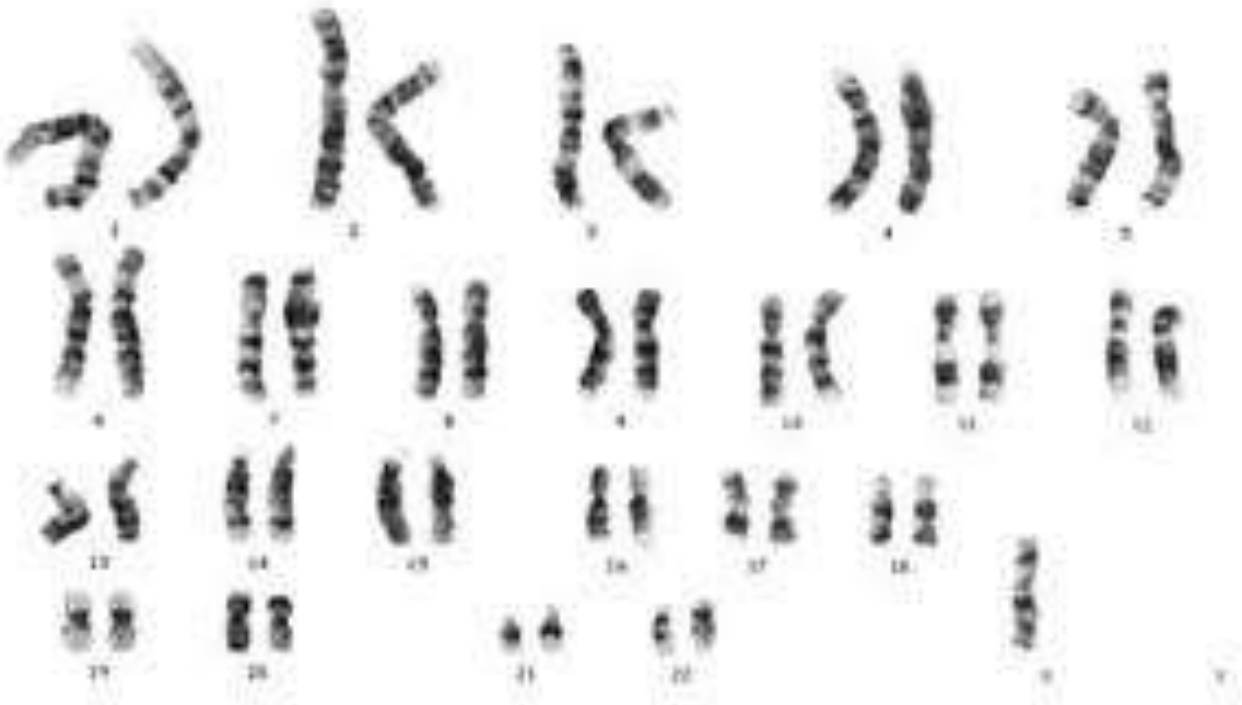


Table 76-10 FINDINGS THAT MAY BE PRESENT IN TRISOMY 13 AND TRISOMY 18

TRISOMY 13	TRISOMY 18
HEAD AND FACE	
Scalp defects (e.g., cutis aplasia) Microphthalmia, corneal abnormalities Cleft lip and palate in 60%-80% of cases Microcephaly Microphthalmia Sloping forehead Holoprosencephaly (arhinencephaly) Capillary hemangiomas Deafness	Small and premature appearance Tight palpebral fissures Narrow nose and hypoplastic nasal alae Narrow bifrontal diameter Prominent occiput Micrognathia Cleft lip or palate Microcephaly
CHEST	
Congenital heart disease (e.g., VSD, PDA, and ASD) in 80% of cases Thin posterior ribs (missing ribs)	Congenital heart disease (e.g., VSD, PDA, ASD) Short sternum, small nipples
EXTREMITIES	
Overlapping of fingers and toes (clinodactyly) Polydactyly Hypoplastic nails, hyperconvex nails	Limited hip abduction Clinodactyly and overlapping fingers; index over 3rd, 5th over 4th; closed fist Rocker-bottom feet Hypoplastic nails
GENERAL	
Severe developmental delays and prenatal and postnatal growth retardation Renal abnormalities Only 5% live >6 mo	Severe developmental delays and prenatal and postnatal growth retardation Premature birth, polyhydramnios Inguinal or abdominal hernias Only 5% live >1 yr

Turner syndrome

- Turner syndrome = 45X
- Maternal age is not a predisposing factor
- Turner syndrome occurs in approximately 1/5,000 female live births.
- In 75% of patients, the lost sex chromosome is of paternal origin
- Most patients tend to be of normal intelligence, but mental retardation is seen in 6%



Karyotype for female with Turner syndrome—45XO

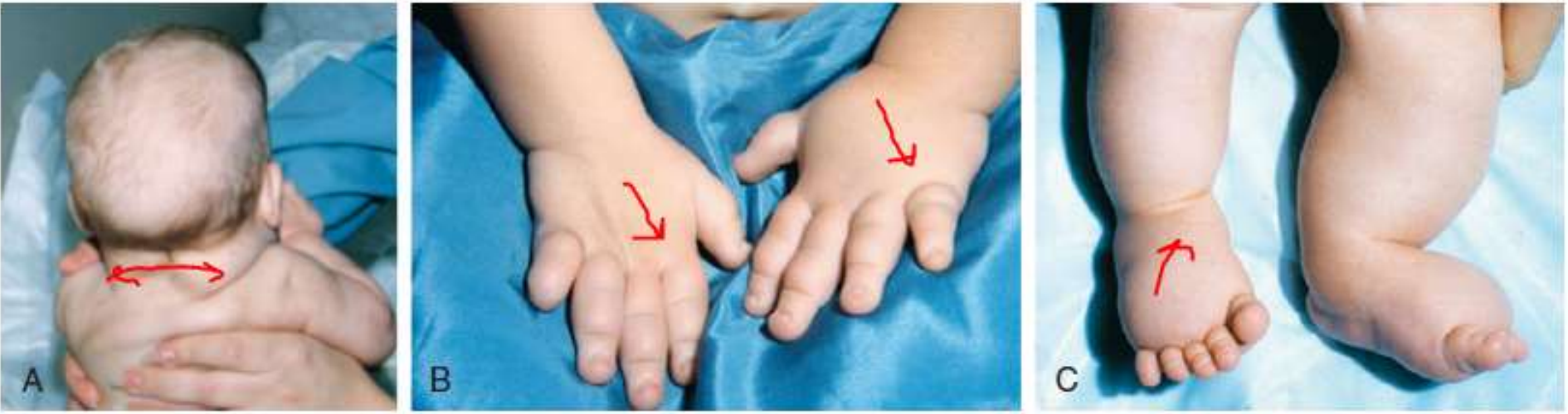


Figure 76-17 Redundant nuchal skin *(A)* and puffiness of the hands *(B)* and feet *(C)* in Turner syndrome. (From Sybert VP, McCauley E: Turner's syndrome, *N Engl J Med* 351:1227–1238, 2004. Copyright © 2004 Massachusetts Medical Society. All rights reserved.)

Turner Syndrome

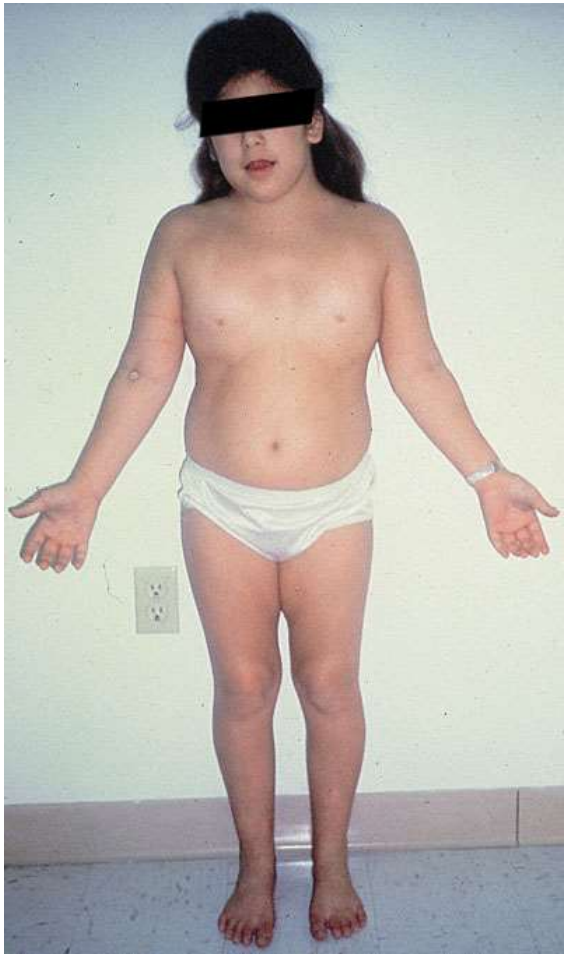


Table 76-15 SIGNS ASSOCIATED WITH TURNER SYNDROME

- Short stature
- Congenital lymphedema
- Horseshoe kidneys
- Patella dislocation
- Increased carrying angle of elbow (cubitus valgus)
- Madelung deformity (chondrodysplasia of distal radial epiphysis)
- Congenital hip dislocation
- Scoliosis
- Widespread nipples
- Shield chest
- Redundant nuchal skin (in utero cystic hygroma)
- Low posterior hairline
- Coarctation of aorta
- Bicuspid aortic valve
- Cardiac conduction abnormalities
- Hypoplastic left heart syndrome and other left heart abnormalities
- Gonadal dysgenesis (infertility, primary amenorrhea)
- Gonadoblastoma (increased risk if Y chromosome material is present)
- Learning disabilities (nonverbal perceptual motor and visuospatial skills) (in 70%)
- Developmental delay (in 10%)
- Social awkwardness
- Hypothyroidism (acquired in 15-30%)
- Type 2 diabetes mellitus (insulin resistance)
- Strabismus
- Cataracts
- Red-green colorblindness (as in males)
- Recurrent otitis media
- Sensorineural hearing loss
- Inflammatory bowel disease
- Celiac disease (increased incidence)

Turner Syndrome

- Phenotypic females with 45,X/46,XY mosaicism have a 15-30% risk of developing **gonadoblastoma.**
- The AAP has recommended the use of FISH analysis to look for Y-chromosome mosaicism in all 45,X patients. If Y chromosome material is identified, laparoscopic gonadectomy is recommended

Noonan Syndrome

- **Noonan syndrome :**autosomal dominant disorder affect both sexes
- Features common to Turner syndrome include short stature, low posterior hairline, shield chest, congenital heart disease, and a short or webbed neck
- Noonan syndrome has different pattern of congenital heart disease typically involving right-sided lesions.

Table 76-16 SIGNS ASSOCIATED WITH NOONAN SYNDROME

Short stature
Failure to thrive
Epicanthal folds
Ptosis
Hypertelorism
Low nasal bridge
Downward-slanting palpebral fissures
Myopia
Nystagmus
Low-set auricles
Dental malocclusion
Low posterior hairline
Short webbed neck, cystic hygroma
Shield chest
Pectus carinatum superiorly
Scoliosis
Cubitus valgus
Pulmonary valve stenosis
Hypertrophic cardiomyopathy
Atrial septal defect, ventricular septal defect
Lymphedema
Cryptorchidism
Small penis
Bleeding disorders, including thrombocytopenia

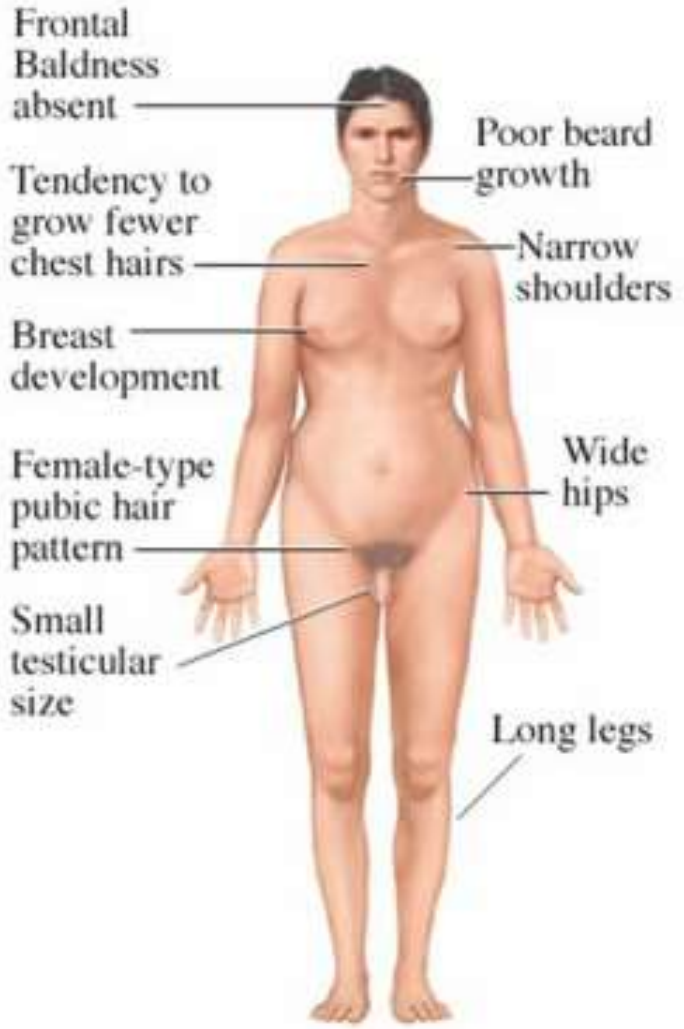
Klinefelter Syndrome

- Klinefelter syndrome pts are phenotypically male
- It is the most common cause of hypogonadism and infertility in males and the most common sex chromosome aneuploidy in humans
- 80% of Klinefelter syndrome have a male karyotype with an extra X chromosome “47,XXY”
- Remaining 20% have multiple sex chromosome aneuploidies (48,XXXY; 48,XXYY; 49,XXXXY), mosaicism (46,XY/47,XXY).
- Each additional X chromosome reduces the IQ by 10-15 points. The main effect is seen in language skills and social domains.

Klinefelter Syndrome

- phenotypically normal male
- Puberty occurs at the normal age, but the testes remain small.
- Taller stature.
- Presentation usually in adulthood as infertility.
- Their intelligence shows variability and ranges from above to below average.
- Persons with Klinefelter syndrome can show behavioral problems, learning disabilities, and deficits in language.

Klinefelter syndrome

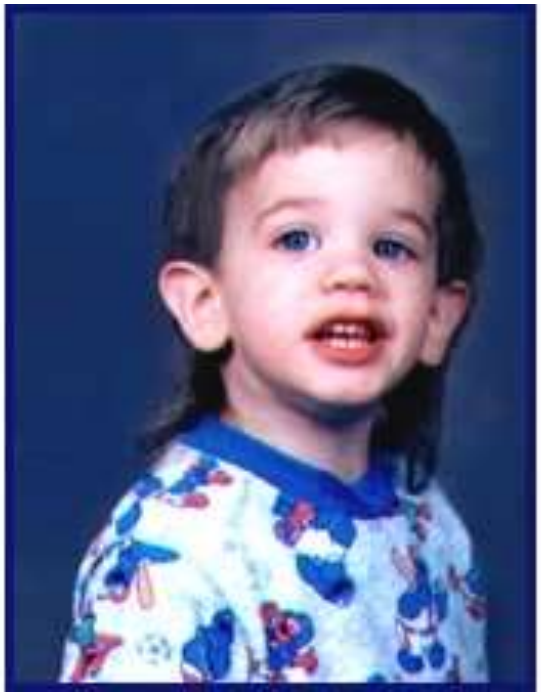


- **Lower IQ than sibs**
- **Tall stature**
- **Poor muscle tone**
- **Reduced secondary sexual characteristics**
- **Gynaecomastia (male breasts)**
- **Small testes/infertility**

Fragile X syndrome

- Fragile X accounts for 3% of males with mental retardation. X linked dominant disorder
- The main **clinical manifestations** in affected males are mental retardation, autistic behavior, macro-orchidism (which may not be evident until puberty), and characteristic facial features
- The facial features, which include a long face, large ears, and a prominent square jaw, become more obvious with age
- Females affected with fragile X show varying degrees of mental retardation and/or learning disabilities.

Fragile X syndrome



Prader Willi Syndrome

- Prader-Willi syndrome results from the loss of paternal chromosome 15q11.2-13 locus.
- C/P: hypotonia as infant, developmental delay, mental retardation, obesity, hypogonadism, short hands and feet, bird{small} like head
- Dx; FISH

Prader-Willi Syndrome

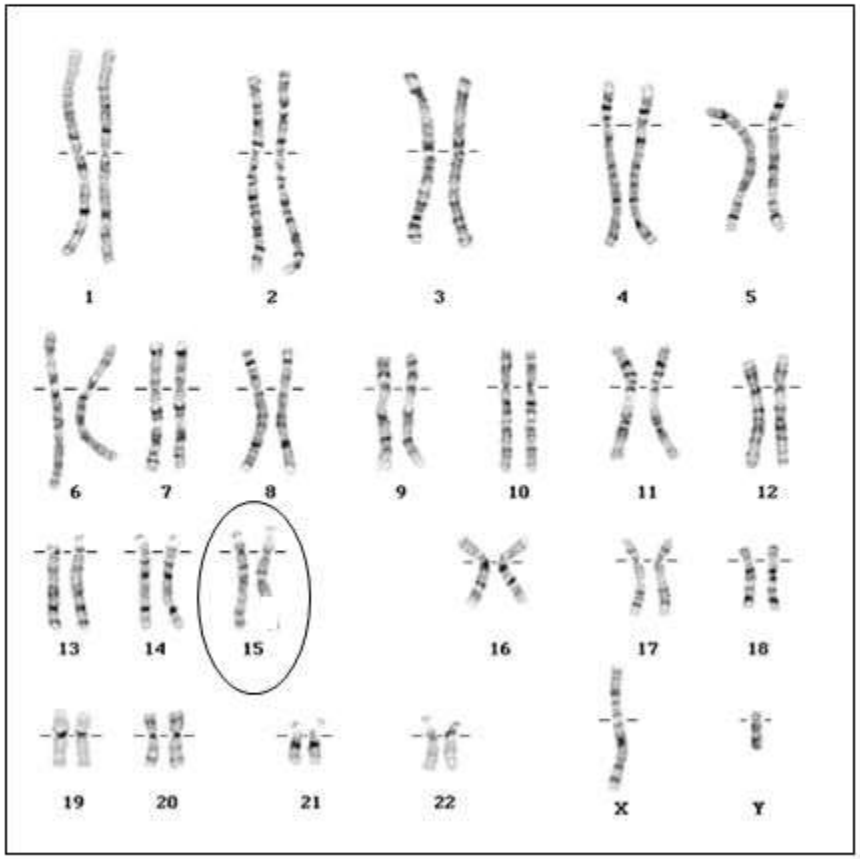
1 in 5,000,000 births

46 chromosomes

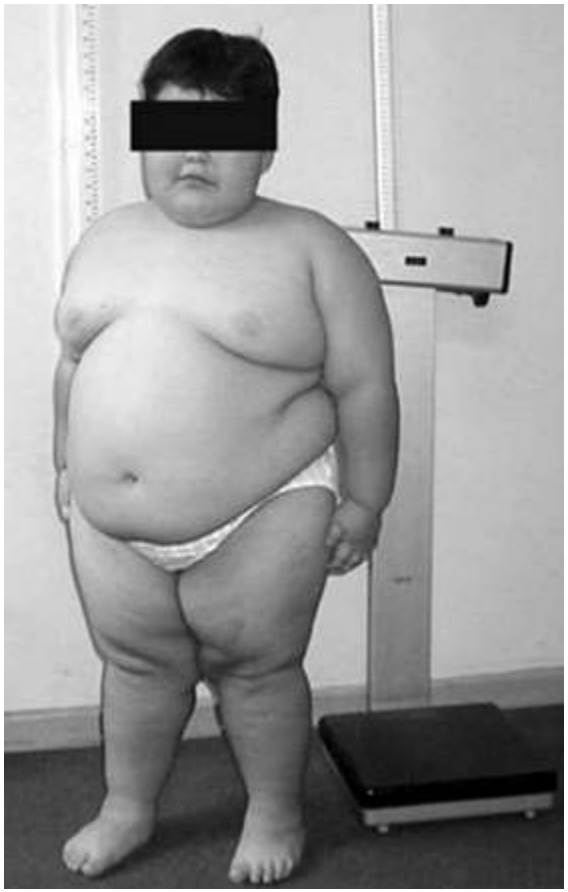
XY=97%

XX=3%

#15 Deletion of lower arm



Prader Willi Syndrome



- Obesity
- Short stature
- Mental retardation
- Short hands and feet
- Hypogonadism

Thanks