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# GENETIC DISEASES

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# Brief History

- First there was Gregor Mendel, a monk who studied inherited characteristics. This was followed by Francis crick and James Watson who unraveled the DNA molecule. This has led us to understanding the human genome sequence

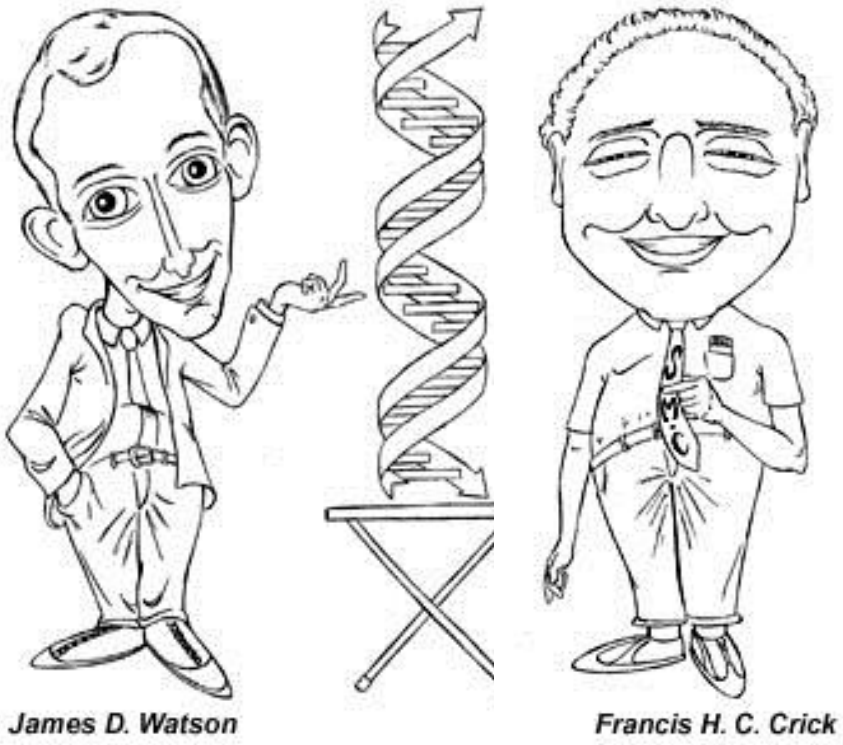
# Gregor Mendel

- 1866
- Gregor Mendel published the results of his investigations of the inheritance of "factors" in pea plants.

# Rosalind Franklin


- 1950's.
- Maurice Wilkins (1916- ), Rosalind Franklin (1920-1957), Francis H. C. Crick (1916- ) of Britain and James D. Watson (1928- ) of the U.S. Discover chemical structure of DNA, starting a new branch of science--molecular biology. .

# Watson and Crick




- Watson and Crick made a model of the DNA molecule and proved that genes determine heredity

# Arthur Kornberg

Arthur Kornberg

- 1957
- Arthur Kornberg (1918- ) of the U.S. produced DNA in a test tube.

# Genetic code

| | U | C | A | G |
|---|---|---|---|---|
| U | UUU Phe | UCU Ser | UAU Tyr | UGU Cys |
| | UUC Phe | UCC Ser | UAC Tyr | UGC Cys |
| | UUA Leu | UCA Ser | UAA End | UGA End |
| | UUG Leu | UCG Ser | UAG End | UGG Trp |
| C | CUU Leu | CCU Pro | CAU His | CGU Arg |
| | CUC Leu | CCC Pro | CAC His | CGC Arg |
| | CUA Leu | CCA Pro | CAA Gln | CGA Arg |
| | CUG Leu | CCG Pro | CAG Gln | CGG Arg |
| A | AUU Ile | ACU Thr | AAU Asn | AGU Ser |
| | AUC Ile | ACC Thr | AAC Asn | AGC Ser |
| | AUA Ile | ACA Thr | AAA Lys | AGA Arg |
| | AUG Met | ACG Thr | AAG Lys | AGG Arg |
| G | GUU Val | GCU Ala | GAU Asp | GGU Gly |
| | GUC Val | GCC Ala | GAC Asp | GGC Gly |
| | GUA Val | GCA Ala | GAA Glu | GGA Gly |
| | GUG Val | GCG Ala | GAG Glu | GGG Gly |

*Genetic Code*

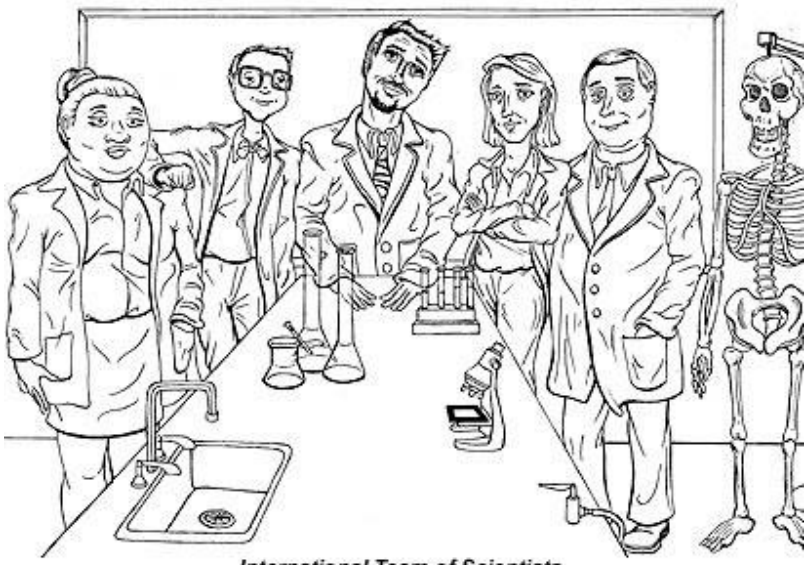
1966

The Genetic code was discovered; scientists are now able to predict characteristics by studying DNA. This leads to genetic engineering, genetic counseling.

# Barbara McClintock


- 1983
- Barbara McClintock (1902-1992) of the U.S. was awarded the Nobel Prize for her discovery that genes are able to change position on chromosomes.

# DNA Fingerprinting



*International Team of Scientists*

The late 1980's.

An international team of scientists began the project to map the human genome.

The first crime conviction based on DNA fingerprinting, in Portland Oregon.

# Gene Therapy


- 1990.
- Gene therapy was used on patients for the first time.

# Dr. Kary Mullis

Kary Mullis

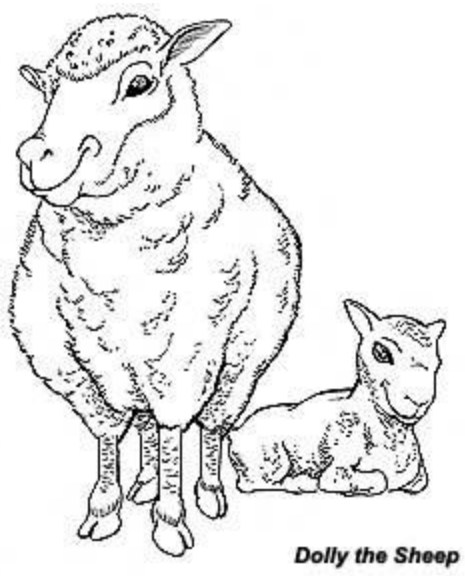
- 1993
- Dr. Kary Mullis discovered the PCR procedure, for which he was awarded the Nobel prize.

# DNA Testing


O.J. Simpson

- 1995.
- DNA testing in forensics cases gains fame in the O.J. Simpson trial.

# Cloning Begins




- 1997.
- Dolly the sheep - the first adult animal clone.

# Genetic diseases

- traditionally - 3 types of diseases
- 1. genetically determined
- 2. environmentally determined
- 3. 1. + 2.
- today - distinctions are blurred
- up to 20% of pediatric in-patients have genetic abnormality
- about 50% of spontaneous abortuses have chromosomal aberration
- only mutations that are not lethal are reservoir of genetic diseases

# Terminology

- hereditary = derived from parents
- familial = transmitted in the gametes through generations
- congenital = present at birth (not always genetically determined - e.g. congenital syphilis, toxoplasmosis)
- ! not all genetical diseases are congenital - e.g. Huntington disease - 3rd to 4th decade of life

# Classification

- 3 groups of genetic diseases

- 1. Disorders with multifactorial inheritance (polygenic)
- 2. Monogenic (mendelian) disorders
- 3. Chromosomal aberrations

# 1. Disorders with multifactorial inheritance (polygenic)

- influence of multiple genes + environmental factors
- relatively frequent
- Diabetes mellitus (see Endocrine pathology)
- Hypertension (see Circulation)
- Gout (discussed here + see Crystals)
- Schizophrenia (Psychiatry)
- Congenital heart disease - certain forms (see Heart)
- Some types of cancer (ovarian, breast, colon) (see Neoplasms)
- often familial occurrence - probability of disease is in $1^{st}$ degree relatives about 5-10%; $2^{nd}$ degree relatives - 0,5-1%

# Gout

- genetically impaired metabolism of uric acid (end product of purine metabolism)
- tissue accumulation of excessive amounts of UA crystals
- recurrent episodes of acute arthritis - precipitation of monosodium urate crystals inside the joints
- formation of large crystalline aggregates - tophi
- chronic destruction of joints - joint deformity
- renal injury
- M>F

- Primary gout (90% of cases)
- unknown enzymatic defect

- Secondary gout (10%)
- known cause of hyperuricemia (increased turnover of nucleic acids - e.g. leukemias; chronic renal disease; increased intake - game, red wine)

# Morphology

- Acute arthritis
- any joint, mostly hallux - abrupt and intense pain
- Chronic arthritis
- permanent precipitation - tophi - inflammation (lymphocytes, histiocytes)
- destruction of cartilage, fibrosis of synovial membrane, ankylosis
- Kidneys - 3 forms
- medulla (papillae), tophi, kidney stones

- tophi are formed in the vicinity of joints, bursa olecrani, bursa preapatellaris, auricle
- less frequently kidneys, other tissues
- urate crystals are soluble in water! - fixation in absolute alcohol (biopsy!!!)
- turns polarized light
- patients with gout - obese, increased risk of hypertension, arteriosclerosis

- Clinical presentation - <u>3 stages</u>
- 1. asymptomatic hyperuricaemia
- 2. acute arthritis - attacks of acute pain (days-weeks), silent periods (months-years)
- 3. chronic changes - tophi, ankylosis, in 20% chronic renal failure

# 2. Monogenic (mendelian) disorders

- mutation of 1 gene, mendelian type of inheritance
- today about 5000 diseases
- Autosomal dominant
- Autosomal recessive
- X-linked

# Autosomal dominant disorders

- both homozygotes and heterozygotes are affected
- usually heterozygotes (inherited from one parent)
- both males and females are affected
- transmission from one generation to the other
- 50% of children are affected

# Familial hypercholesterolemia

- (= subgroup of hyperlipoproteinemia)
- most frequent mendelian disorder - 1:500
- mutation of gene encoding LDL-receptor (70% of plasma cholesterol)
- heterozygotes 2-3× elev. of plasma cholesterol levels
- homozygotes 5× elevation of plasma cholesterol levels
- heterozygotes asymptomatic until adulthood - xanthomas along tendon sheets, coronary AS
- homozygotes - xanthomas in childhood, death due to MI by the age of 15Y

# Marfan syndrome

- French pediatrician Marfan - 1896 - young girl with typical habitus
- abnormal protein fibrillin - secreted by fibroblasts, part of ECM
- impairment of collagenous and elastic tissue - decreased firmness of connective tissue
- principal clinical manifestations - 3 systems

# 1. skeleton

- slender, elongated habitus
- long legs, arms and fingers (arachnodactyly) - El Greco!
- high, arched (Gothic) palate
- hyperextensibility of joints
- spinal deformities, pectus excavatum, pigeon breast - pres. Lincoln???

# 2. ocular changes

- dislocation or subluxation of the lens (weakness of suspensory ligaments)

# 3. cardiovascular system

- fragmentation of elastic fibers in tunica media - aorta
- aneurysmal dilatation - aortic dissection - rupture (35-45% of pts.)
- incompetence (dilatation) - aortic valve
- tricuspidal and/or mitral valve - floppy valve

# Ehlers-Danlos syndrome

- similar to Marfan syndrome
- genetic defect of collagen fibrils - several types - both autosomal dominant and recessive
- hyperextensibility of skin, hypermobility of joints - contortionist!
- joint dislocations, vulnerability
- rupture of large vessels, colon, cornea

# 2. Autosomal recessive

- majority of mendelian disorders
- only homozygotes are affected, heterozygotes (parents) are only carriers
- 25% of descendants are affected
- if the mutant gene occurs with low frequency - high probability in consanguineous marriages
- onset of symptoms often in childhood
- frequently enzymatic defect
- testing of parents and amnial cells

# Cystic fibrosis

- 1:2000 live births - most common lethal genetic disease in white population
- defect in the transport of chloride ions across epithelia - increased absorption of Na+ and water to the blood
- widespread defect in the exocrine glands - abnormally viscid mucous secretions
- blockage of airways, pancreatic ducts, biliary ducts

- Pancreatic abnormalities (85%) - dilatation of ducts, atrophy of exocrine part, fibrosis
- Pulmonary lesions - dilatation of bronchioles, mucus retention, repeated inflammation, bronchiectasis, lung abscesses, emphysema and atelectasis (100%), cor pulmonale chronicum
- GIT - meconium ileus (newborns) (25%), biliary cirrhosis (2%)
- Male genital tract - sterility (obstruction of vas deferens, epididymis, seminal vesicles) (95%)

# Clinical symptomatology

- recurrent pulmonary infections
- pancreatic insufficiency, malabsorption syndrome (large, foul stool), hypovitaminosis A, D, E, K, poor weight gain
- high level of sodium in the sweat - "salty" children - mother's diagnosis
- death usually in 3. decade due to respiratory failure

# Phenylketonuria (PKU)

- absence of enzyme phenylalanine-hydroxylase (PAH) Phe ->Tyr
- increase of plasmatic Phe since birth - rising levels - impairs brain development
- after 6M - severe mental retardation - IQ under 50
- decreased pigmentation of hair and skin - absence of Tyr
- EARLY SCREENING TEST!!!
- DIET!!!
- mothers with PKU - increased levels of Phe - transplacental transport - child with severe mental defect (although heterozygous!) - maternal PKU - DIET!!!

# Galactosemia

- defect of galactose metabolism
- lactose -> Gal+Glc
- Gal -> Glc - defect - accumulation of Gal in blood
- liver, eyes, brain are affected
- hepatomegaly (fatty change - fibrosis - cirrhosis)
- lens - opacification - cataracts
- brain - loss of neurons, gliosis, edema
- Symptomatology - from birth
- vomiting, diarrhea, jaundice, hepatomegaly
- later - cataracts, mental retardation
- DIET!

# Glycogen storage diseases (glycogenoses)

- deficiency of any one of the enzymes involved in degradation or synthesis
- depending on the type of defect - tissue distribution, type of accumulated product
- 12 forms - most important:
- type I. - von Gierke disease - hepatorenal type
- type II. - Pompe disease - generalized type (liver, heart, skeletal muscle)
- type V. - McArdle syndrome - skeletal muscle only
- biopsy: PAS, Best's carmine

# Lysosomal storage diseases

- defect of lysosomal enzymes, hydrolyzing various substances (a.o. sphingolipids, mucopolysacharides) - storage of insoluble metabolites in lysosomes
- extremely rare

## Sphingolipidoses

- more frequent in Ashkenazi Jews

# Gaucher disease

- defect of glucocerebrosidase - 3 types (type 1 - survival, type 2 - lethal, type 3 - intermediate)
- accumulation of glucocerebroside (Glc-ceramide) - kerasin
- Gaucher cells - spleen (red pulp), liver (sinuses), bone marrow

# Niemann-Pick disease

- defect of sphingomyelinase
- accumulation of cholesterol and sphingomyelin in spleen, liver, BM, LN, lungs - massive visceromegaly
- CNS (foamy cells) - severe neurological deterioration
- death during first 4-5 years

# Tay-Sachs disease (gangliosidosis)

- neurons and glial cells of CNS - mental retardation, blindness

# Mucopolysacharidoses

- MP synthesized in the connective tissue by fibroblasts - part of the ground substance
- several clinical variants (I-VII)
- involvement of liver, spleen, heart (valves, coronary arteries), blood vessels
- Symptoms: coarse facial features (gargoylism), clouding of the cornea, joint stiffness, mental retardation
- usually death in childhood (cardiac complications)
- most frequent Hurler syndrome and Hunter syndrome (X-linked!)

# X-linked diseases

- transmitted by heterozygous mother to sons
- daughters - 50% carriers, 50% healthy
- sons - 50% diseased, 50% healthy
- Children of diseased father - sons are healthy, all daughters are carriers
- Hemophilia A (defect of Factor VIII)
- Hemophilia B (defect of Factor IX)
- Muscle dystrophy (Duchen disease)

# 3. Chromosomal aberrations (cytogenetic disorders)

- alternations in the number or structure of chromosomes
- autosomes or sex chromosomes
- studied by cytogenetics
- cell cycle arrested in metaphase (colchicin) - staining by Giemsa method (G-bands) - photographing - karyotype
- 2 sets of 23 chromosomes
- 22 pairs of autosomes, 2 sex chromosomes (XX or XY)
- cytogenetic disorders are relatively frequent! (1:160 newborns; 50% of spontaneous abortions)

# Numerical abnormalities

- euploidy - normal 46 (2n)
- polyploidy (3n or 4n) - spontaneous abortion
- aneuploidy
- trisomy (2n+1) - 47 - compatible with life
- monosomy (2n-1) - autosomal - incompatible with life
- - sex chromosomal - compatible with life

# Structural abnormalities

- breakage followed by loss or rearrangement
- deletion, translocation

Generally:

- loss of chromosomal material is more dangerous than gain
- abnormalities of sex chromosomes are better tolerated than autosomal
- abnormalities of sex chromosomes sometimes symptomatic in adult age (e.g. infertility)
- usually origin de novo (both parents and siblings are normal)

# Autosomal disorders

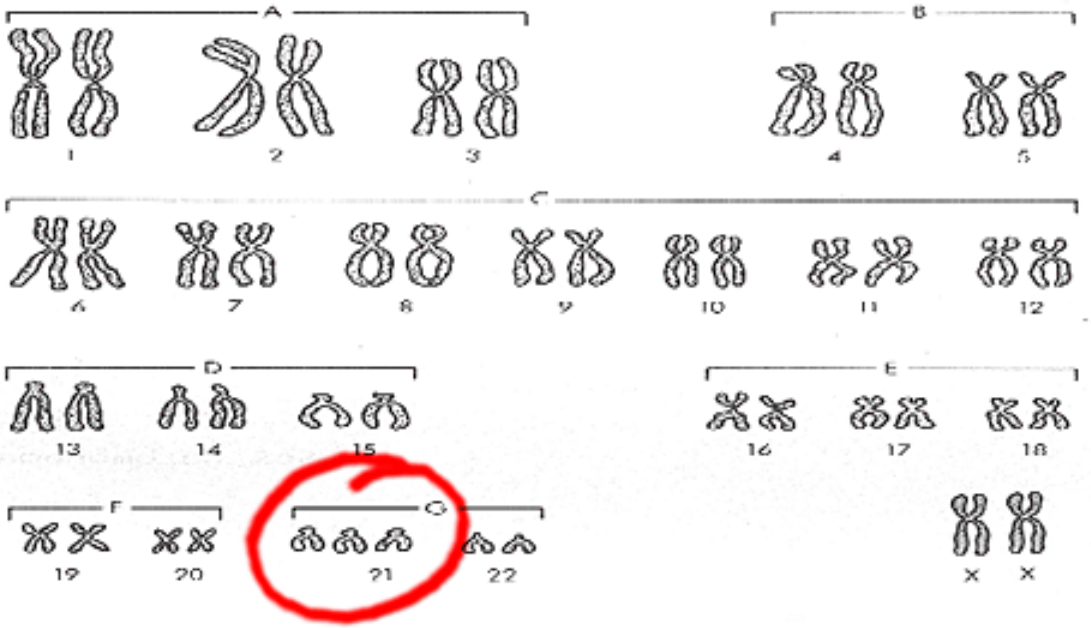
## Trisomy 21 (Down syndrome)

- most frequent - 1:700 births; parents have normal karyotype
- maternal age has a strong influence: <20 y. 1:1550 live births, >45 y. 1:25 live births
- most frequently is abnormality in ovum (ovum is under long-time influence of enviroment)

# Clinical symptoms

- mental retardation (IQ 25-50)
- flat face + epicanthus
- congenital heart defects
- neck skin folds
- skeletal muscle hypotonia
- hypermobility of joints
- increased risk of acute leukemias
- mortality 40% until 10Y (cardiac complications)

# Down's Syndrome
# or Trisomy 21



# Less frequent disorders

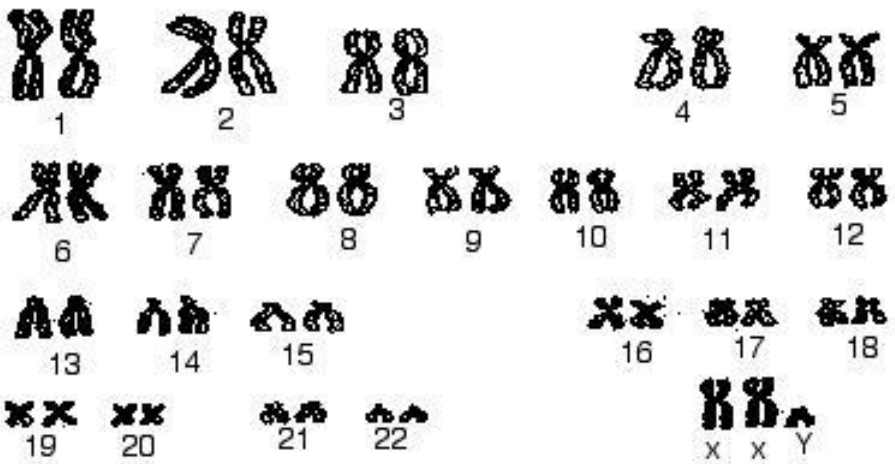
- Trisomy 18 (Edwards syndrome) 1:8000
- Trisomy 13 (Patau syndrome) 1:15000

# Sex chromosomal disorders

- a number of karyotypes from 45(X0) to 49 (XXXXY) - compatible with survival
- normally - in females 1 of X is inactivated (all somatic cells contain Barr body)
- ! male phenotype is encoded by Y

# Klinefelter syndrome (47, XXY)

- 1:1000 males
- additional X is either of paternal or maternal origin
- advanced maternal age, history of irradiation of either of parents
- wide range of clinical manifestations
- distinctive body habitus - increase length between soles and pubic bone
- reduced body and facial hair
- gynecomastia
- testicular atrophy - impaired spermatogenesis - sterility (rarely fertility! - mosaics)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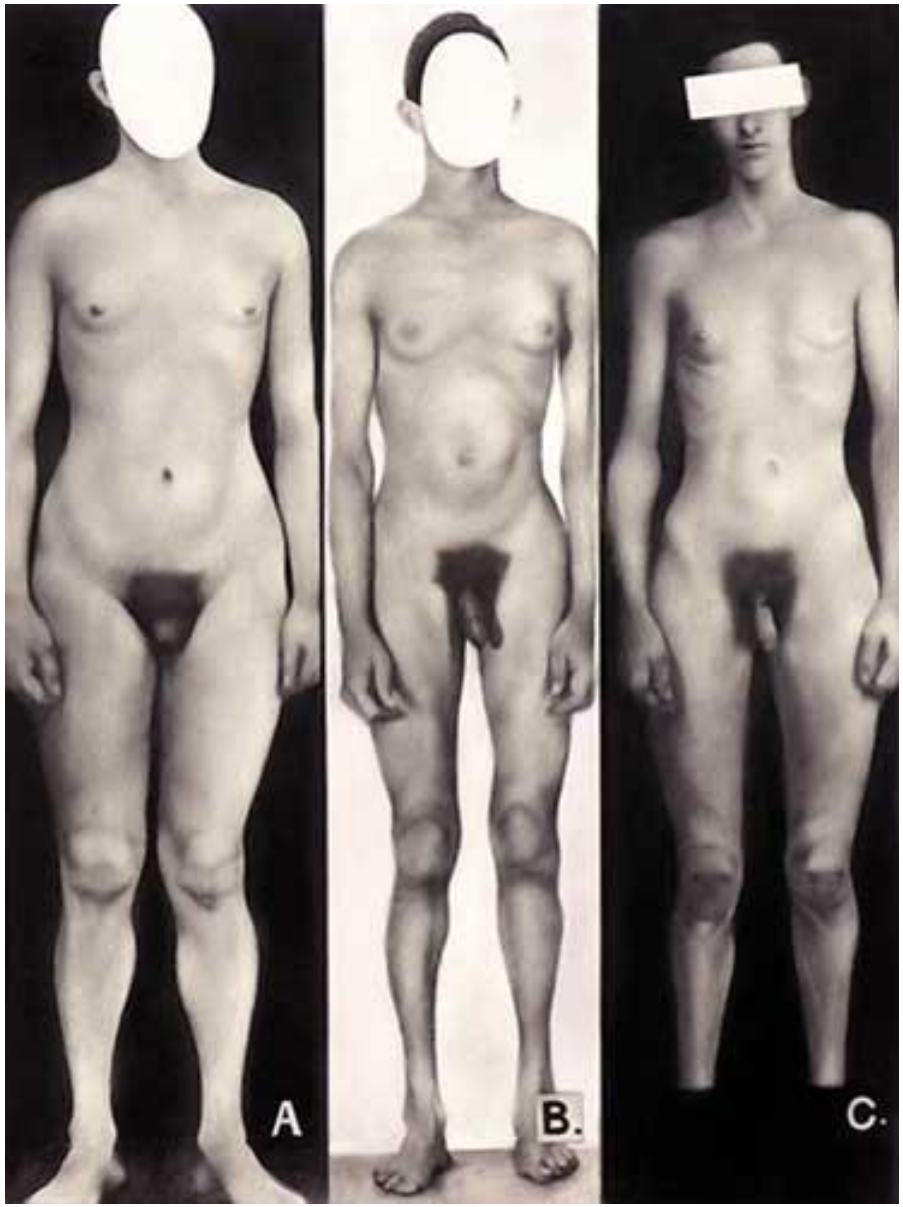
x x Y


A
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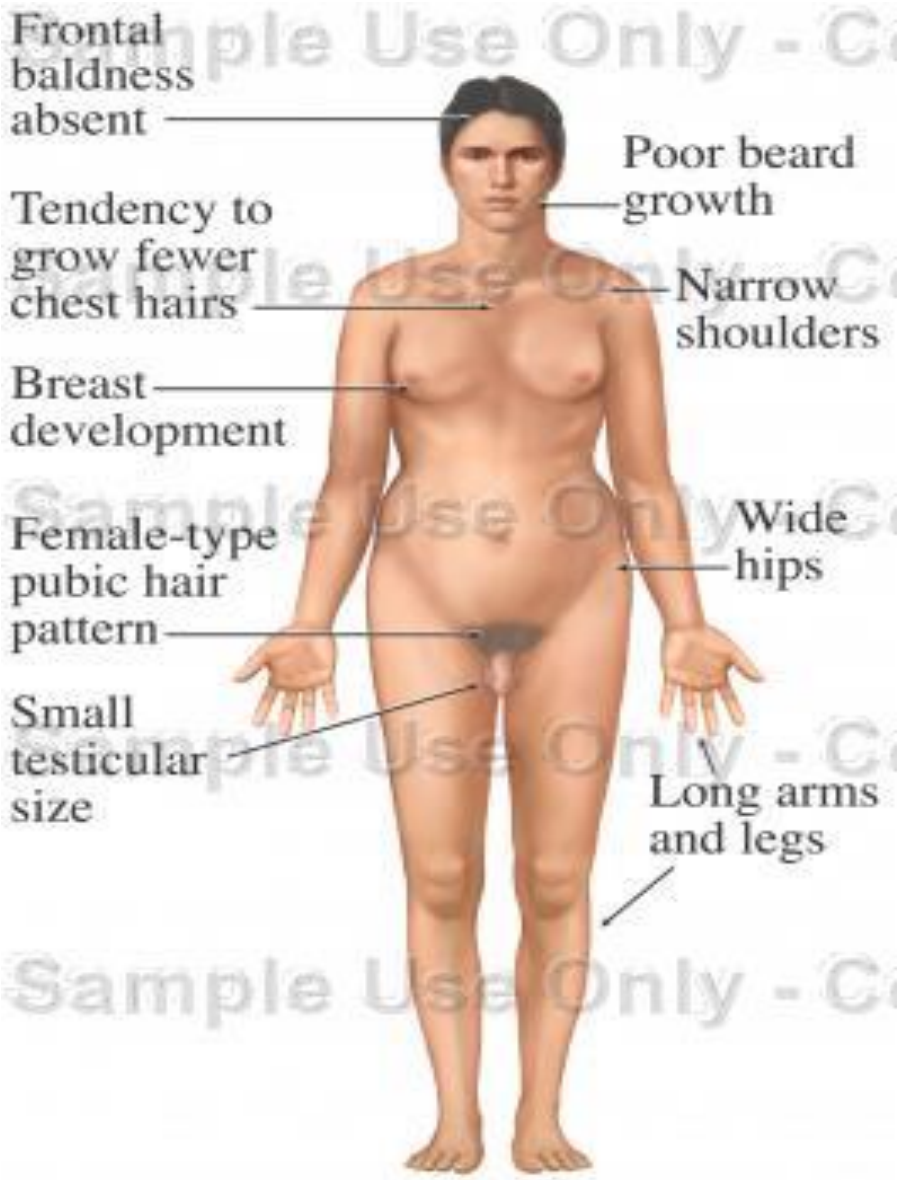
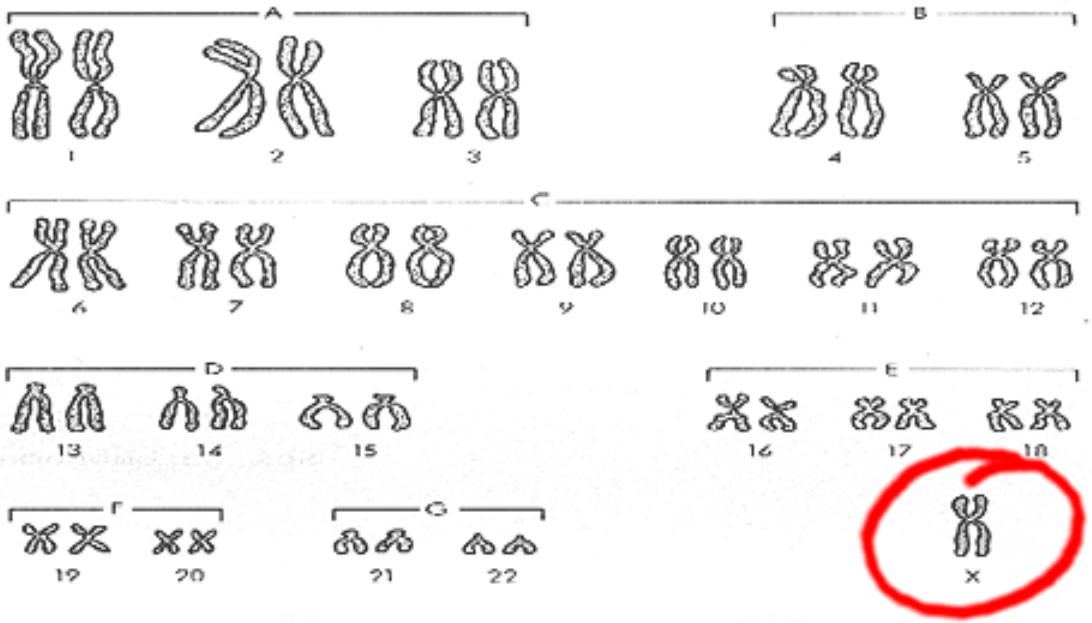
- Klinefleter's



# Turner syndrome (45, X0)

- 1:3000 females
- primary hypogonadism in phenotypic female
- growth retardation (short stature, webbing of the neck, low posterior hairline, broad chest, cubitus valgus)
- streak ovaries - infertility, amenorrhea, infantile genitalia, little pubic hair

# Turner's Syndrome



# Prenatal diagnostics

- amniocentesis - analysis of amniotic fluid
- cytogenetic analysis (karyotype - e.g. Down)
- biochemical activity of various enzymes (e.g. Tay-Sachs)
- analysis of various specific genes (CF gene - PCR)
- sex of the fetus (X-linked disorders - hemophilia)

# Pediatric diseases

- infants and children
- first year of life - high mortality
- highest mortality - neonatal period (first 4W; perinatal first 1W)
- between 1Y and 15Y of age - the leading cause of death = injuries from accidents

# Congenital malformations

- structural defects present at birth - some may become apparent later!
- etiology is either genetic or environmental
- viral infections (rubella, CMV) - during first 3M
- other infectious (toxoplasmosis, syphilis, HIV)
- drugs (thalidomide, alcohol, cytostatics)
- irradiation
- in 40-60% is the cause unknown!

# Perinatal infections

- ascending (transcervical) - in utero or during birth (HSV, HIV)
- transplacental - syphilis, toxoplasmosis, rubella, CMV

# Prematurity

- higher morbidity and mortality than in full term babies
- before 37.-38. W
- high risk - weight <2500g
- intracerebral bleeding (immature vessels in basal ganglia)
- infant respiratory distress syndrome RDS - decrease in surfactant synthesis; 15-20% 32.-36.W vs. 60% <28.W
- SIDS - sudden infant death syndrome (crib death, cot death)
- Erythroblastosis fetalis - hemolysis due to ABO or Rh incompatibility between mother and fetus