Types of genetic injury

I. Mutation of one gene

II. Polygenic diseases

III. Aberration of chromosomes: **numerical:** trisomy,
structural: deletion, inversion, translocation microdeletion,

IV. Single gene disorders with nonclassic inheritance (mitochondrial DNA, imprinting

Mutation of one gene

point mutation: *indifferent:* changed triplet codes for the same amino acid
missense: triplet codes for different amino acid : sickle cell anamia
nonsense: stop
frameshift: insertion, deletion

trinucleotide repeat : expansion of nucleotide triplet:
polyglutamin diseases CAG repeat (Huntington)
not CAG repeat : Fragile X syndrome FMRI (familiar mental retardation) gene 200-4000 repeat of CGG

I. Mutation of one gene:

Mendelian inheritance

Mendelian disorders: single gene defect follows mendelian pattern of inheritance

1. Autosomal dominant
2. Autosomal recessive
3. X linked recessive

Single gene mutation → many consequence : **pleotrophy** :Marphan syndrome

Same genetic trait → several genetic loci: **genetic heterogeneity**: retinitis pigmentosa

1. Autosomal dominant disorders:

Characteristics:

•Symptoms expressed in heterozygous state

•One parent of index case is affected, they affect males and females equally and
•both sex can transmit the disease.
•50% probability to inherit the disease if one parent is affected

•Enzyme proteins are not affected (generally no symptoms). Mutation of receptor or structural proteins.
•Sometimes same disease is due to a new mutation
•Clinical feature is influenced by variable penetrance and expressivity.
•Sometimes onset is in adulthood (Huntington disease Trinucleotide repat of huntington gene).
•Dominant negativ protein product inhibits the function of the normal protein.

•Receptor protein: LDL receptor: familial hypercholesterinaemia

•Structural protein: collagens: Ehler Danlos collagens, Marfan sy.fibrillin

Autosomal dominant diseases:

Nervous system: Huntington disease (CAG trinucl repeat), impairment of basal ganglia;
neurofibromatosis,-neurofibromin

Urinary: polycystic kidney disease

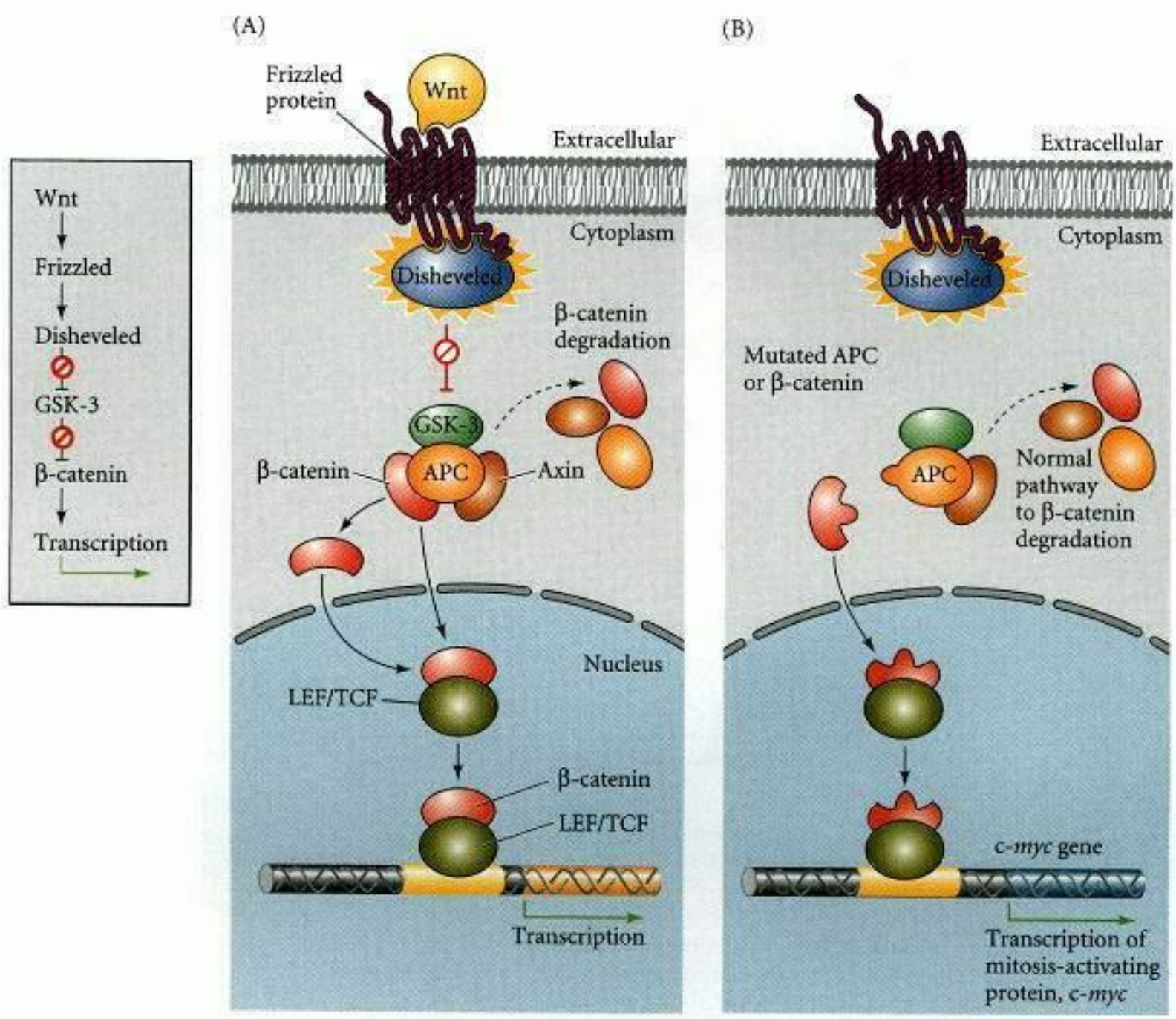
Gastrointestinal: familial polyposis APC gene mutation Peutz Jeghers syndrome

Hematopoetic: von Willebrand disease
hereditary spherocytosis

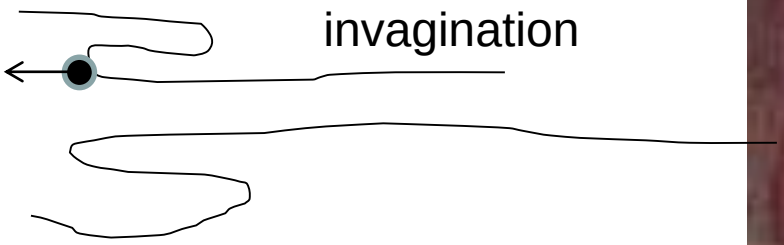
Skeletal: Marfan syndrome: fibrillin mutation (protein of elastic fibers)
tall stature- long fingers , subluxation of lens, aortic aneurysm
floppy valves, aortic dissection

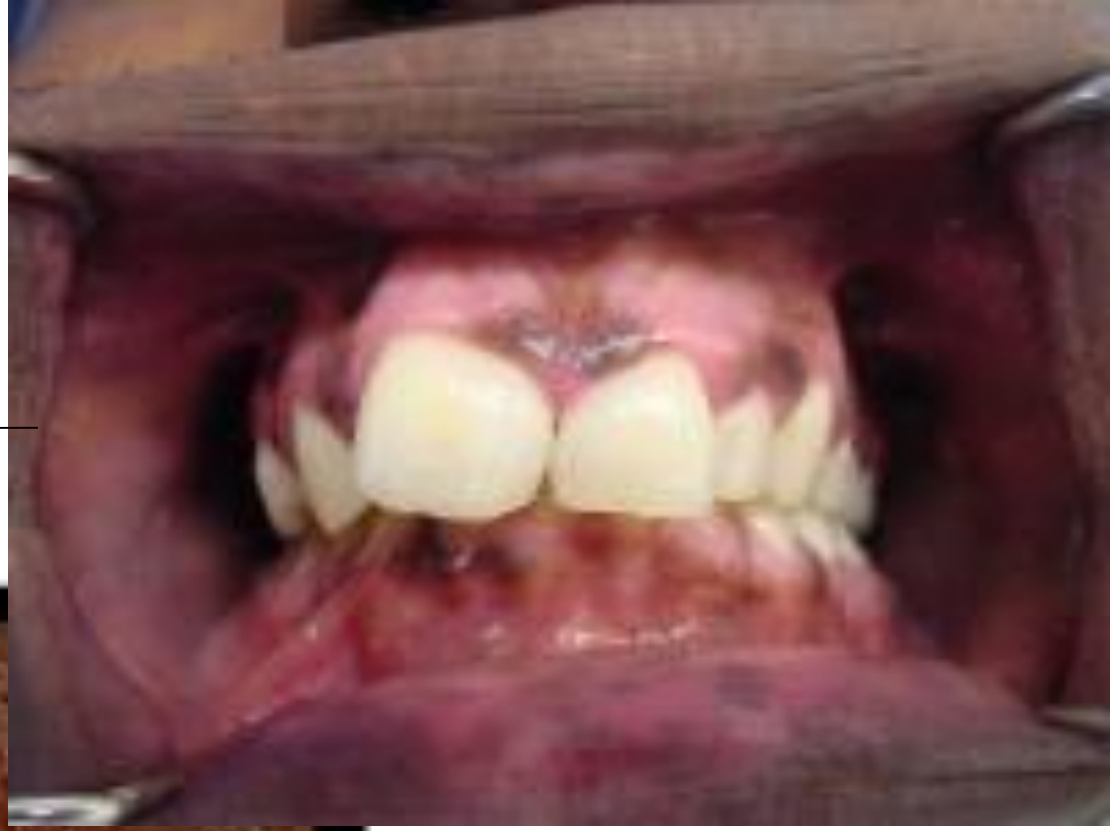
Ehlers-Danlos: defect of collagen synthesis (6 variants)
fragile hyperexensible skin, hypermobile joints, rupture of internal organs. Wound healing is poor.

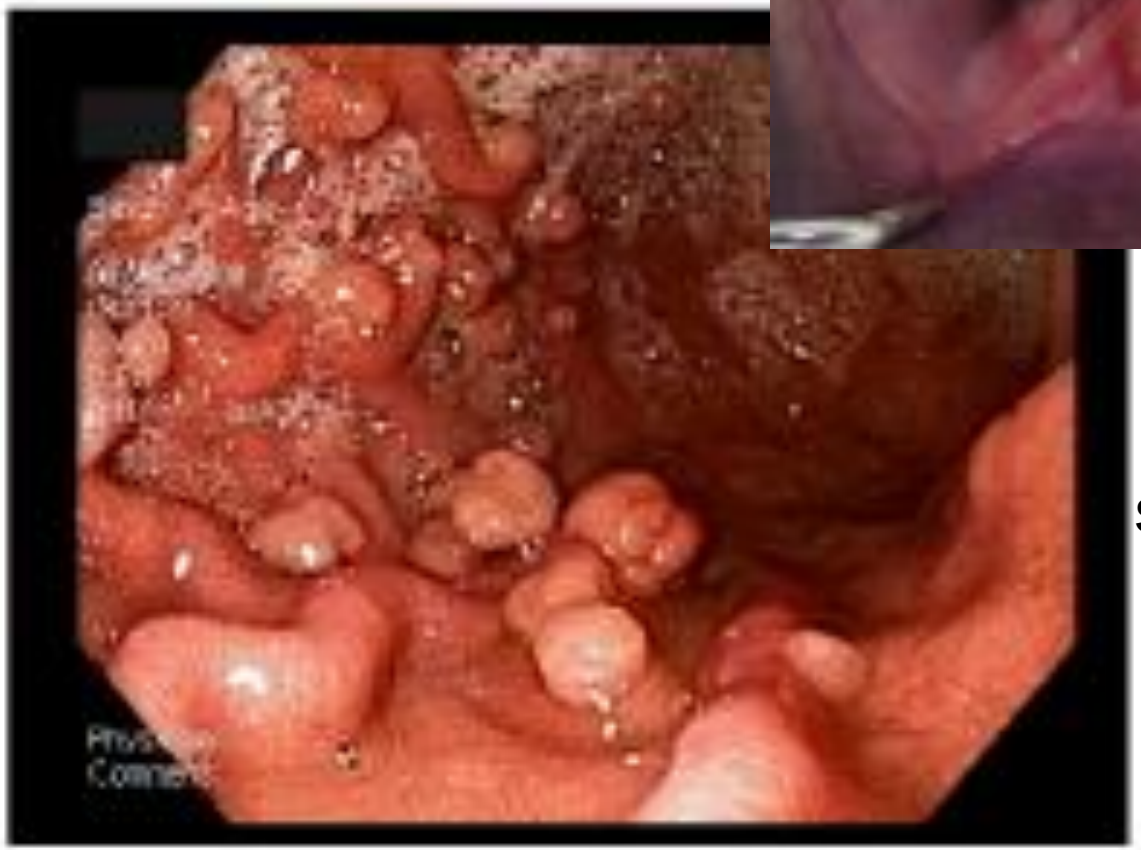
Metabolic: Familial hypercholesterinaemia: mutation of LDL receptor
hypercholesterinemia, increased risk of arterioclerosis,coronary artery disease, xantomas


Wnt
Frizzled
Disheveled
GSK-3
β-catenin
Transcription
(A)
Frizzled protein
Wnt
Extracellular
Cytoplasm
Disheveled
β-catenin degradation
GSK-3
β-catenin
APC
Axin
Nucleus
LEF/TCF
β-catenin
LEF/TCF
Transcription
(B)
Extracellular
Cytoplasm
Disheveled
Mutated APC or β-catenin
APC
Normal pathway to β-catenin degradation
c-myc gene
Transcription of mitosis-activating protein, c-myc

Peutz –Jegher syndrome



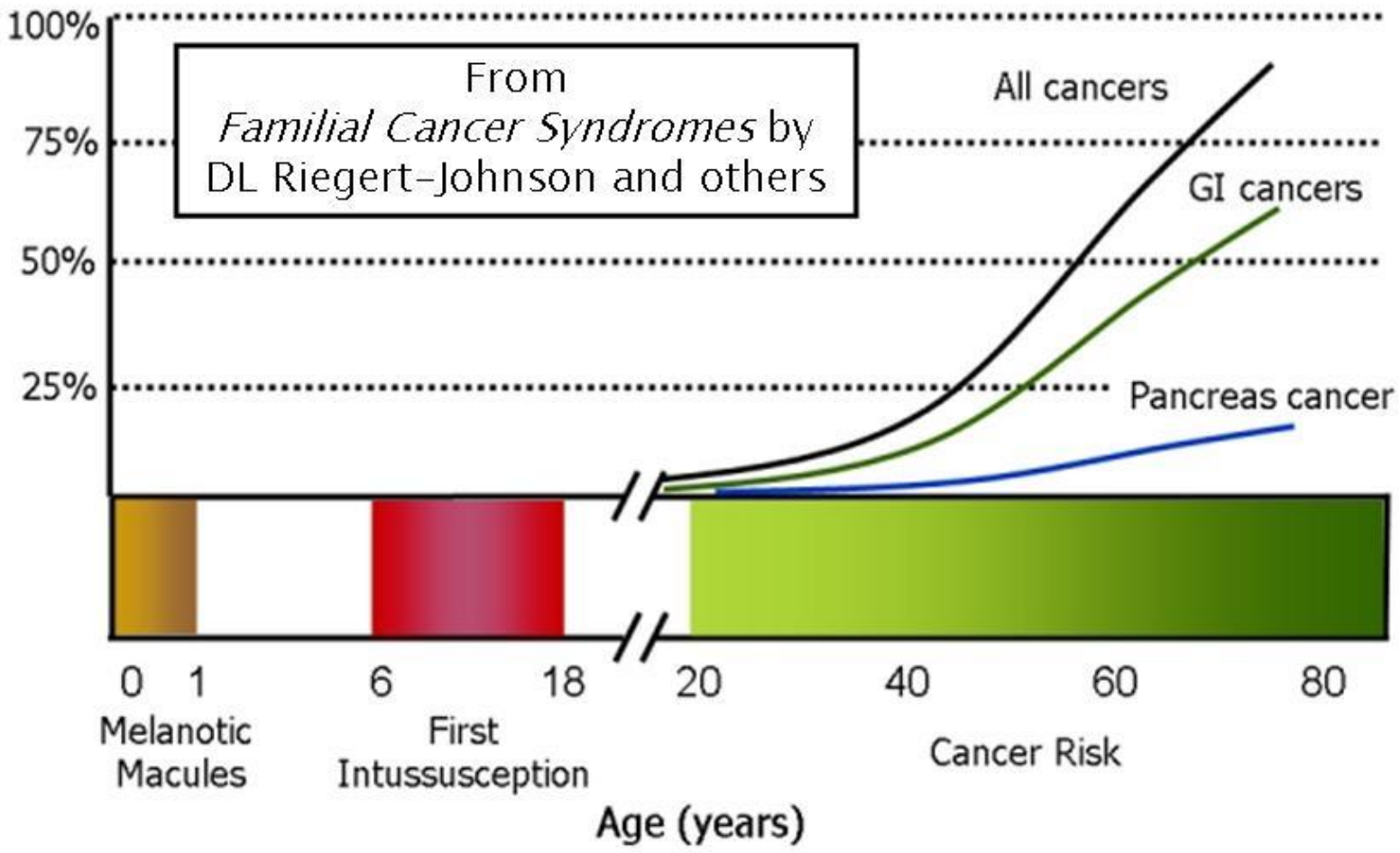




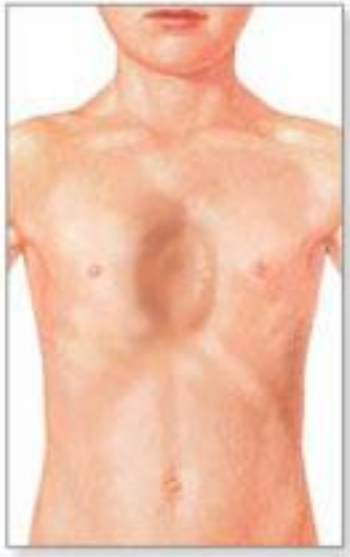
Serine/threonine kinase 11 (STK11

Natural History of Peutz-Jeghers Syndrome

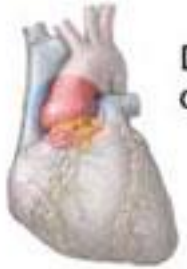
Cumulative Cancer Risk



Pectus excavatum

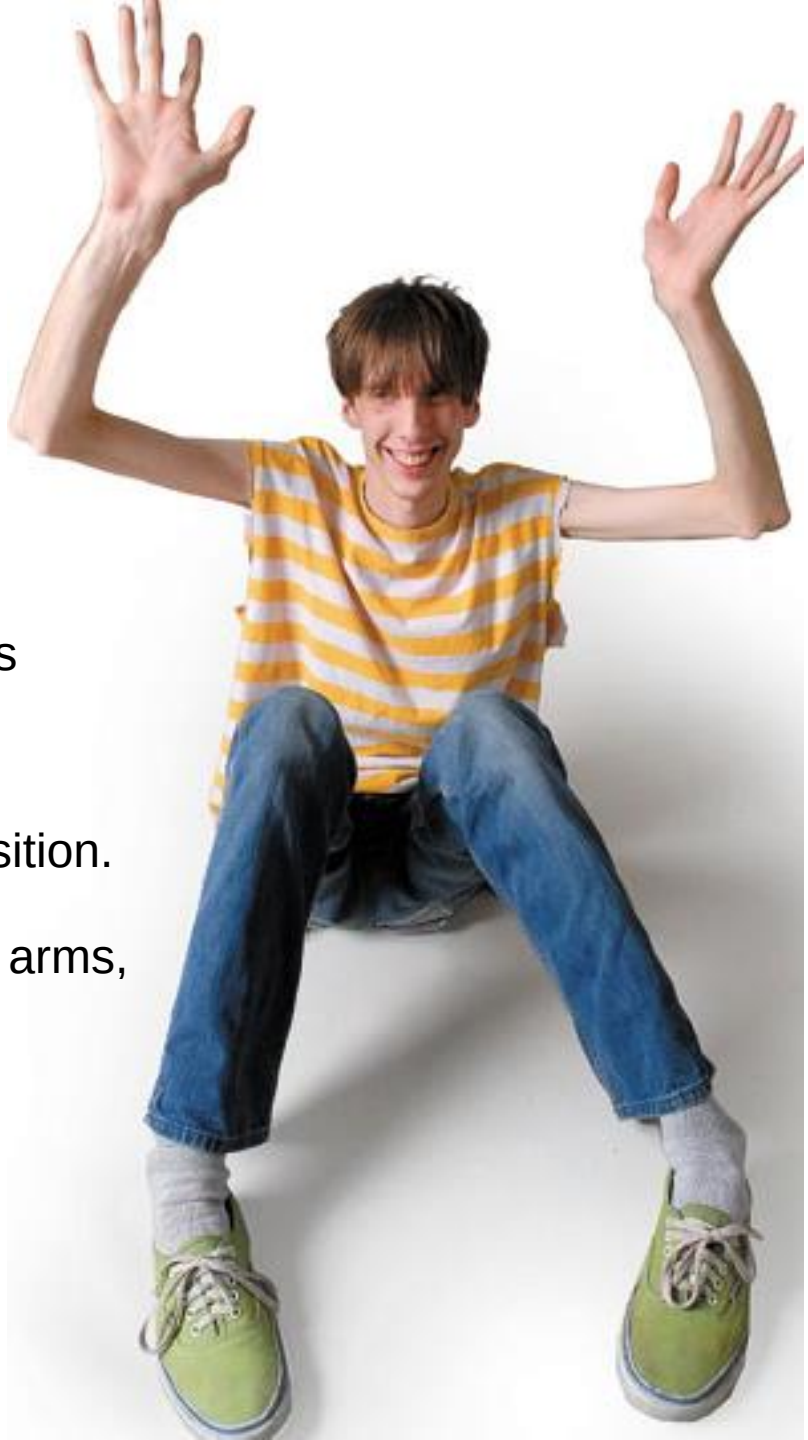


arachnodactyly



Dilation of aorta

Floppy valves



ADAM.

Fibrillin provide a structure to elastine deposition.

Skeleton: Slender elongated habitus, long legs, arms, long fingers. High, arched palate, Hyperextendibility of joints

Eyes: bilateral dislocation of lens

Cardiovasc: aorta aneuryms, aorta dissection

Dilatation of valves


Ehler-Danlos syndrome

Ehler-Danlos syndrome autosomal dominamnt or recessive

Defect of collagen synthesis or structure – 30 distinct collagene genes

There are 6 genetic and clinical variant.

Some clinical feature is common: skins are hyperextensible, fragile, vulnerable
joints are hypermobile-grotesque contortions
serious internal complications: rupture of colon
diaphragmatic hernia
ocular fragility,rupture of
cornea, retinal detachment
Poor wound healing

Types: deficiency of collagen type III synthesis mutation of COL3A1 weakness tissues
collagen type I „ „ COL1A1
lysil hydroxylase defect of collagen crosslinking /kyphoscoliosis


Online Journal of Ophthalmology · www.onjoph.com

Familiall hypercholesterinaemia frequency 1:500

Mutation of LDL receptor – most present in the liver

LDL receptor is implicated in the uptake of circulating LDL and IDL.
Mutation of receptor results in increased serum cholesterol level.

In this case circulating acetylated and oxidized LDL binds to scavenger receptors of macrophages. These macrophages are directly relate to the development of arteriosclerotic plaques.

LDL receptor mutation heterozygotes 2-3 time increased LDL level

homozygotes 5x „ xantogranulomas of skin
dies in 15 searys .AMI

Types of mutation: Class I: no receptor synthesis
Class II. transport from ER to Golgy is impaired
Class III receptor does not bind LDL
Class IV receptor fails to internalize
Class V receptor-LDL comples can not dissociate, LDL traps in the endosomes.

No LDL receptor LDL is taken up by scavenger receptors- deposition in blood vessels

2. Autosomal recessive disorders

Characteristic

Both alleles have to be impaired

The trait does not necessary affect the parents,but sibling may show the disease

Recurrence risk 25% (1 sibling from four)

The expression of the defect is more uniform than in autosomal dominant disorders

Complet penetrance is common

Onset is frequently early

New mutation is rare. Disease may not show up for several generations.

(two heterozygous persons have to marry).

Enzyme proteins are frequently affected

Autosomal recessive disorders

Metabolic

Cystic fibrosis ion transport impaired (chloride ion) 1:2500
mutation in the gene:*cystic fibrosis transmembrane conductance regulator*
Impaired chloride transport resulting in the decreased transport of Na and H2O- dehydration of mucus –bronchitis-bronchiectasia, pancreatitis, meconium ileus

Phenylketonuria: phenylalanin hydroxylase defficiency 1:12000
hyperphenylalaninaemia-phenylketonuria :hypopigmentation, mental retardation.

Galactosemia: galactose 1 phosphate uridyltransferase mutation
accumulation of galactose 1-phosphate and its metabolits
vomiting, diarrhea, jaundice, liver injury, cirrhosis, cataracta, impairment of aminoacid transport. Early diagnosis!!!

Lysosomal storage diseases

Glycogen storage diseases

Wilson disease, Hemochromatosis

Hemopoetic

sickle cell anaemia, thalassemia

Skeletal:

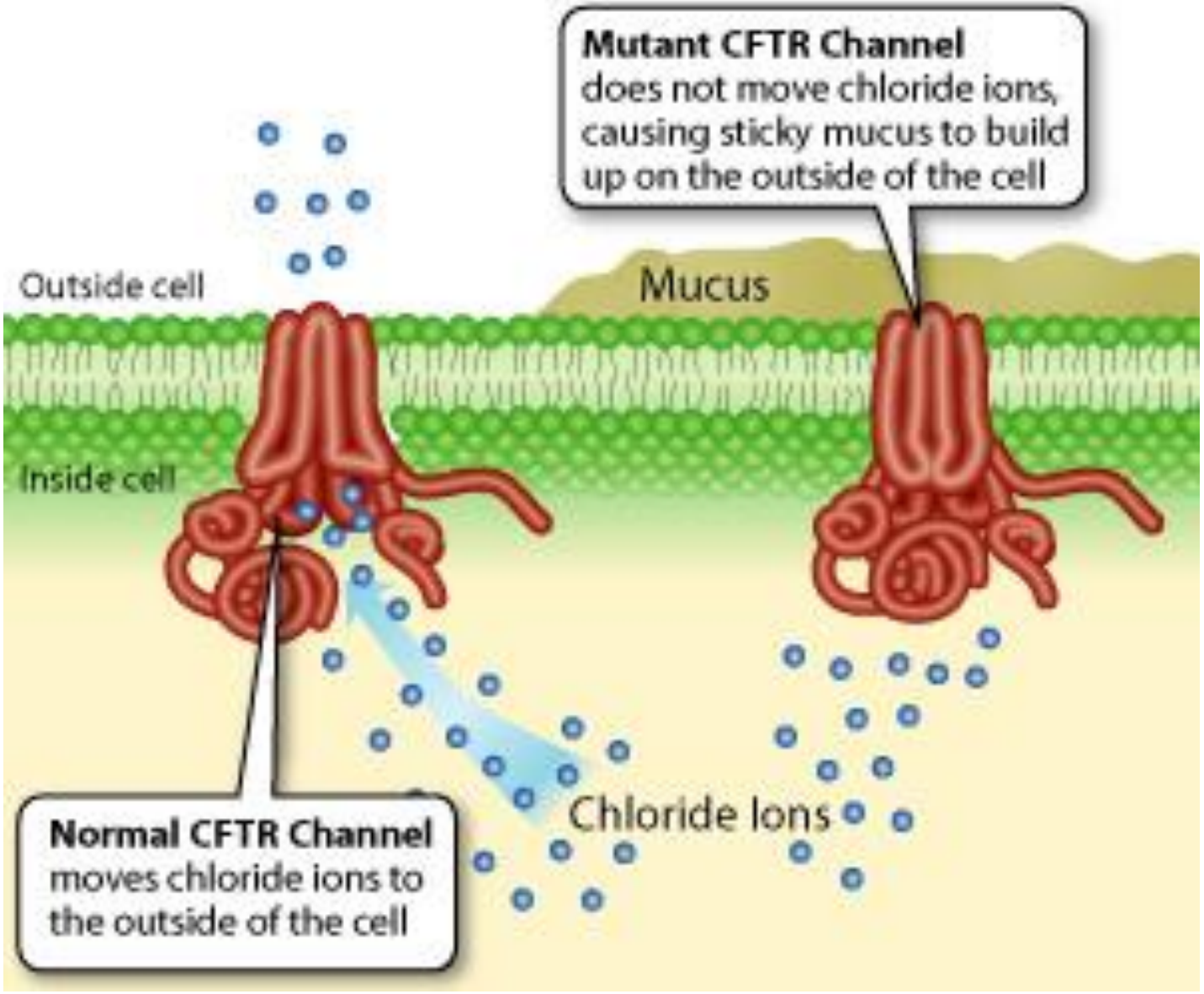
Ehler Danlos , Alkaptonuria

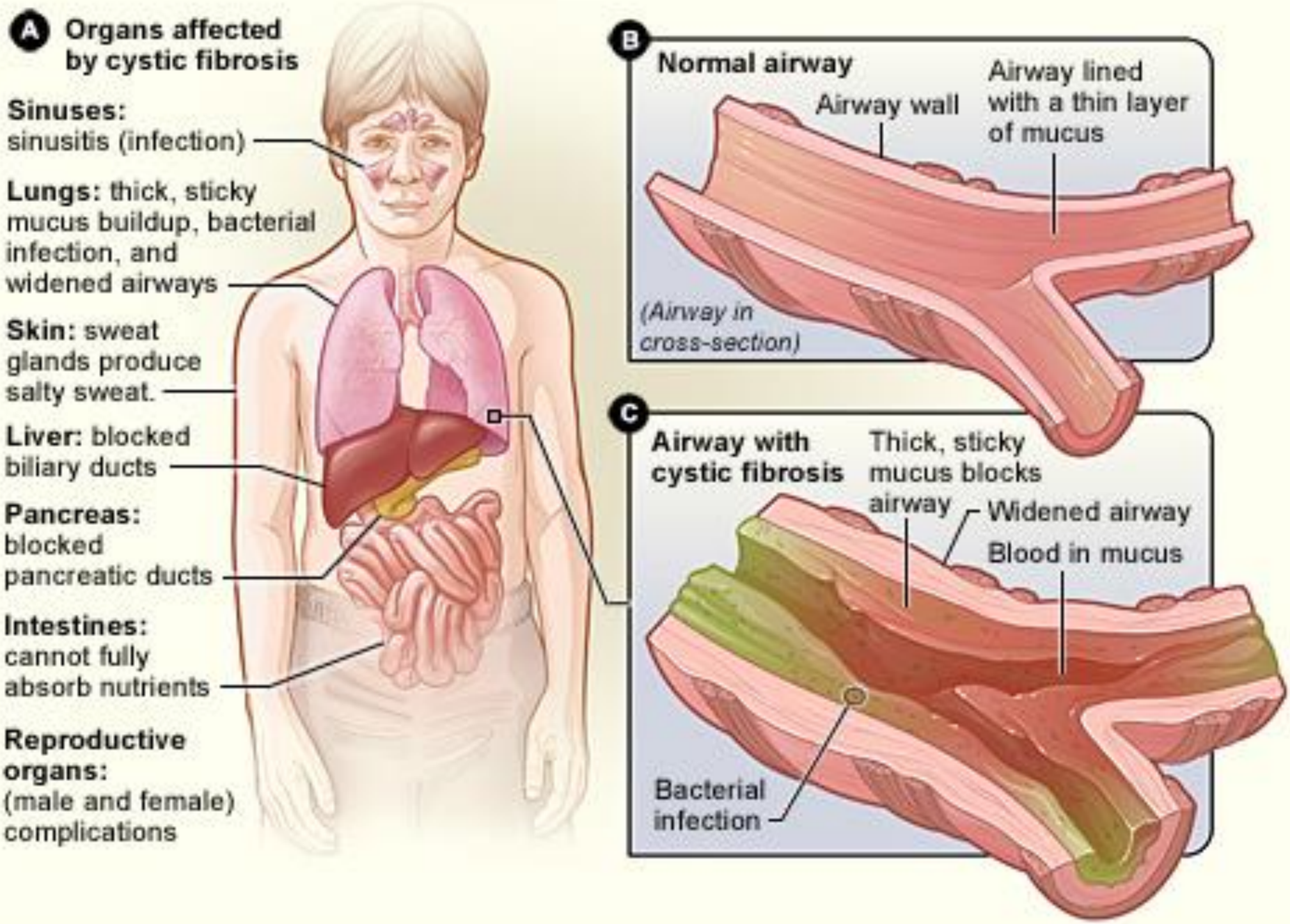
Endocrine: Congenital adrenal hyperplasia (21 hydroxylase defficiency)

Nervous atrophies: Neurogenic muscular atrophy:

Fridreich ataxia GAA trinucleotide repeat >30 impairment of sensory neurons, directing the movement of arms and legs.

Spinal muscular atrophy –motoneurons (first proximal and lung)


Mutant CFTR Channel
does not move chloride ions, causing sticky mucus to build up on the outside of the cell
Outside cell
Mucus
Inside cell
Chloride Ions
Normal CFTR Channel
moves chloride ions to the outside of the cell


A Organs affected by cystic fibrosis
Sinuses: sinusitis (infection)
Lungs: thick, sticky mucus buildup, bacterial infection, and widened airways
Skin: sweat glands produce salty sweat.
Liver: blocked biliary ducts
Pancreas: blocked pancreatic ducts
Intestines: cannot fully absorb nutrients
Reproductive organs: (male and female) complications
B Normal airway
Airway wall
Airway lined with a thin layer of mucus
(Airway in cross-section)
C Airway with cystic fibrosis
Thick, sticky mucus blocks airway
Widened airway
Blood in mucus
Bacterial infection

Lysosomal storage diseases:

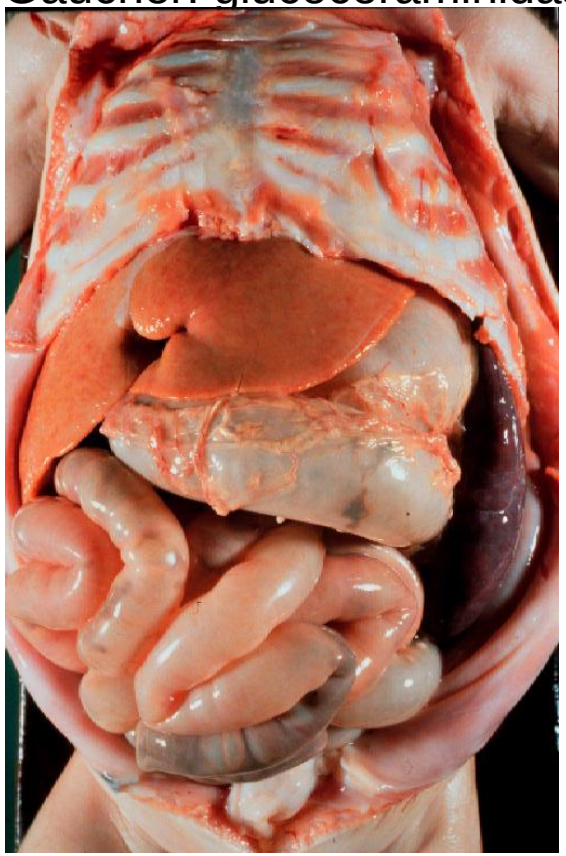
affects infants and children

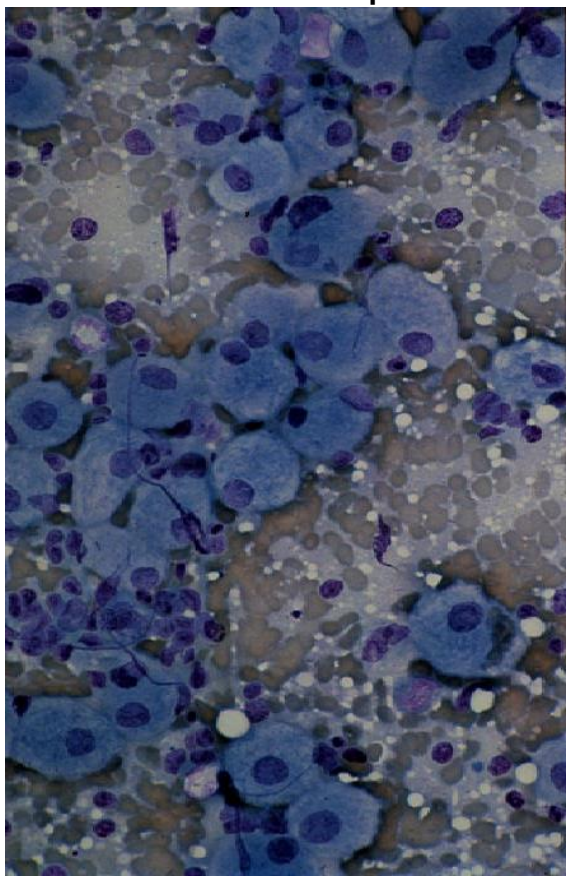
storage of insoluble intermediates in the monocyte-macrophage system

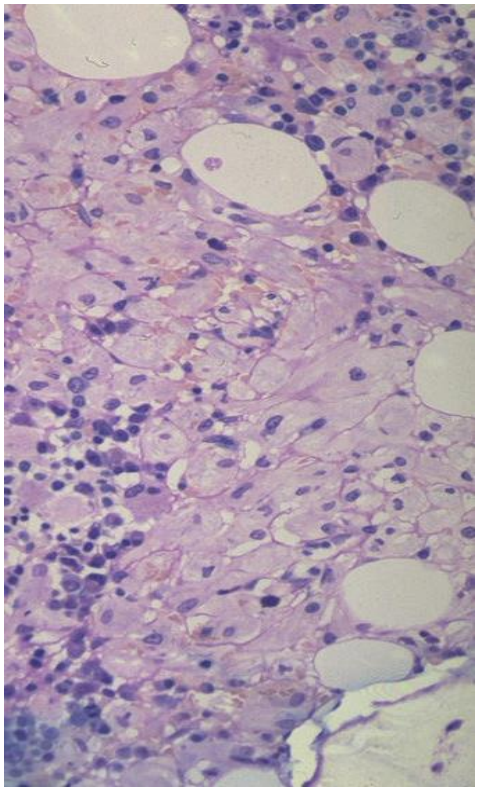
hepatosplenomegaly, mental retardation,

Lipid metabolism: Impaired degradation of lipids of cell membranes

Gaucher: glucoceraminidase: accumulation of lipid in the macrophages No CNS



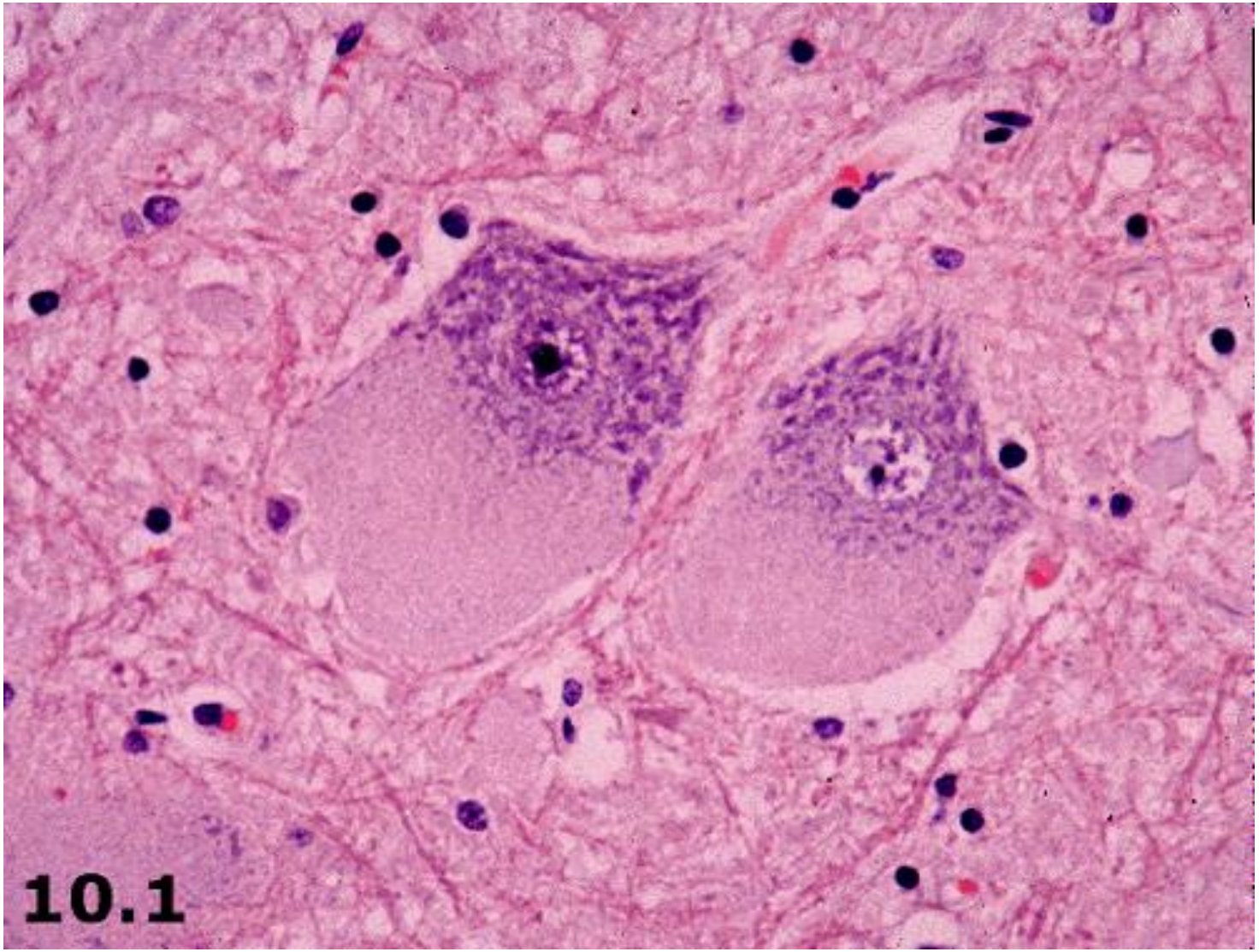




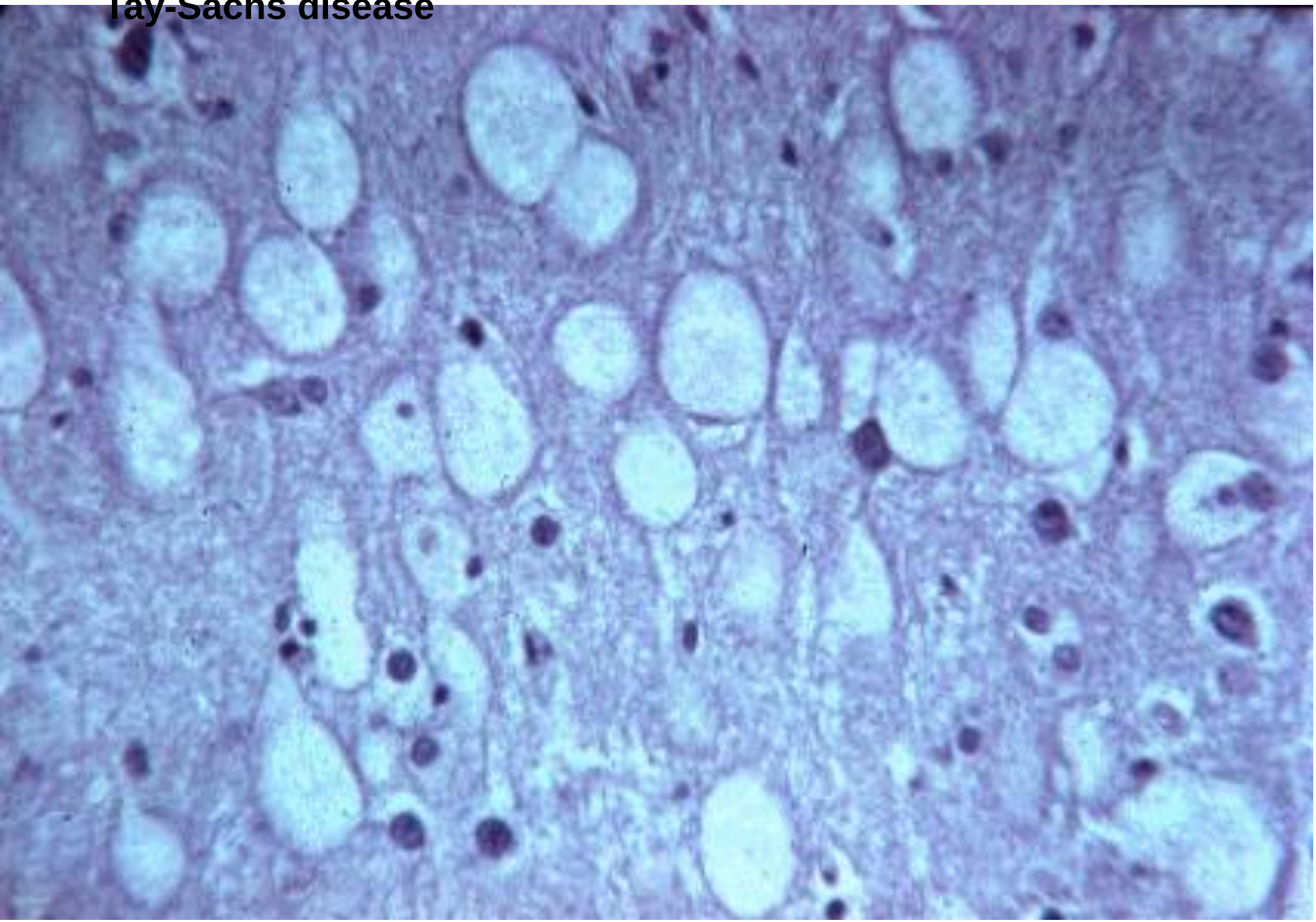
Gaucher disease- glucoceraminidase defficiency

Tay-Sachs disease

Tay –Sachs: mainly CNS: hexosaminidase defficiency, GM2 ganglioside storage
Mental retardation, blindness, convulsion, motor weakness, death.



Tay-Sachs disease



Tay-Sachs disease
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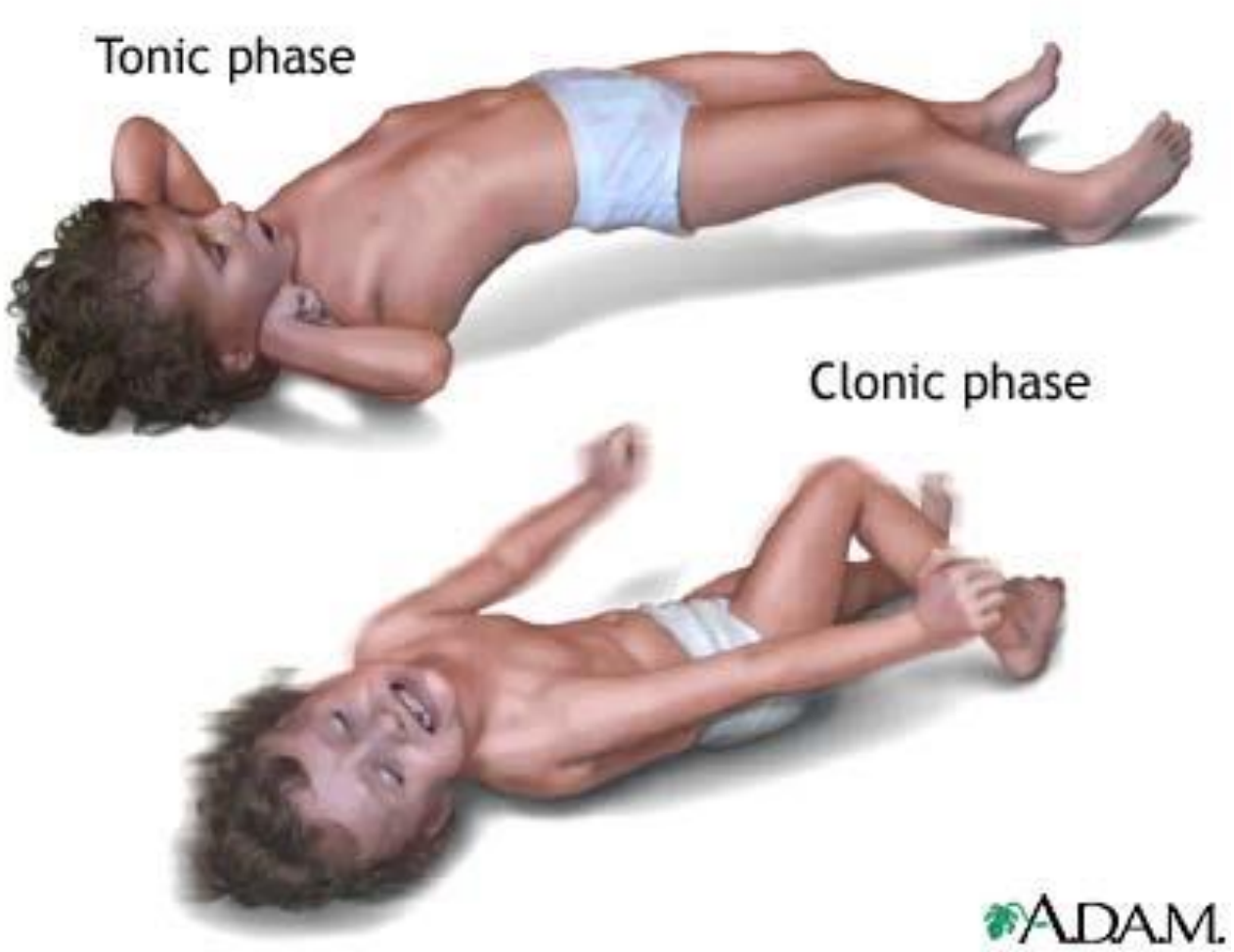
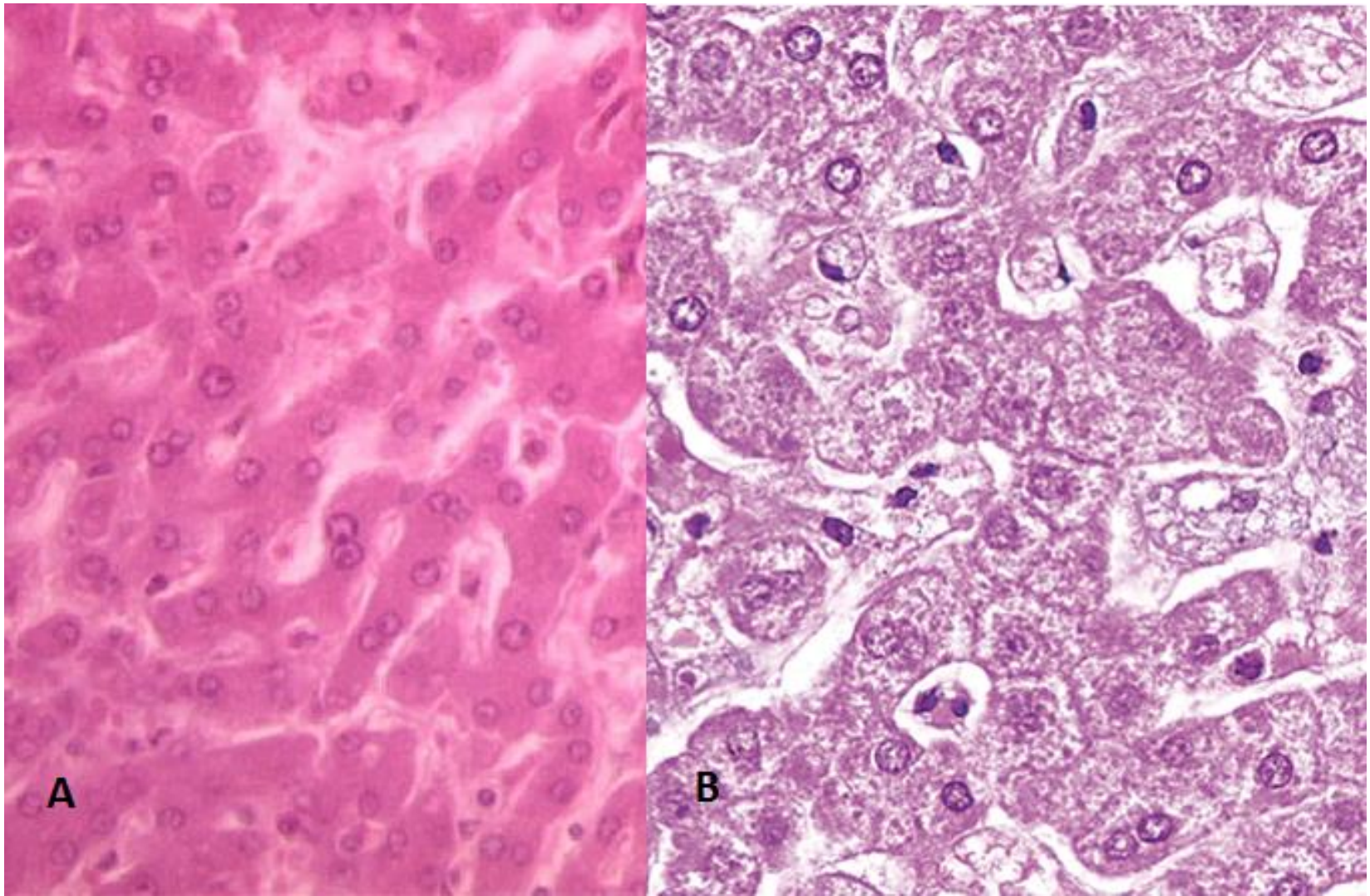
Mental retardation, blindness, convulsion, motor weakness, death.



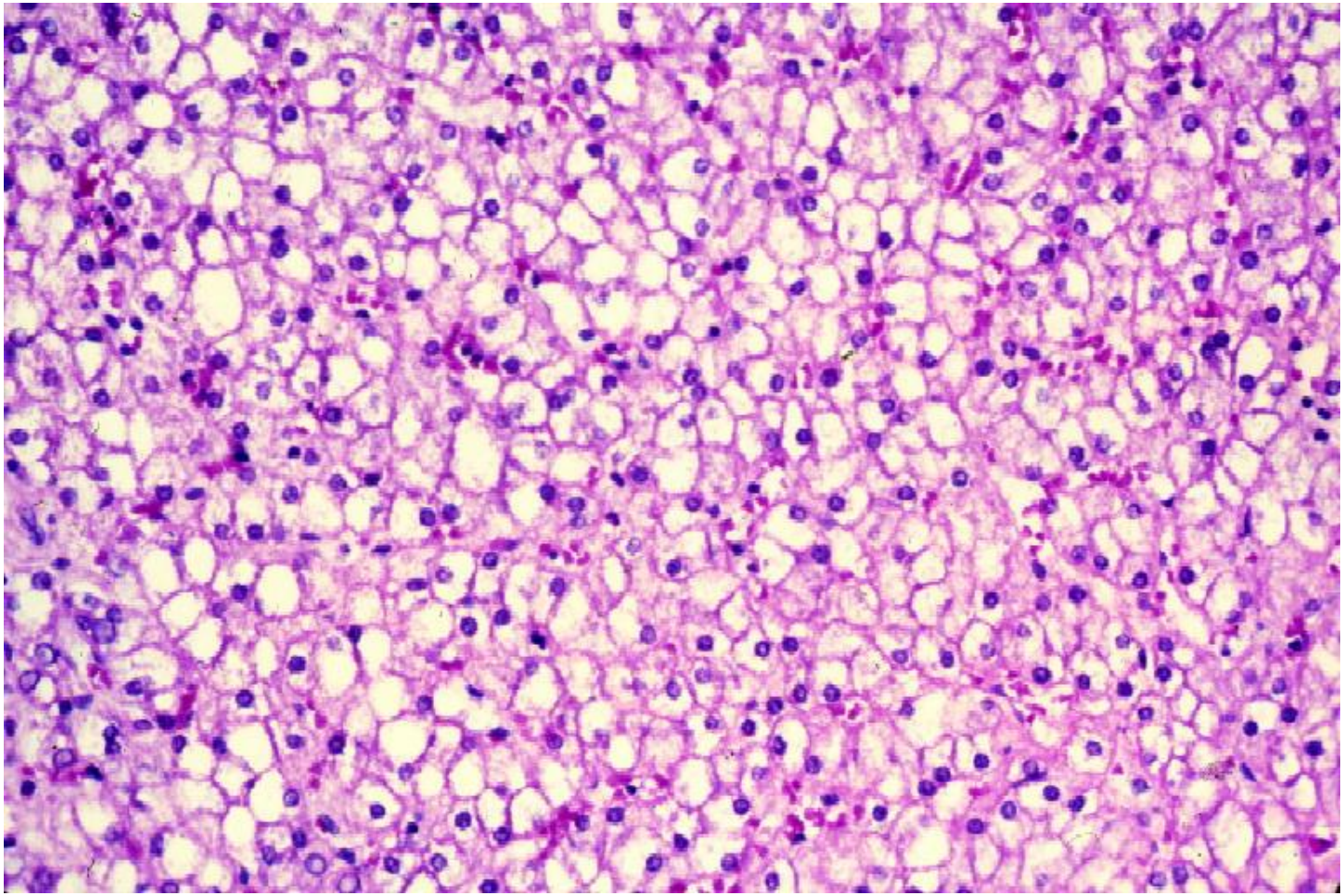
Nieman-Pick

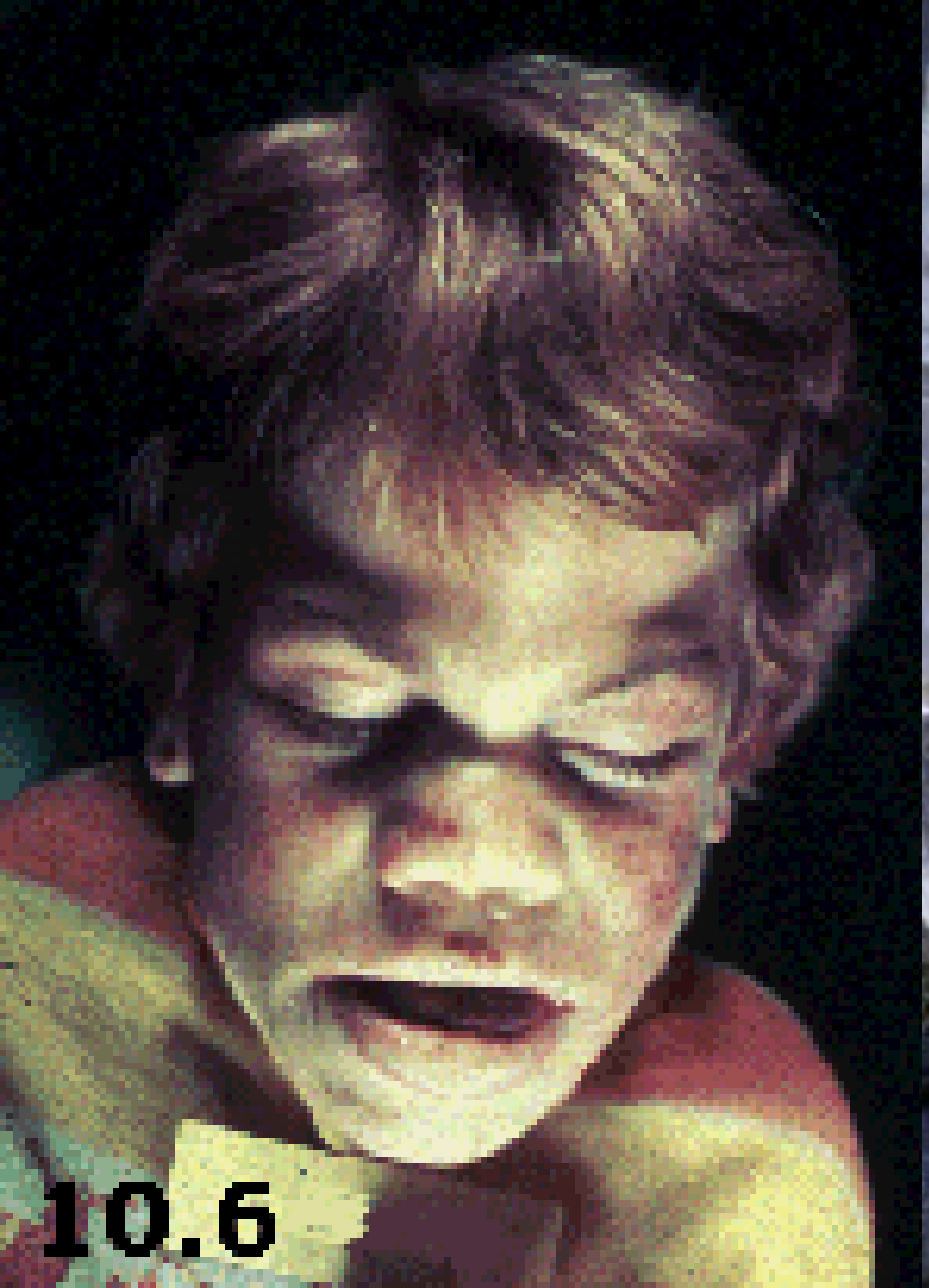
Nieman-Pick: sphyngomyelinase defficiency, sphyngomyelin storage
Hepatosplenomegaly, mental retardation, seizures, ataxia, dysarthria



Glycosaminoglycans: 13 different forms

Deposition of heparan and dermatan sulfate in the liver, spleen, heart, blood vessels, brain, valves of the heart. . Coarse face gargoylismus, skeletal deformities, mental retardation, clouding of cornea

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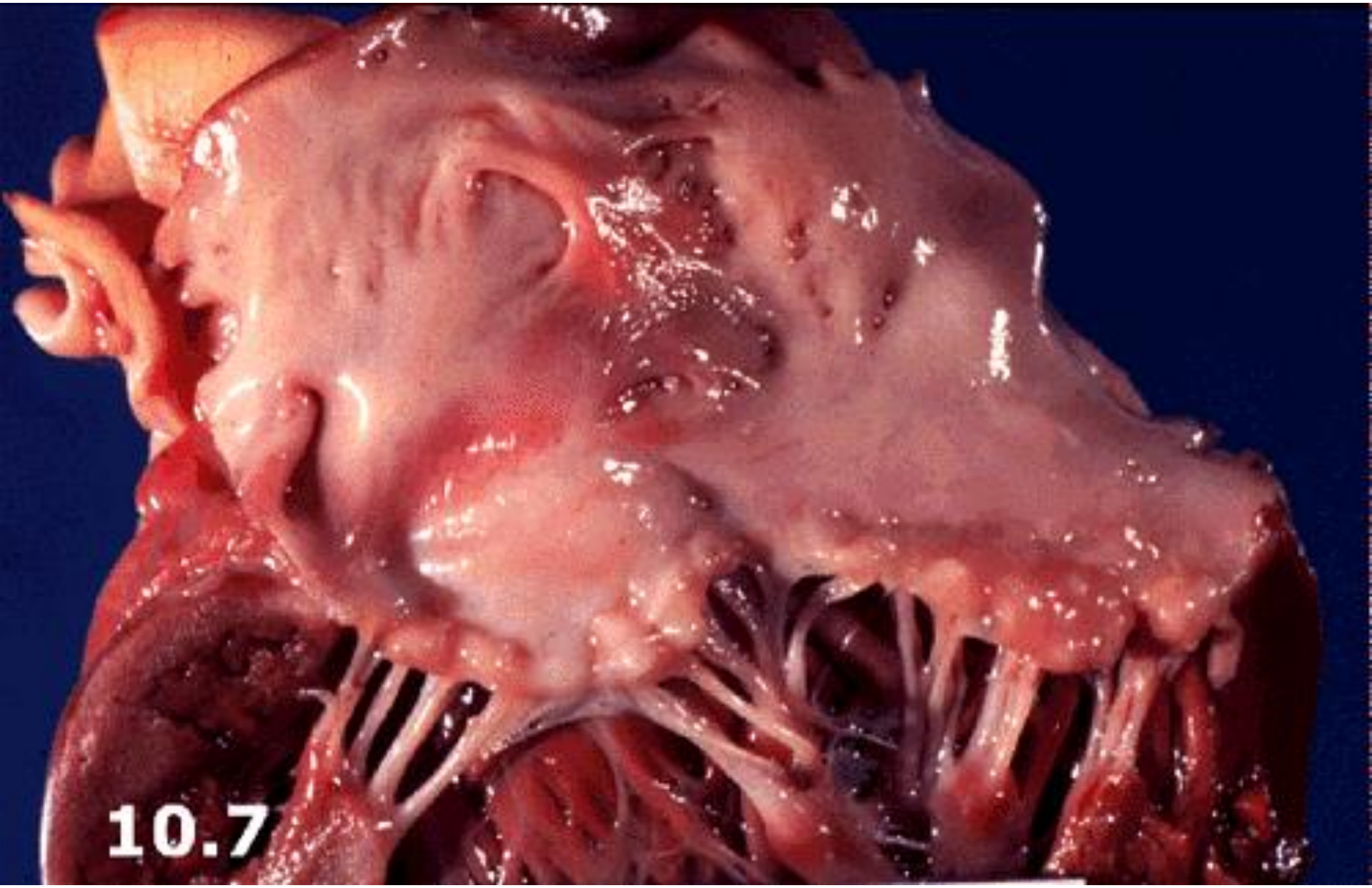


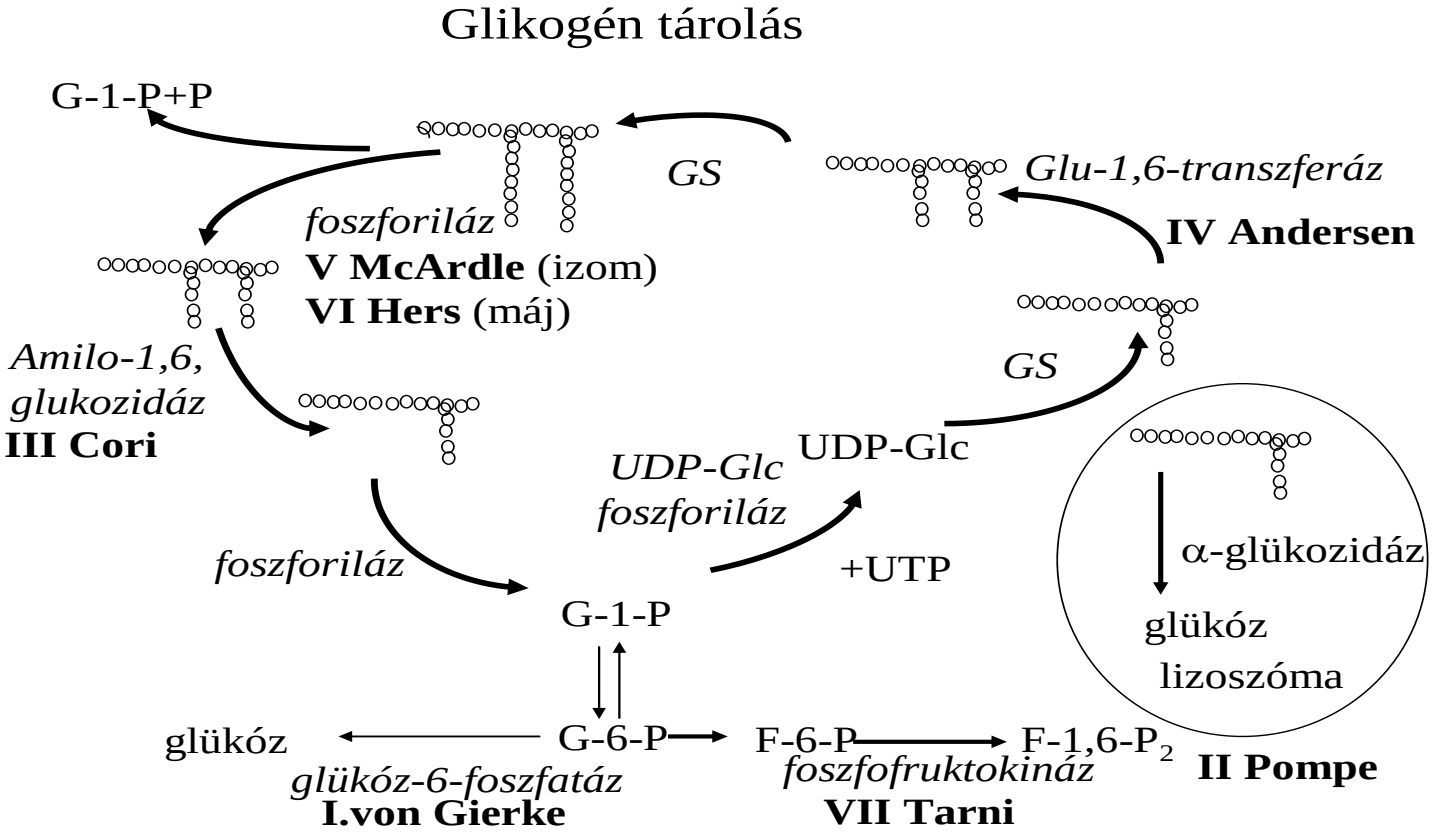
mucopolysaccharidosis

Glycogen storage diseases

Hepatic type: von Gierke disease-
glucose-6 phosphatase defficiency

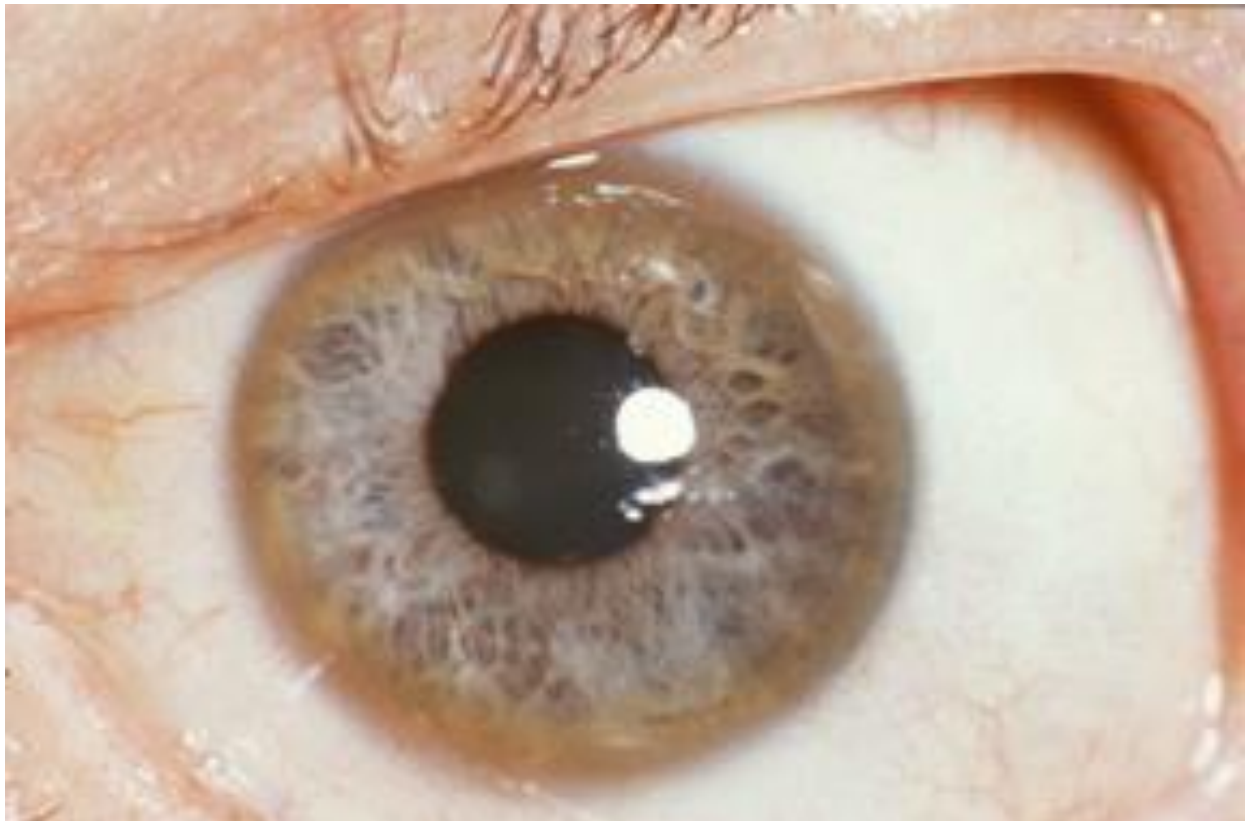
Myopathic type: type V
Muscle cramps, weakness myoglobinury

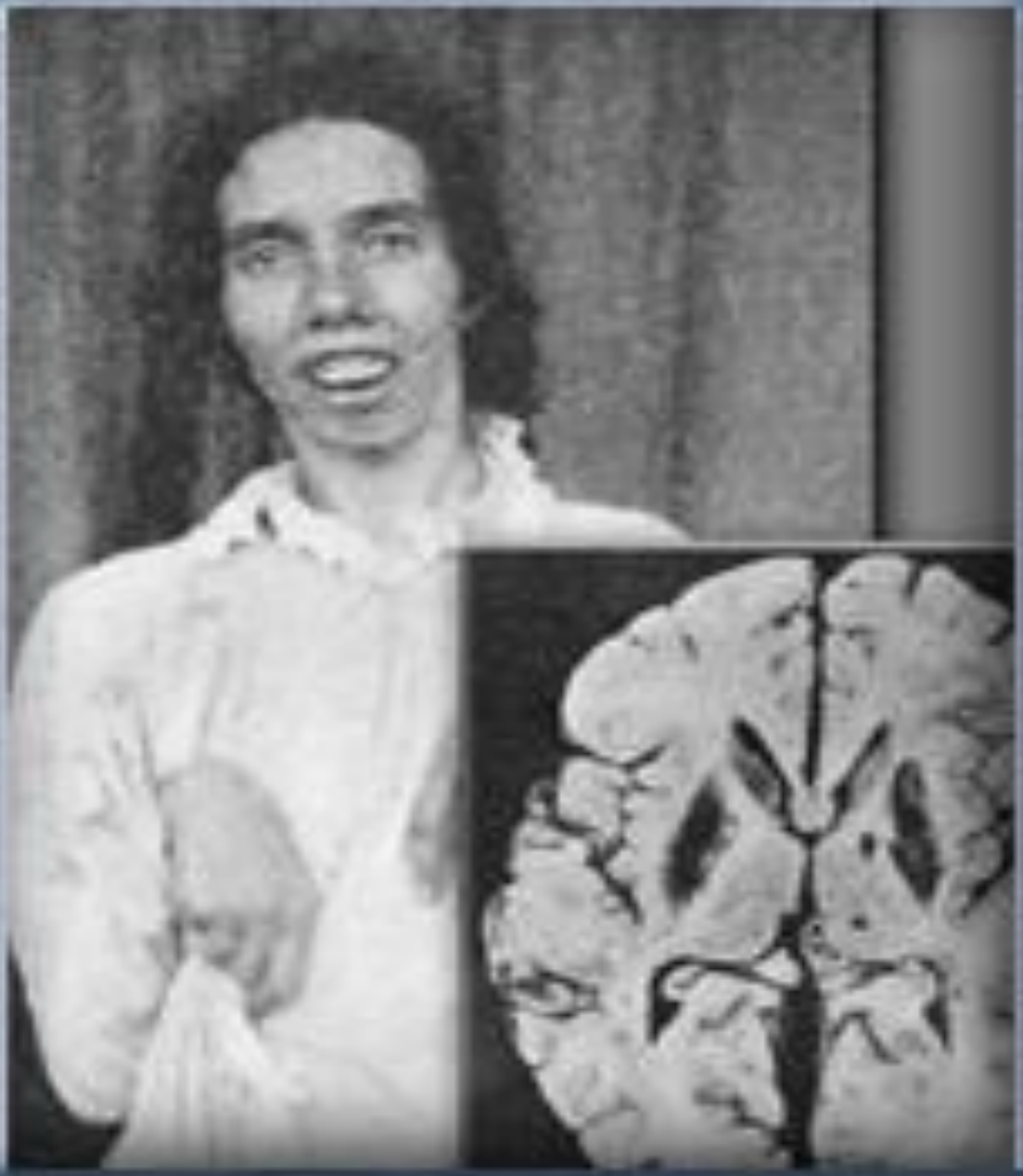
Type II: Pompe: lysosome storage disease
deposition in cardiac muscle



Wilson disease copper storage : 1:200 deposition of copper in liver-cirrhosis, brain,
Kaiser Fleisher ring gold ring around the iris ., CNS basal ganglia
Liver: necrosis, inflammation cirrhosis, neuropsychiatric problems, increased rigidity, ataxia, dystonia
ATP7B insufficiency.

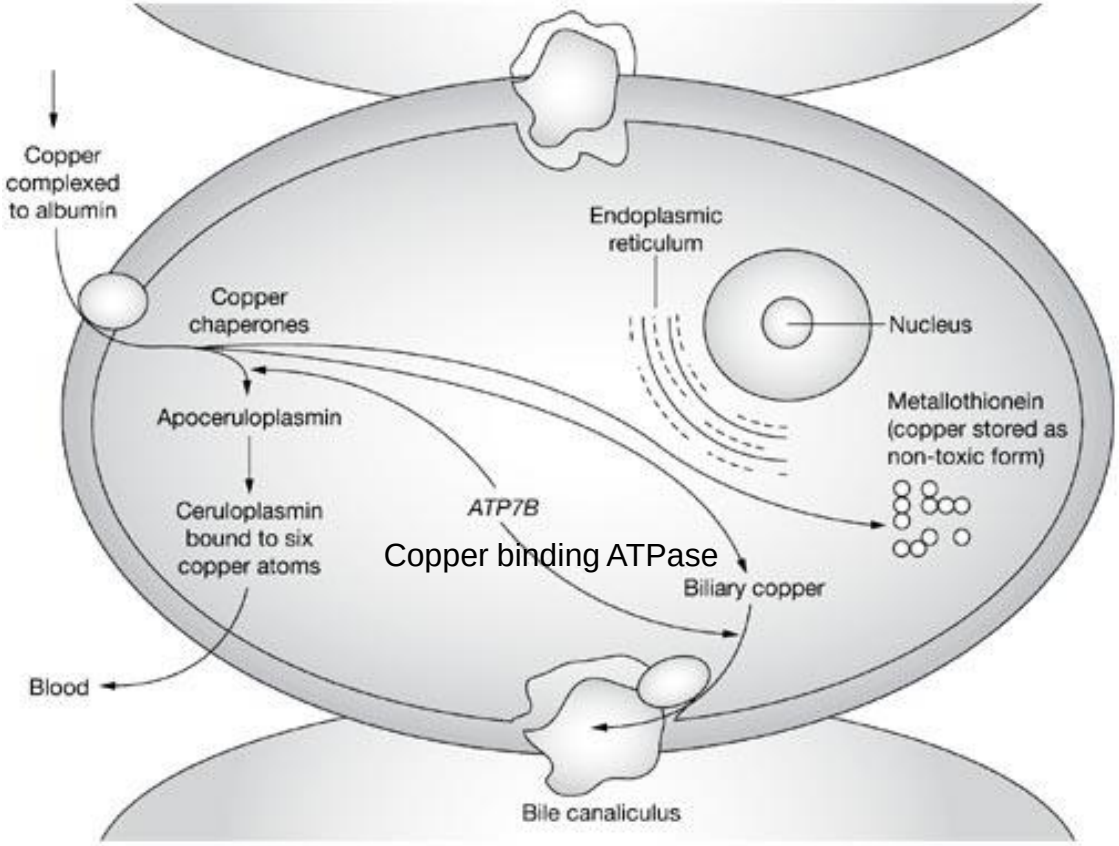
Low level of ceruloplasmin in the blood





Click to enlarge

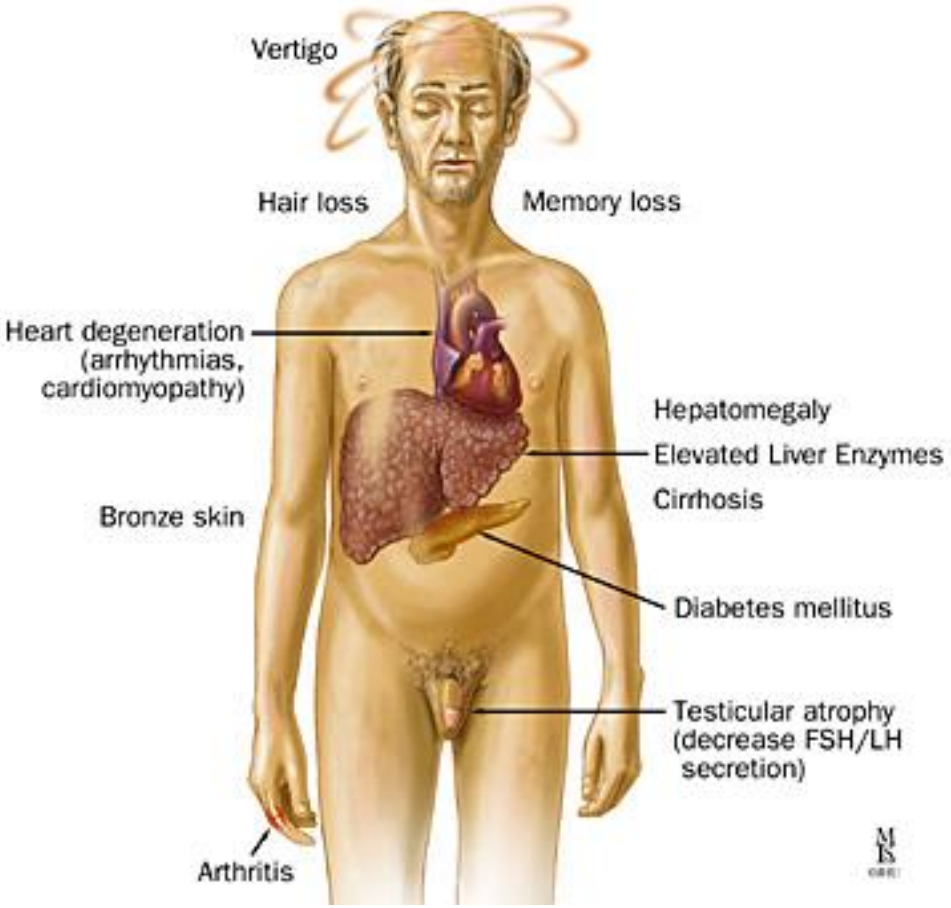
Figure 1 Schematic representation of copper metabolism within a liver cell



Das SK and Ray K (2006) Wilson's disease: an update
Nat Clin Pract Neurol **2:** 482–493 10.1038/ncpneuro0291

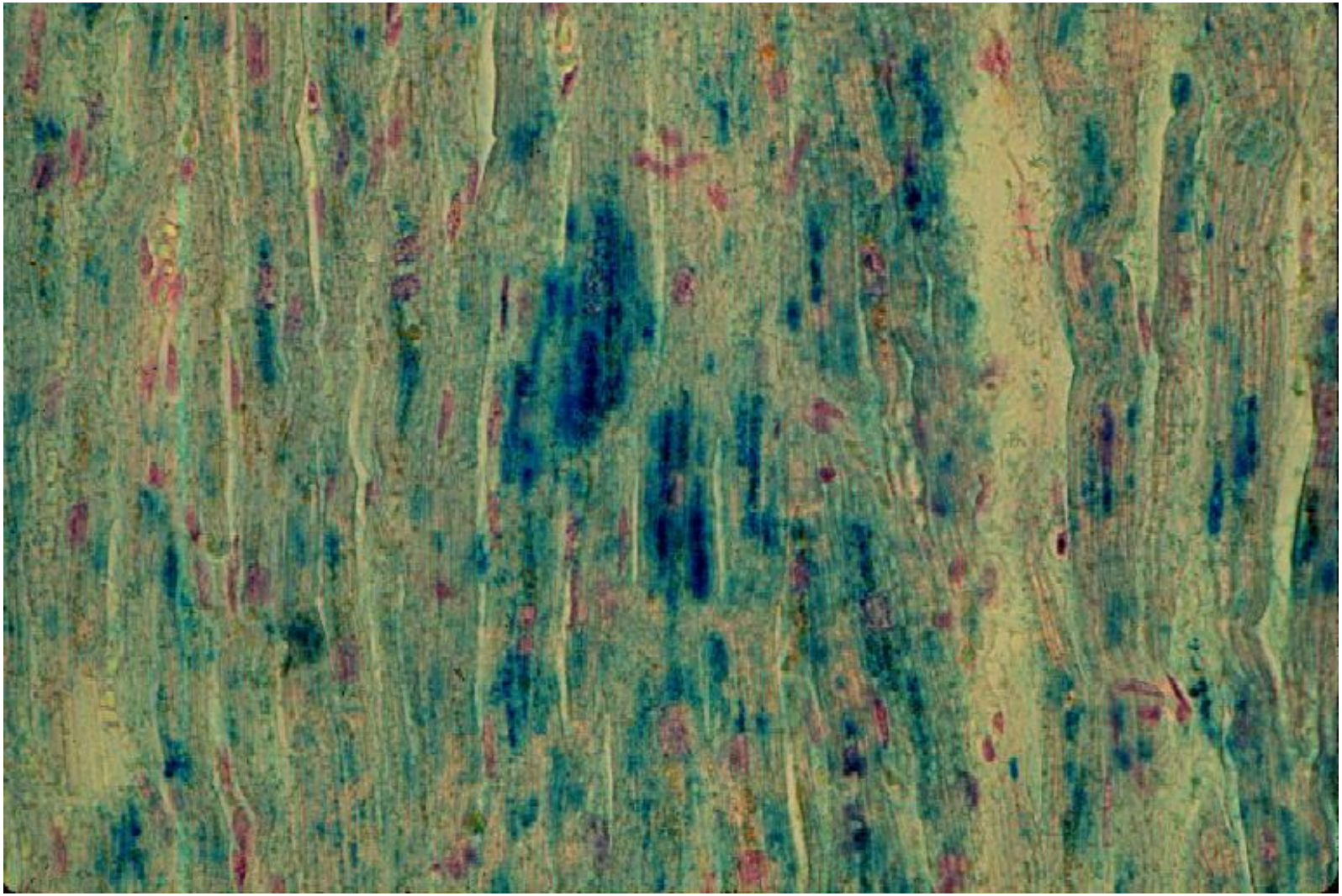
nature CLINICAL PRACTICE NEUROLOGY

Hemochromatosis : broze diabetes :HFE gene mutation- iron absorption is not regulated. Hepcidin.
1:300 frequency
Iron deposition in skin, pancreas, liver, heart

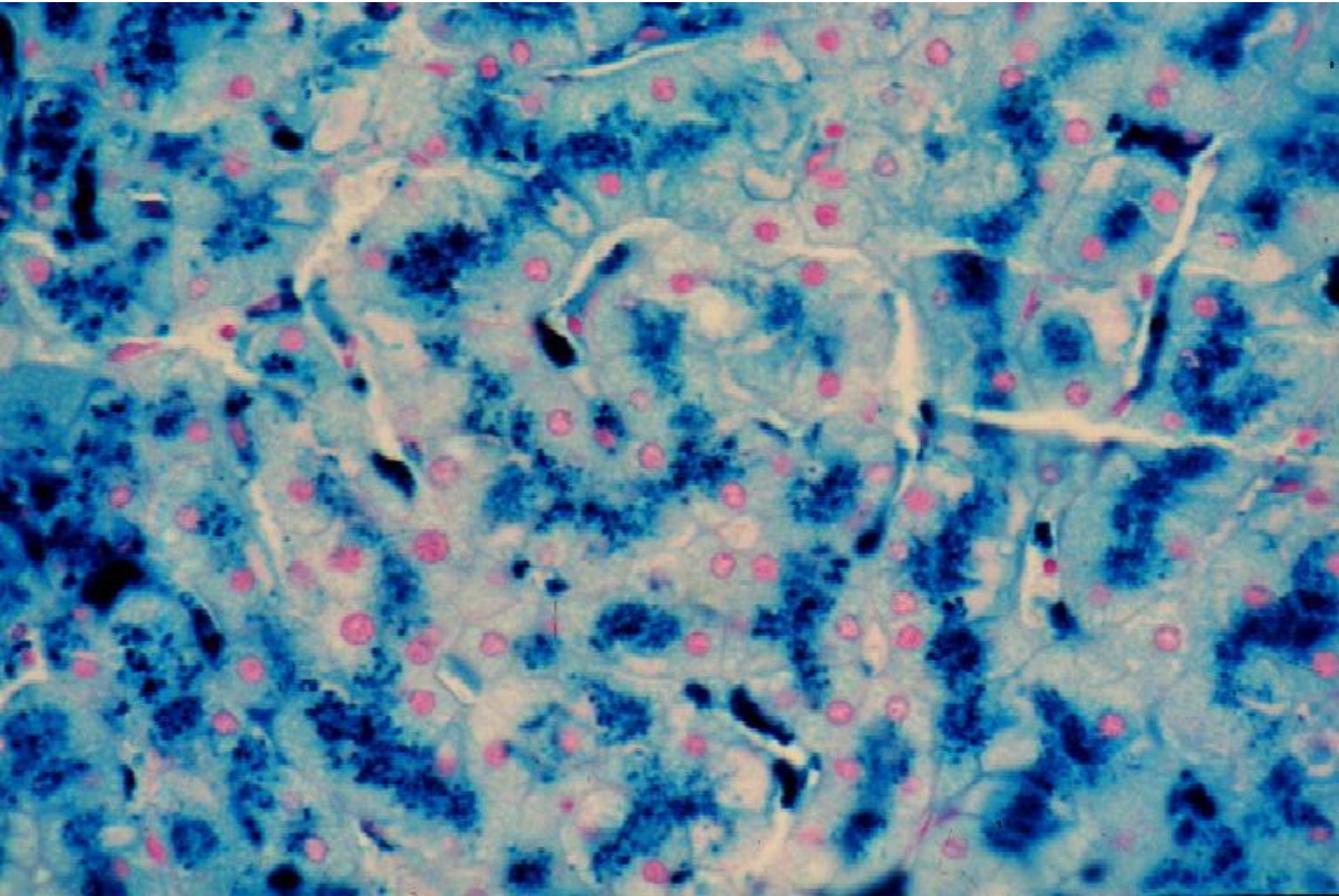


Symptoms and signs of hemochromatosis.

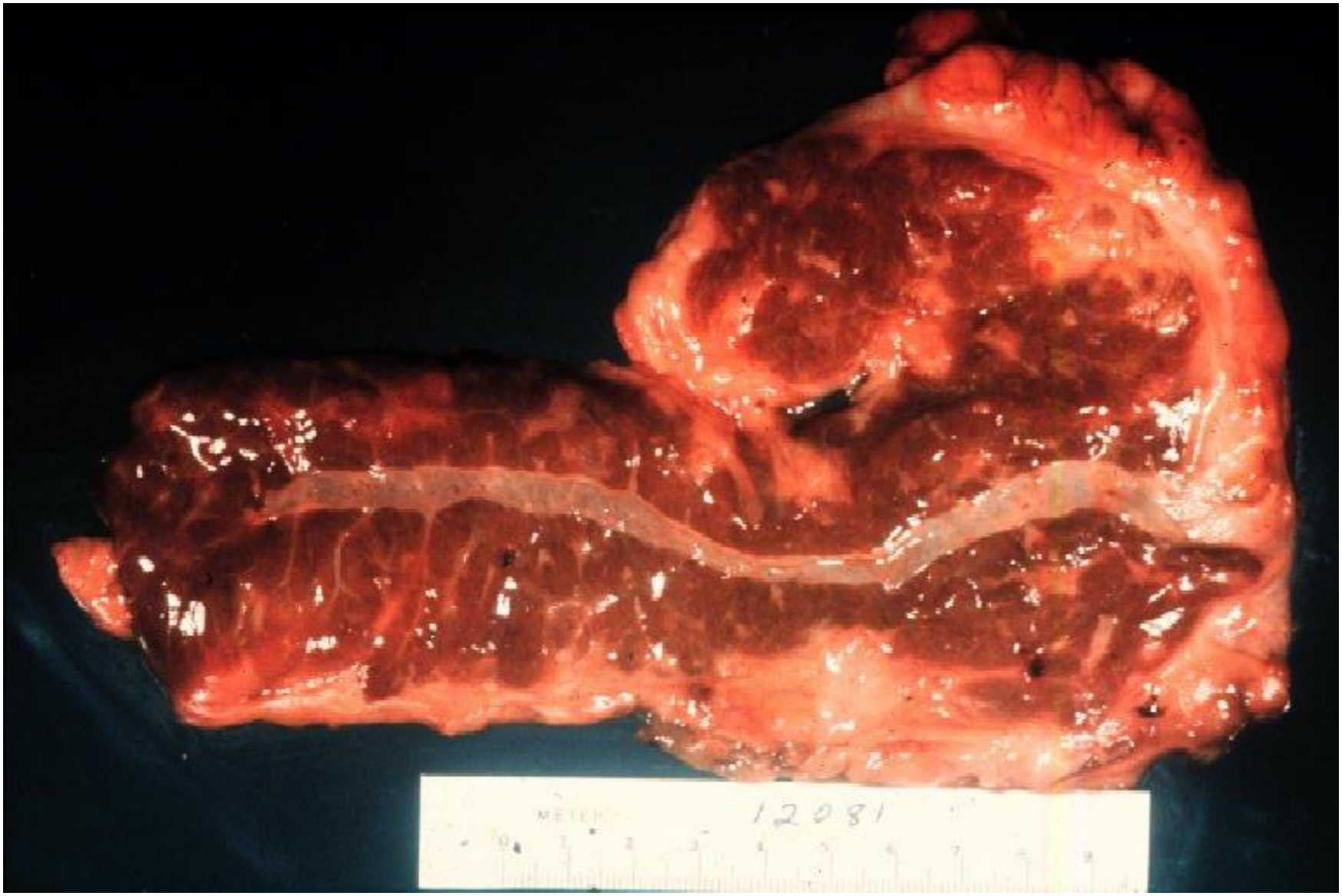
Haemochromatosis in the heart



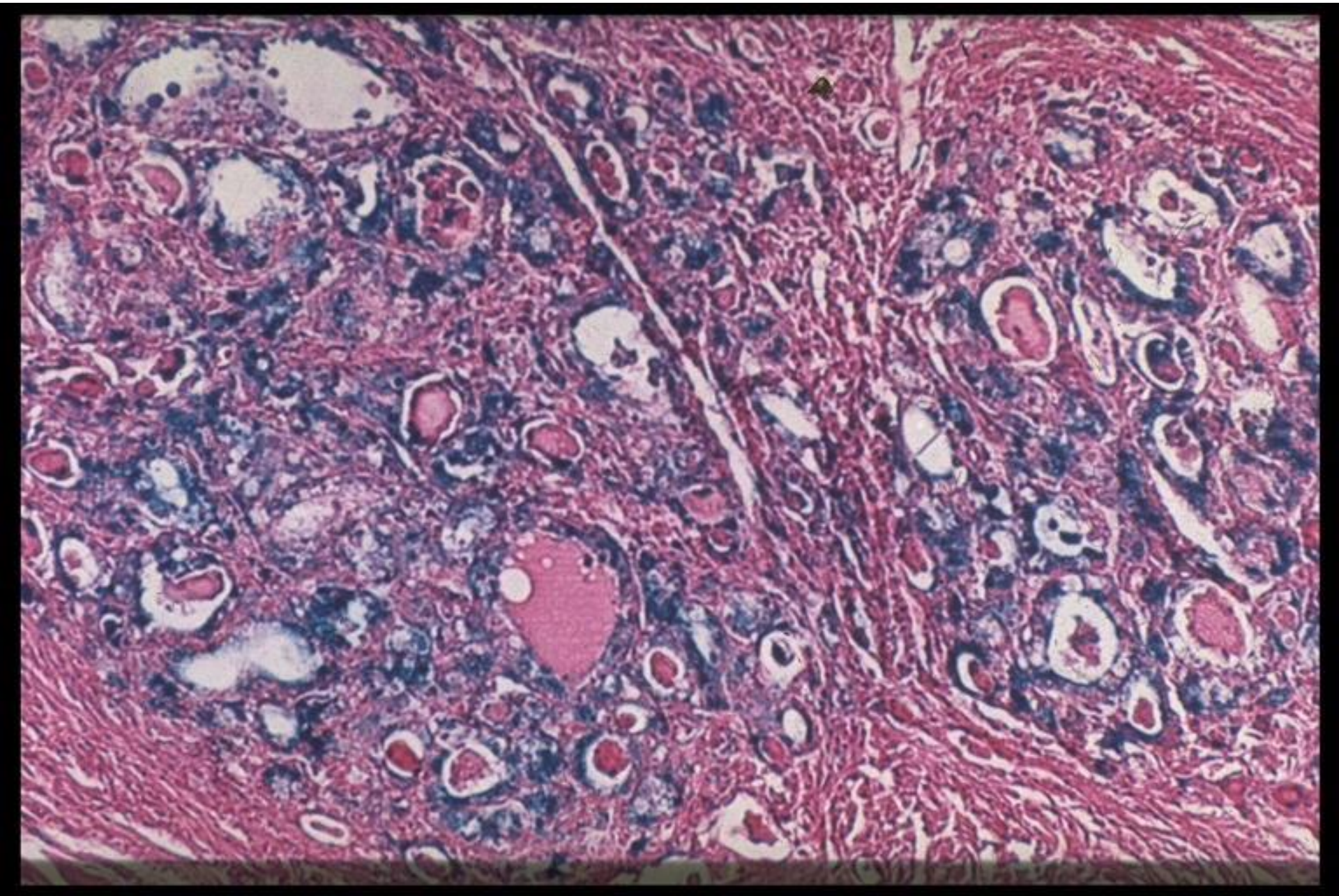
Haemochromatosis a májban



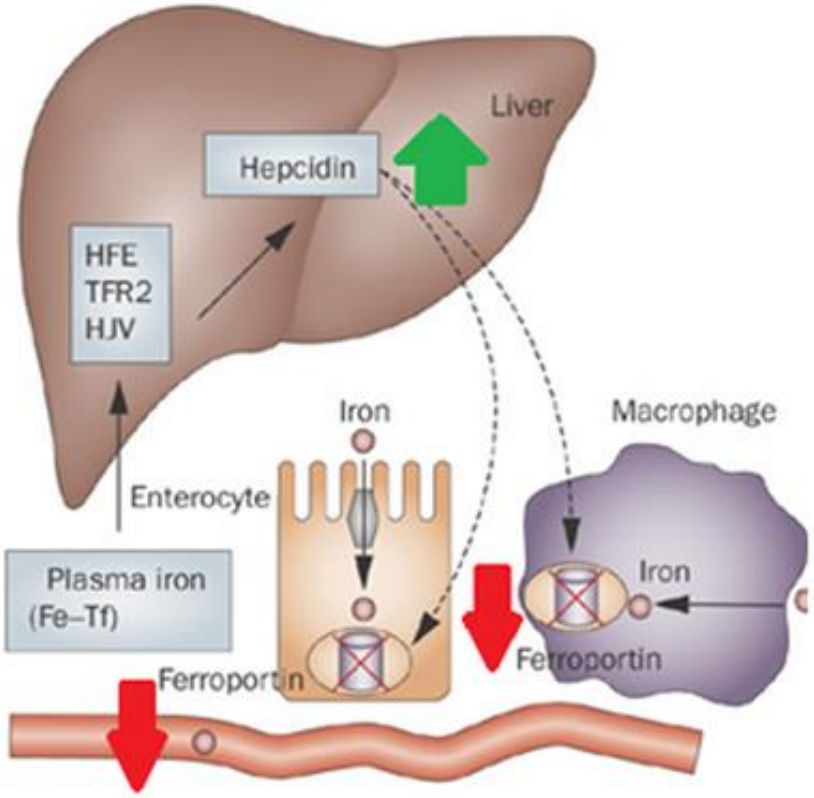
Haemochromatosis pancreas



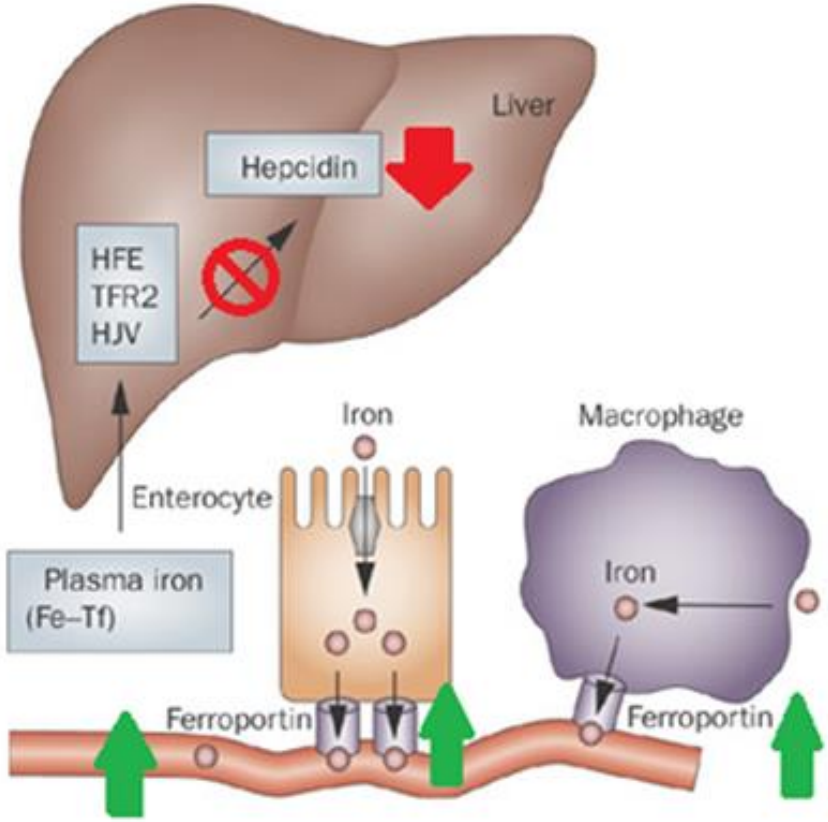
Haemochromatosis a pancreasban



Normal



Hereditary Hemochromatosis



3. X-linked disorders

Characteristic features

Heterozygous female carrier transmit to her sons
Female do not express the phenotype
Affected male do not transmit the disease to males, daughter will be carrier

Diseases:
Musculoskeletal: Duchanne dystrophy- dystrophin gene

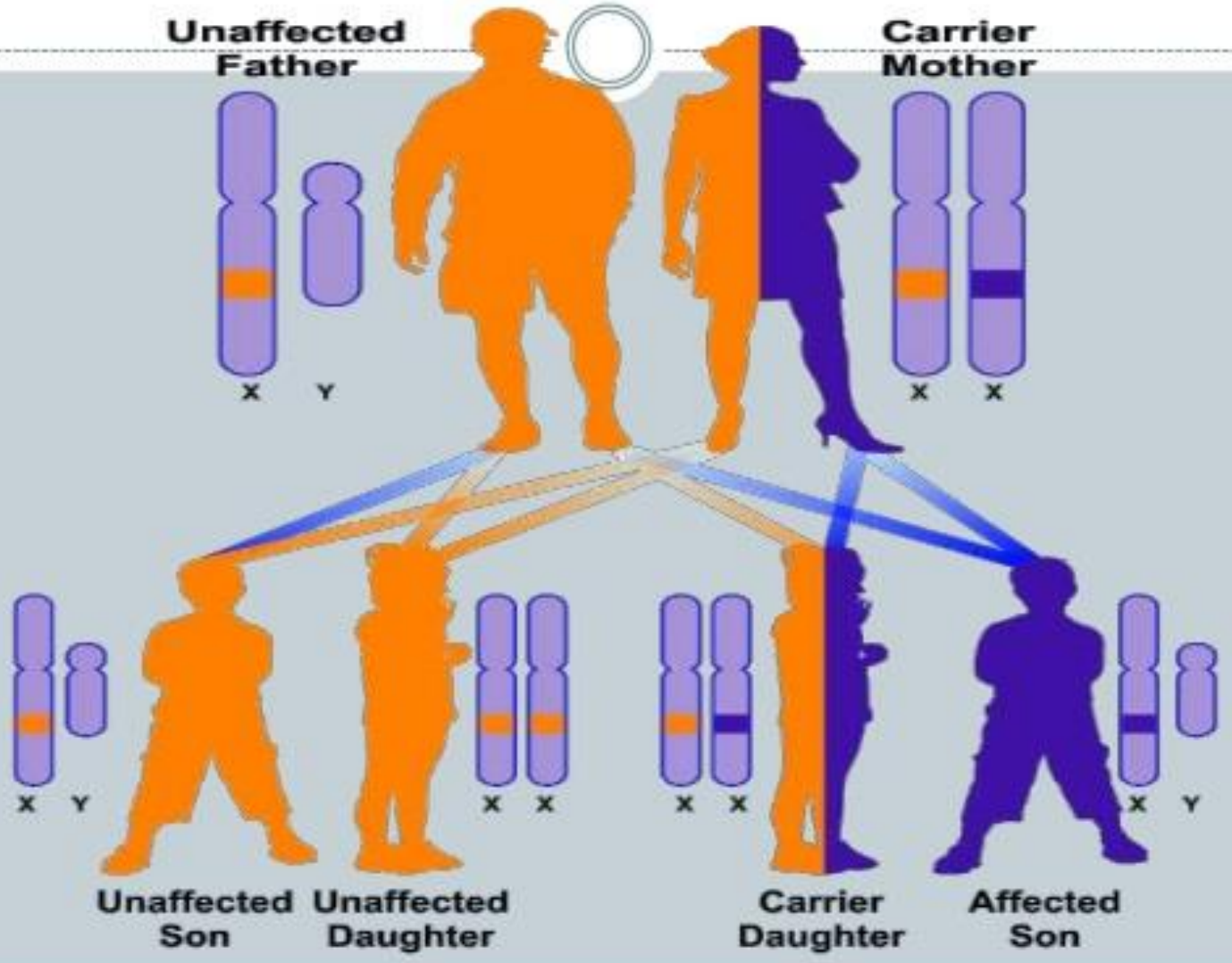
Blood: Hempohilia A, B

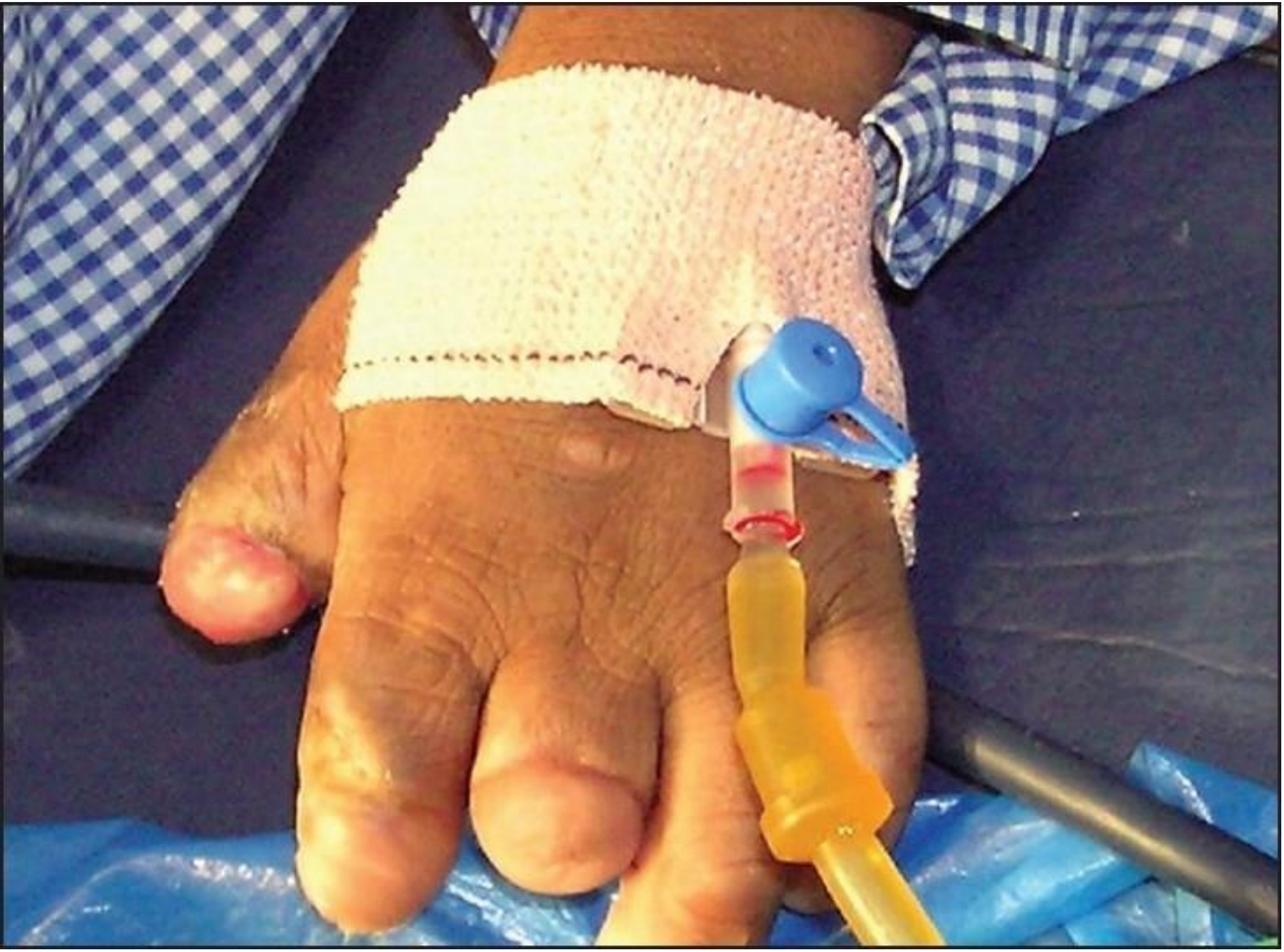
Immune: agammaglobulinaemia
X linked severe combined immundefficiency

Metabolic: Diabetes insipidus

Lesh Nyhan syndrome hyperuricamia, hyperuricuria, gout, mental retardation, self mutilation (lip and finger biting)
Hypoxanthine-guanine phosphoribosyltransferase

X-linked Recessive, Carrier Mother





Duchanne muscular dystrophy (DMD) 1:3500

3/1

Most common dystrophy

Clinically evident by age 5

Progressive weakness- wheelchair by age 12

death by age 20

Morphology: marked variation of muscle fiber size

hypertrophy and atrophy of myofibers

degenerative changes-fiber splitting, necrosis

End stage : extensive myofiber loss, adipose infiltrate

Pathomechanisms: deletion of portions of dystrophin gene (Xp21)

dystrophin attaches sarcomere to cell membrane,

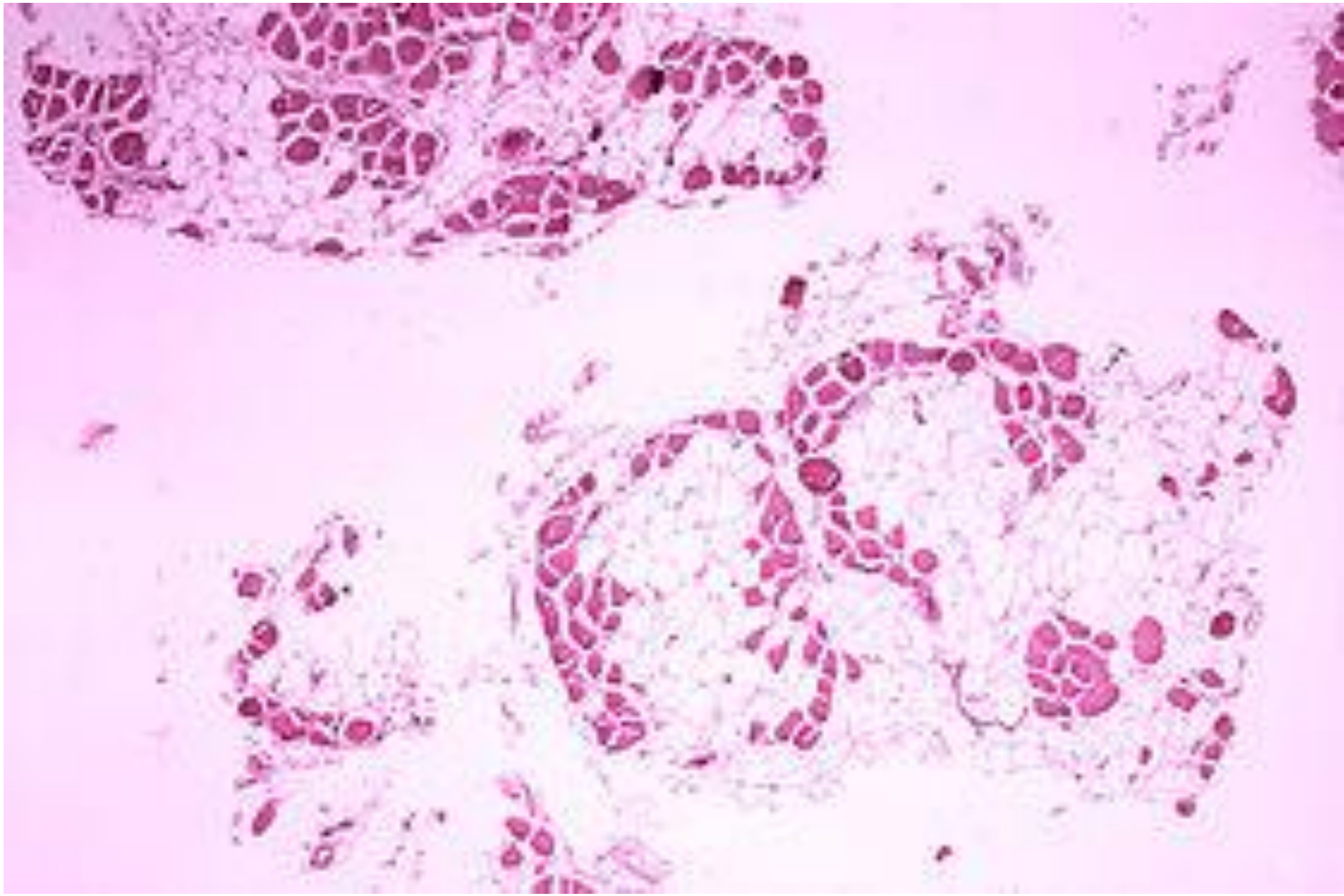
maintain structural integrity of muscle cells

Tissue muscle, brain, peripheral nerves

Clinical symptoms: normal birth

delayed walking, weaknes starting at pelvic muscles, progress to shoulders, pseudohypertrophy of calfs (musculus gastrognemius), heart failure and arrhythmias may occure.

death? Respiratory insuff. Pulm.infection-



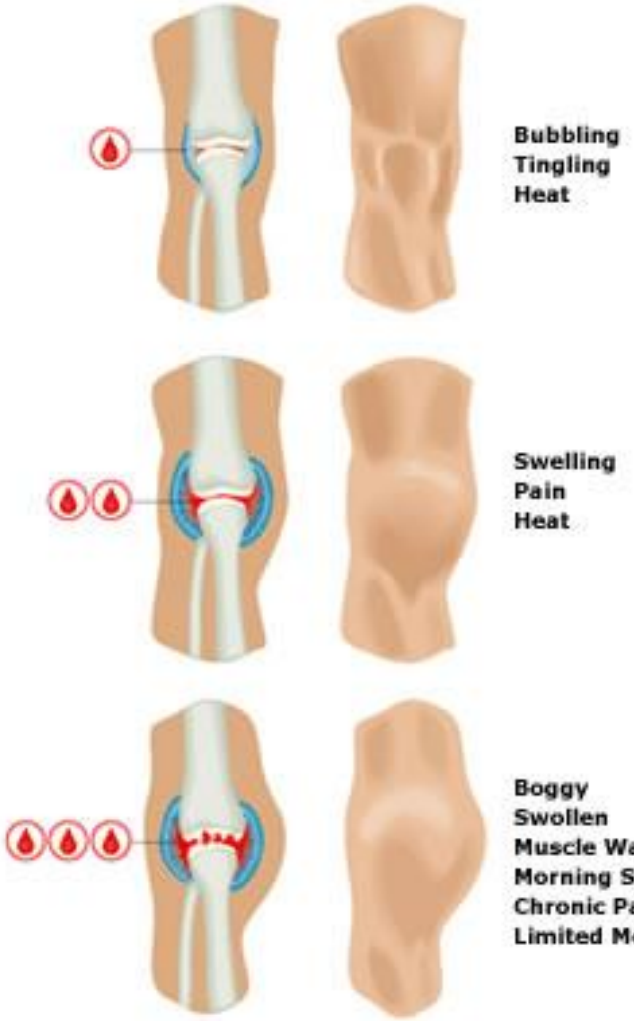
Duchenne dystrophy

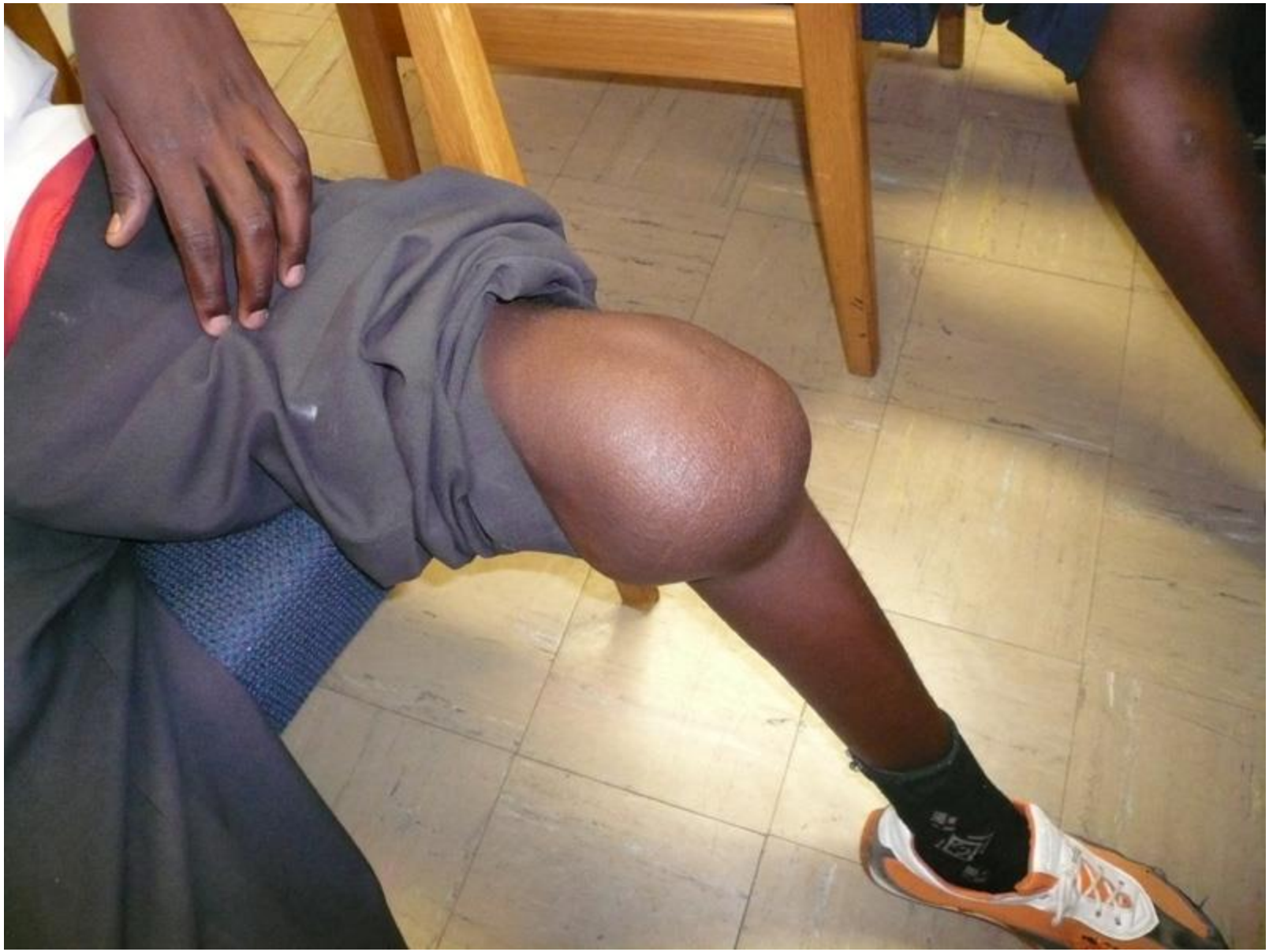
3/2

Disorders of clotting factors
Hemophilia A,B
Bleeding after minute injury
Factor VIII is a complex:
- FVIII coagulation molecule
- von Willebrandt factor
- ristocetin cofator

Hemophilia A: deficiency of FVIII cogulant molecule
- X linked recessive trait 75%
- spontan mutation 25%

common in males
Spontaneous bleeding-joints-hemarthros, joint deformities
Hemophilia B: factor IX deficiency
- sex linked, similar to hemophilia A.

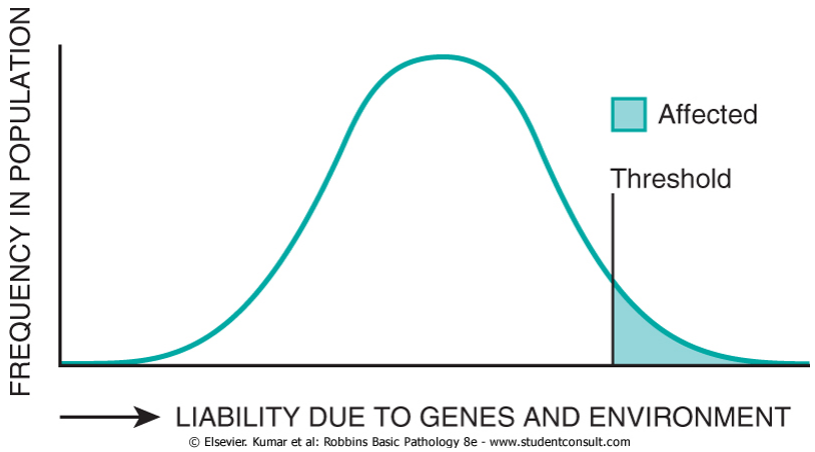




Polygenic (Multifactorial) Inheritance

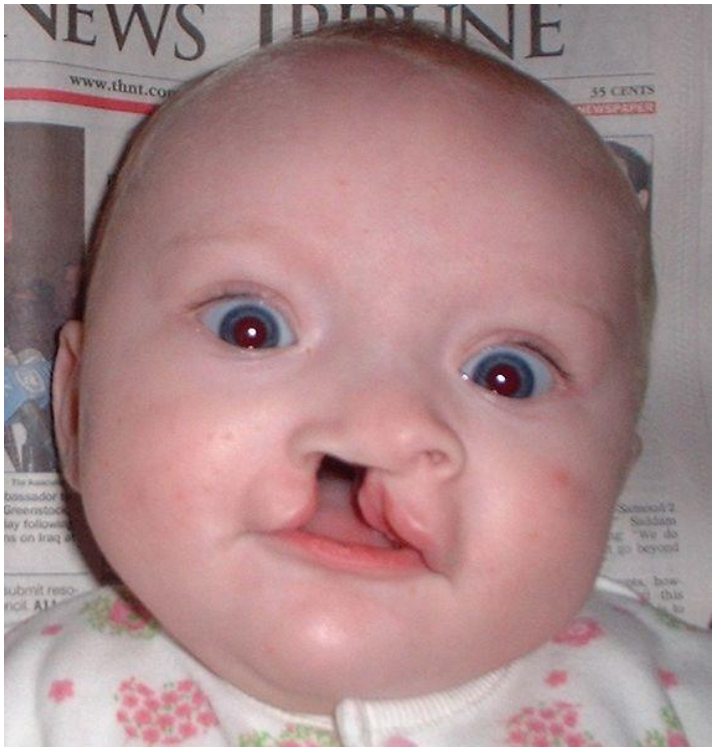
- More common than monogenic disorders
  - Abnormalities of complex processes regulated by the protein products of two or more genes
  - Environmental factors also play an important role in the modulation of the genetic defects
    - 'Normal traits' - height, eye color, intelligence
    - Diabetes mellitus, hypertension, ischemic heart disease, gout, schizophrenia, bipolar disorder, neural tube defects, dwarfism, cleft lip/palate, periodontal disease and some cancers
  - Risk of occurrence of disease is higher in first-degree relatives and in subsequent pregnancies

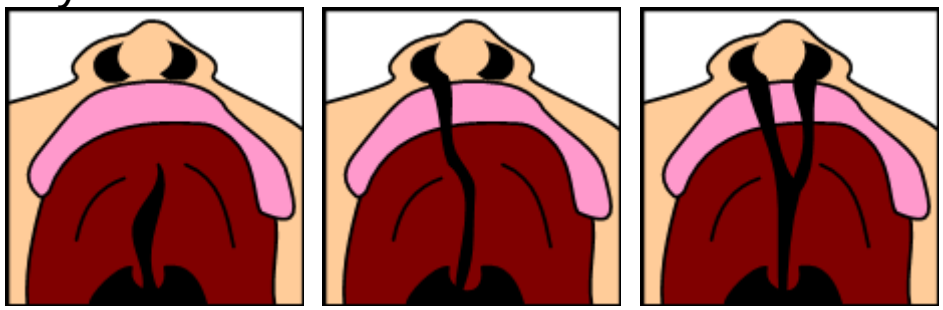
II Disorders with multifactorial inheritance (polygenia)



The risk of disease is related the number of affected genes
The risk is higher in children whose both parents are affected
Rate of recurrance is 2-7%
Next child =%
Identical twins: less than 100% (20-40%)
Disorderes:Diabetes mellitus, Hypertension, Gout, schisophrenia
Cleft palate

Cleft lip and palate, which can also occur together as **cleft lip and palate**, are variations of a type of clefting congenital deformity caused by abnormal facial development during gestation.. A **cleft** is a fissure or opening—a gap. It is the non-fusion of the body's natural structures that form before birth. Approximately 1 in 700 children born have a cleft lip and/or a cleft palate. In decades past, the condition was sometimes referred to as **harelip**, based on the similarity to the cleft in the lip of a hare, but that term is now generally considered to be offensive.





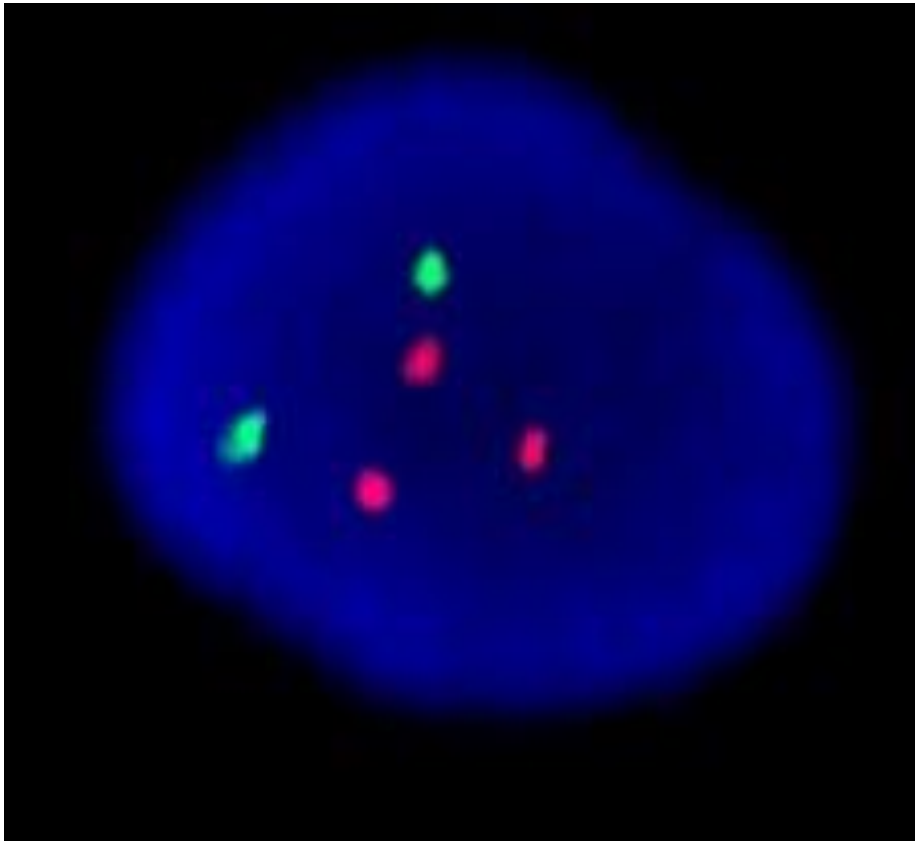
ERBB2, CDH2 and IRF6, FGFR collagen11, glypican3, FGFR2 Sonic hedgehog, etc

III. Citogenetic disorders

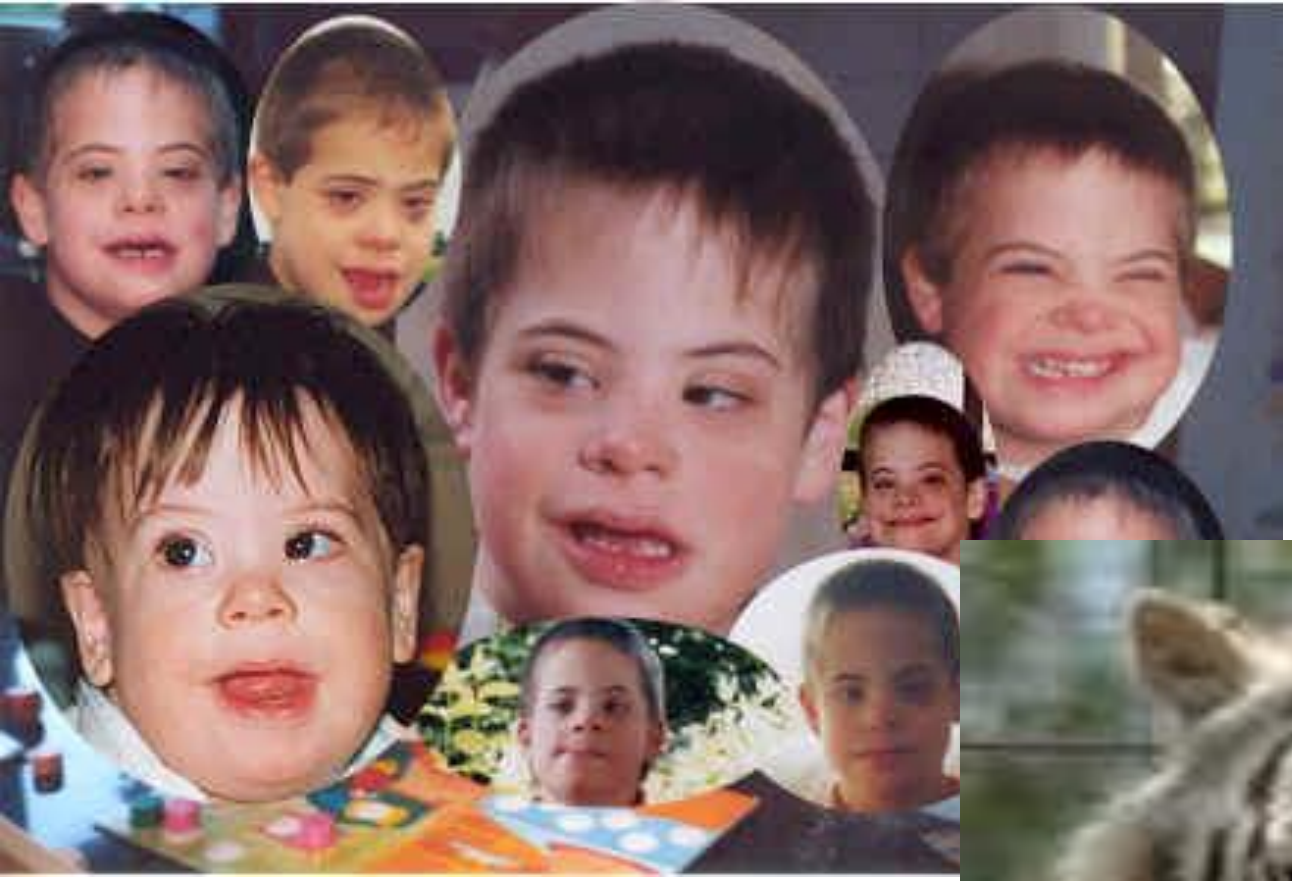
Alteration the number or the structure of chromosomes may affect autosomes:
sex chromosomes

III. a Numerical disorder

Trisomies
Down disease 21 trisomy



Frequency increases with the age of the mother. Abnormal chromosome comes generaly from her.
Flat face, epicanthic fold, short neck, congenital heart defect, umbilical hernia, prone for Leukaemia. Mental retardation., Alzheimer disease



III/b Structural abnormalities of chromosomes

Chromosomal brekage, followed by lost of rearranged material

p: short arm, q: long arm numbered from centromere

1.Translocation
2. Isochromosomes
3.Deletion
4. Inversion
5. Ring chromosome

21q deletion syndrome: a spectrum of disorders
heart malformations including outflow tract
facial dysmorphism, developmental delay,
thymic hypoplasia, impaired T cell immunity
parathyroid hypoplasia, hypocalcaemia.

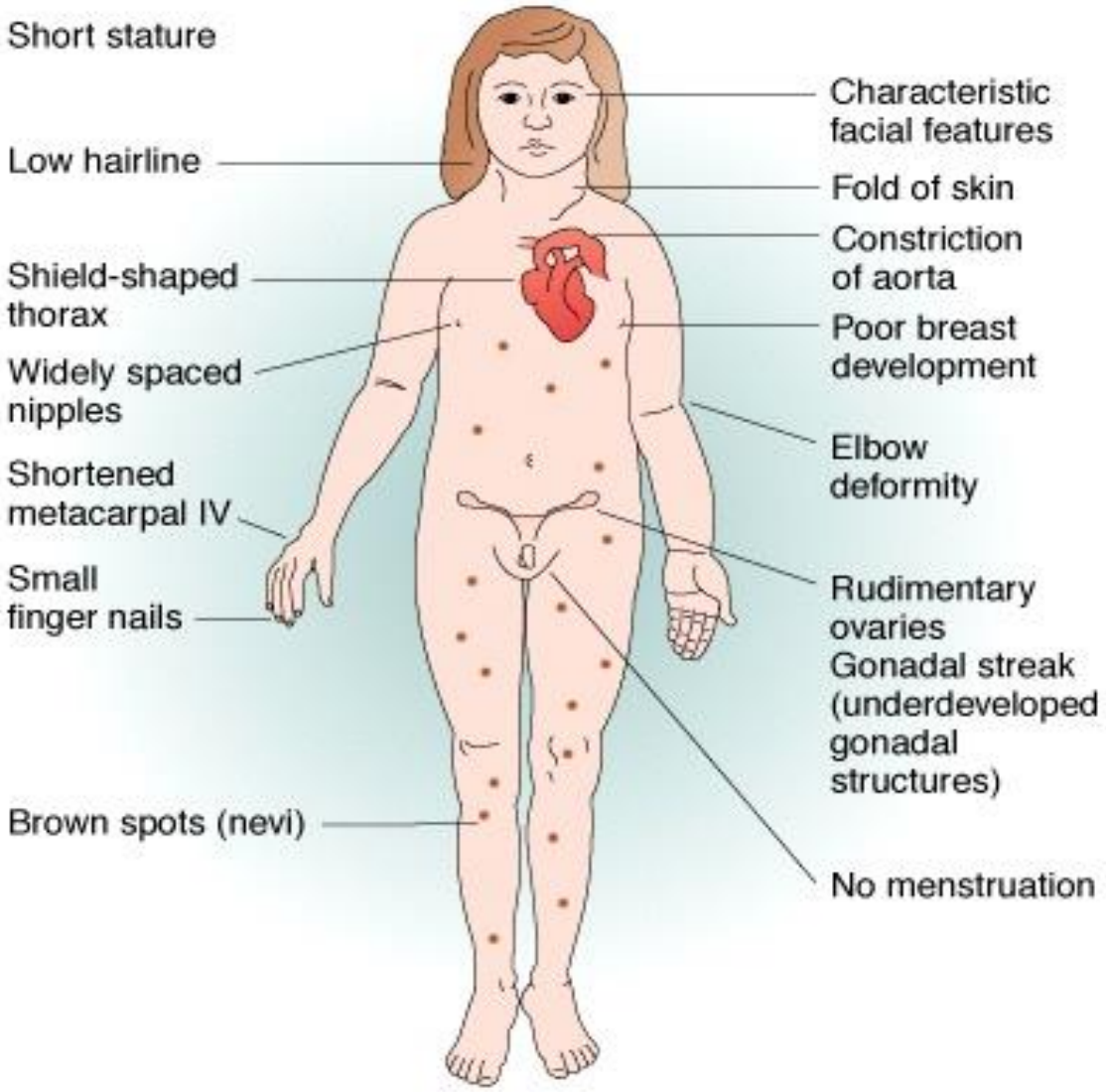
Types: DiGeorge syndrome: Thymus, parathyroid

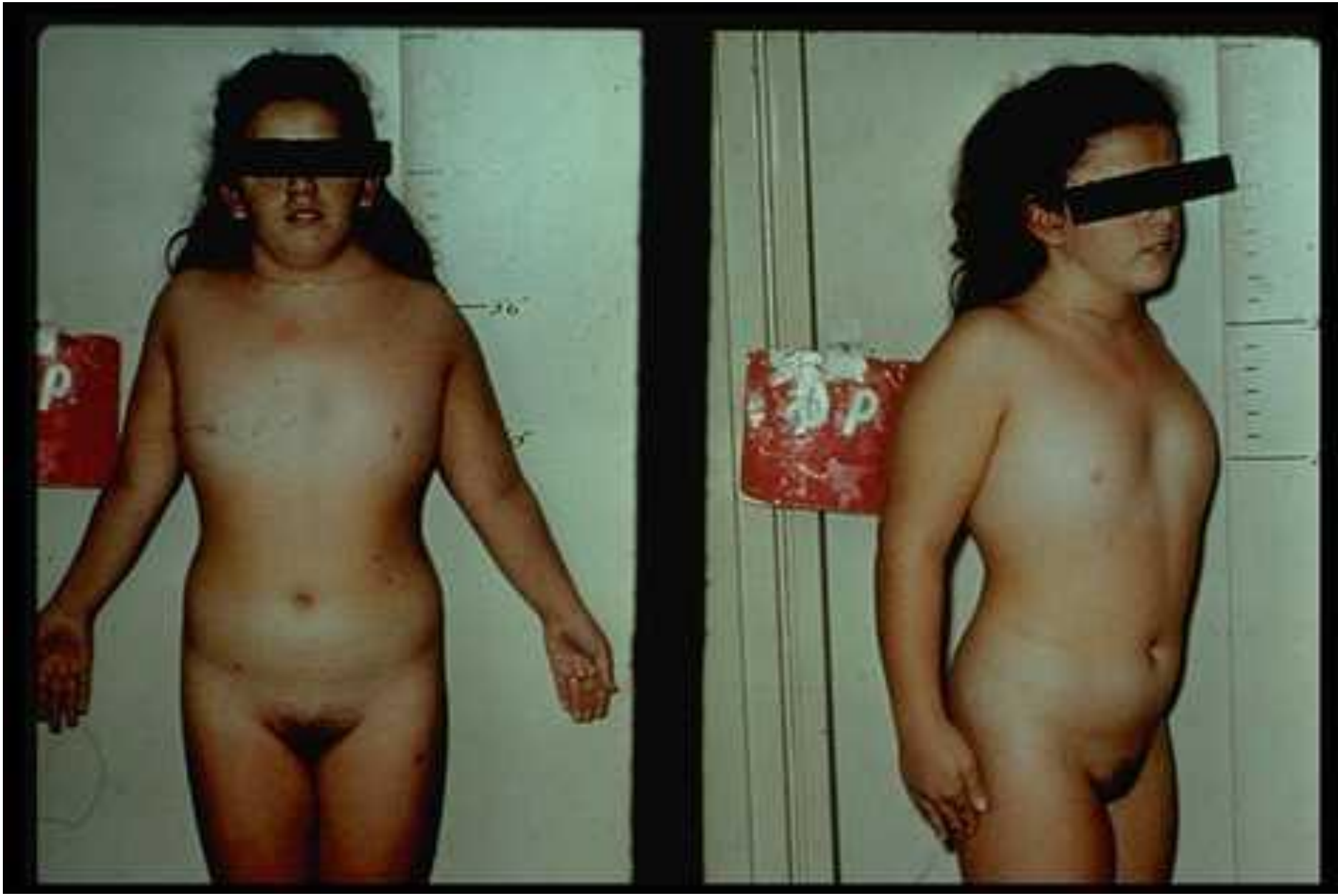
Velocardiofacial syndrome: face, heart

III/c Cytogenetic disorders of sex chromosomes

Turner syndrome 45X karyotype
Female phenotype-hypogponadism

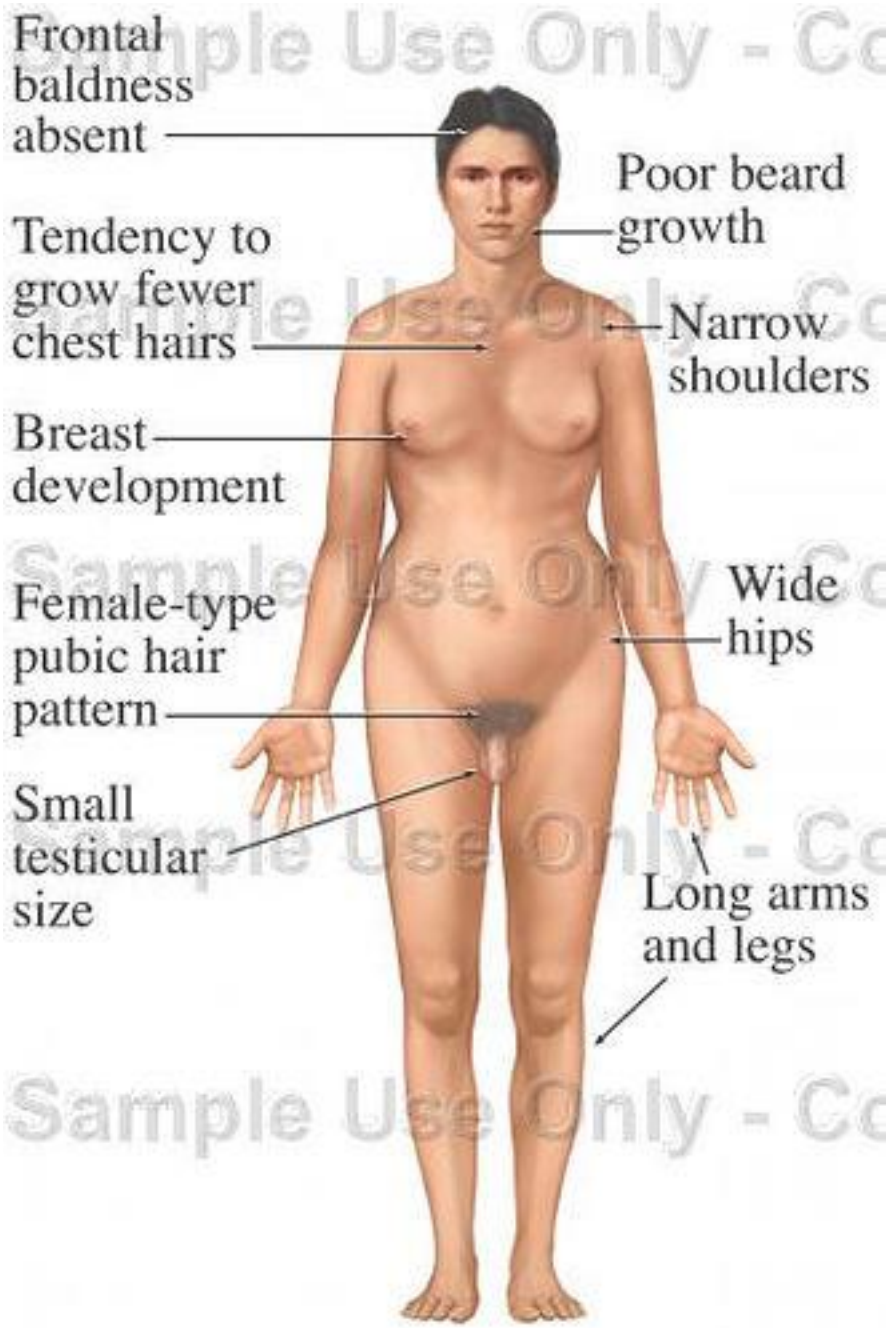
Short statue, webbing neck , broad chest, cubitus valgus
Coarctation aortae
Pigmented nevi
Hypofunction of ovaries, amennorhea, infertility





Klinefelter syndrome XXY

Hypogonadism



Diverticulosis is a type of condition in which small sacs (diverticula) form in the colon . Although the exact cause of the condition is not known at this time, it is believed to be linked to a low-fiber diet (which can cause constipation).

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They can cause problems difficult to explain abdominal pain, cramps, anaemia, inflammation, perforation, bleeding.

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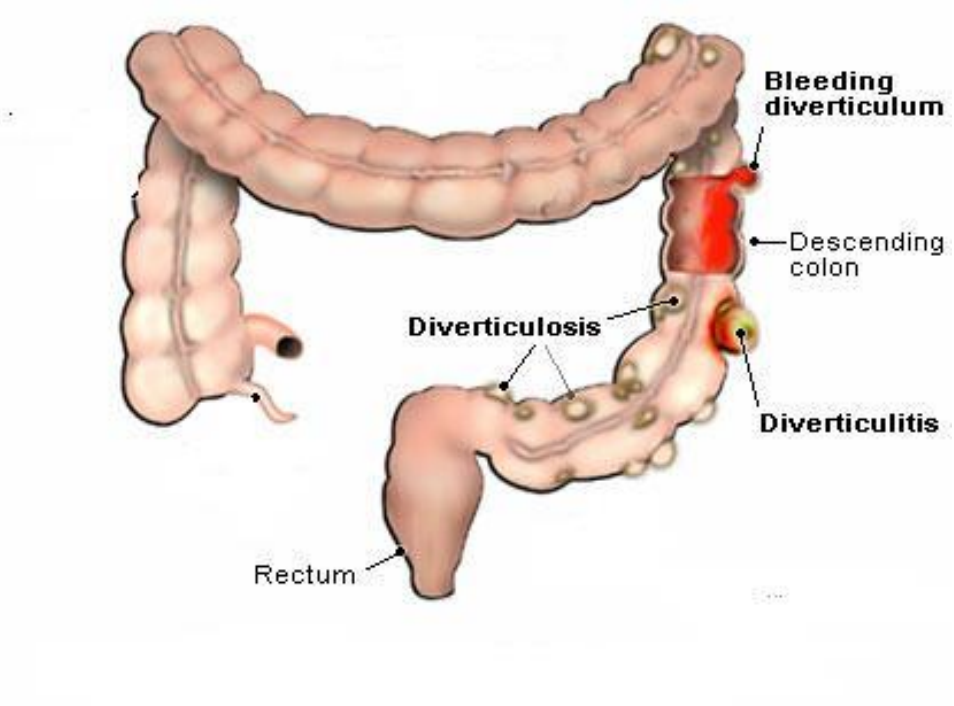


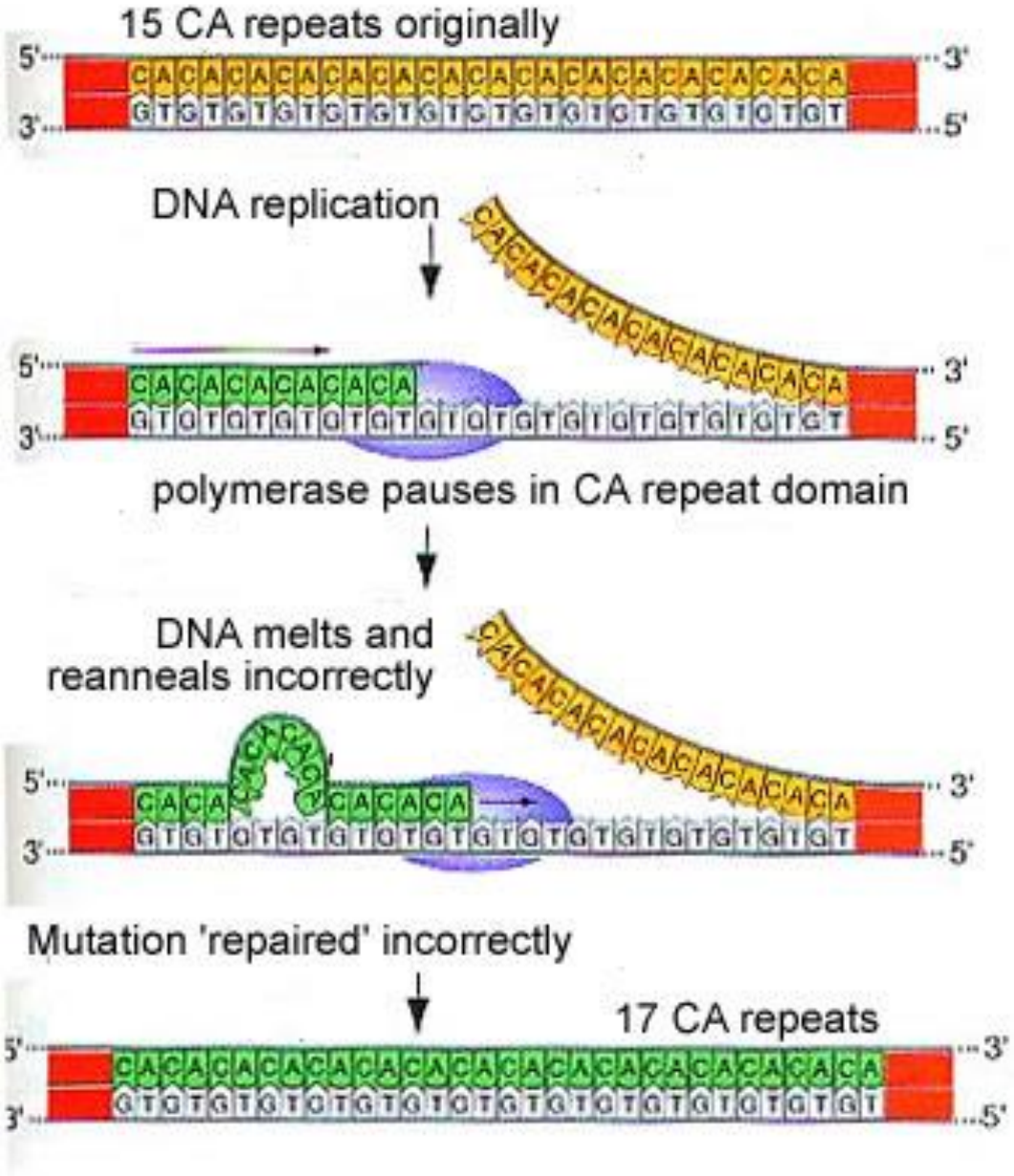
A **Meckel diverticulum**, a real congenital diverticulum on the ileum It is the remnant of omphalomesenteriali duct.

Frequency: 2 % and symptoms are more frequent at males. It lengths is 3-5 cm and it has separate blood supply.
It is named after Johann Friedrich Meckel who recognised its embrional origine in 1809.

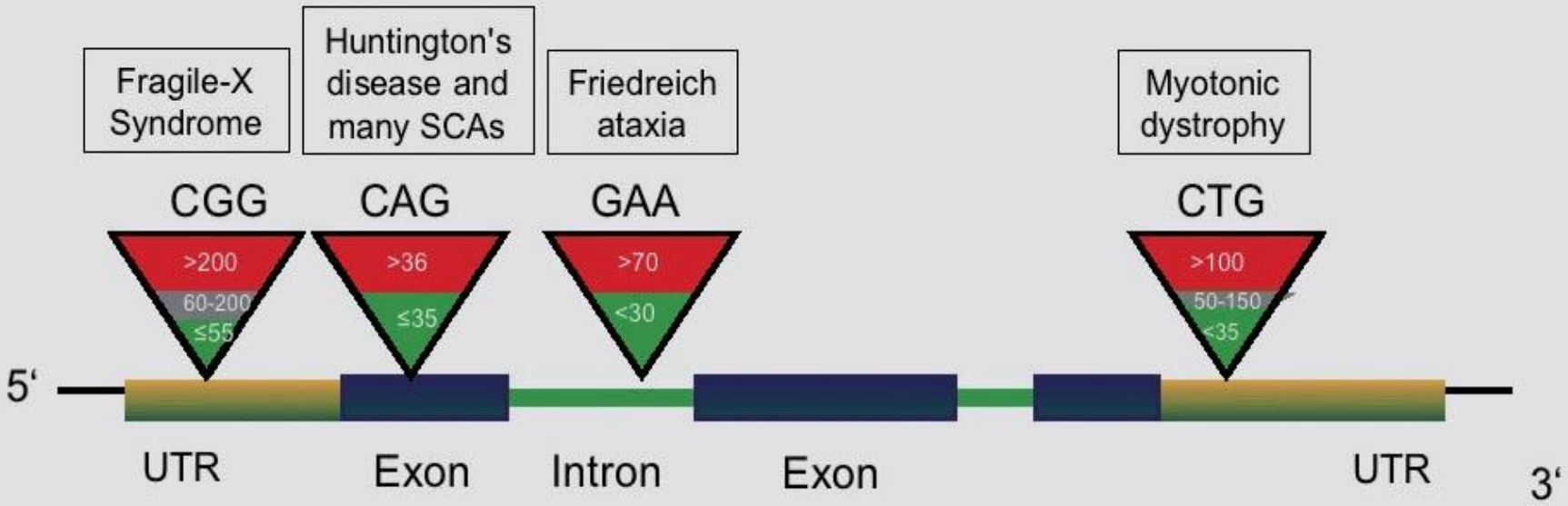
IV Single gene disorders with atypical pattern of inheritance

1 Triplet repeat mutations (about 30 disease related to 3 repeat disorder, all of them cause neurodegenerative changes)

Fragile X syndrome: familial mental redation
long face, large mandibule, large ears, large testis
discontinuity of staining in the long arm of X chromosome, mutation of FMR gene Xp27.3
20% of males carry the mutation are physically normal.
CGG repeats in normal case : 29
affected individuals 200-400-
Carriers: 52-200 repeat (premutation) conversion to fully mutation in oogenesis.
Symptoms: tremor, ataxia.
Mechanism: repeats on the 5' untranslated region became hypermethylated, expansion toward promoter region- hypermethylation- silencing of FMR gene
FMR is an mRNA binding protein, carries mRNA to ribosomes in the dentrite and axons.


15 CA repeats originally
5'
3'
DNA replication
polymerase pauses in CA repeat domain
DNA melts and
reanneals incorrectly
Mutation 'repaired' incorrectly
17 CA repeats

Trinucleotide repeat diseases



Full mutation

Premutation range (may expand to a full mutation in the next generation)

Normal alleles

UTR = untranslated region
SCA = spinocerebellar ataxia

2. Mutation of mitochrondrial genes : they encode enzymes of oxidative phosphorylation- maternal inheritance- no mitochondria in the sperms
Skeletal muscle, heart and brain is involved.
Leber hereditary optic neuropatrhy: loss of central vision by age 15.

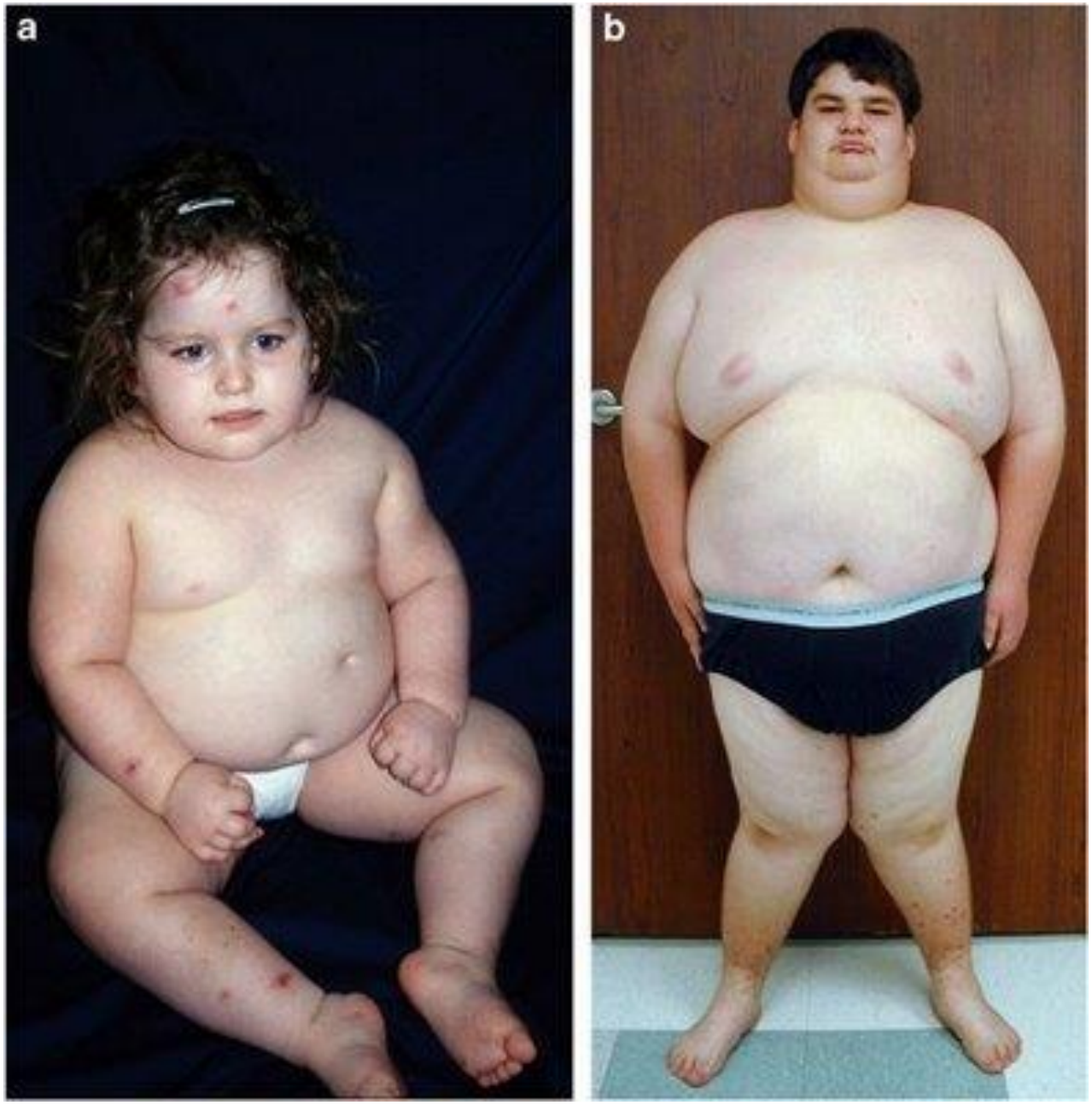
3. Genomic imprinting
all humans inherit 2 copies of gene (maternal, paternal)
in many gene there are no difference between homologus genes.

In some genes functional differences exists between maternal and paternal gene.
genomic imprinting: genes differentially inactivated
maternal imprinting $\longrightarrow$ transcriptional silensing of maternal gene
paternal imprinting $\longrightarrow$ transcriptional silencing of paternal gene
Imprinting occure in ovum and sperm then stably transmitted to all somatic cells.

Del 15(q11;q13

Prader –Willi syndrome
Paternal chromosome affected
Hypotonia, obesity, mental retardation
hands, hypogonadism

Angelman synrome
maternal chromosome affected
mental retardation, ataxia, small
inappropriate laughter
„ happy puppet” syndrome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