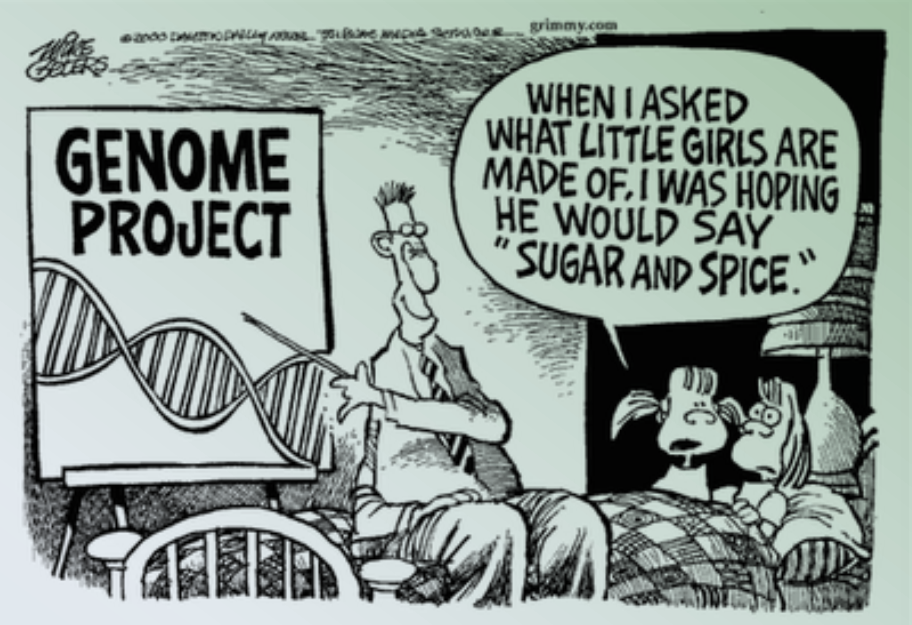

Medical Genetics

Dr. Mazin Al-Salihi

Course Info

- Textbook
  - Medical Genetics, (Jorde, Carey, Bamshad) 5th Edition

- 12 Lectures
  - Quick review of cell biology
  - Short history
  - Genetic variation, mutational, non-mutational, and their detection
  - Single gene disorders
  - Clinical cytogenetics
  - Biochemical genetics

Clinical Impact of Genetic Disease

TYPE OF GENETIC DISEASE	LIFETIME PREVALENCE PER 1000 PERSONS
Autosomal dominant	3-9.5
Autosomal recessive	2-2.5
X-linked	0.5-2
Chromosome disorder	6-9
Congenital malformation	20-50
Total	31.5-73

Quick Review

STUDIES ON THE CHEMICAL NATURE OF THE SUBSTANCE INDUCING TRANSFORMATION OF PNEUMOCOCCAL TYPES

Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III

By OSWALD T. AVERY, M.D., COLIN M. MacLEOD, M.D., and MACLYN McCARTY,* M.D.

(From the Hospital of The Rockefeller Institute for Medical Research)

Plate 1

(Received for publication, November 1, 1943)

Biologists have long attempted by chemical means to induce in higher organisms predictable and specific changes which thereafter could be transmitted in series as hereditary characters. Among microörganisms the most striking example of inheritable and specific alterations in cell structure and function that can be experimentally induced and are reproducible under well defined and adequately controlled conditions is the transformation of specific types of Pneumococcus. This phenomenon was first described by Griffith (1) who succeeded in transforming an attenuated and non-encapsulated (R) variant derived from one specific type into fully encapsulated and virulent (S) cells of a heterologous specific type. A typical instance will suffice to illustrate the techniques originally used and serve to indicate the wide variety of transformations that are possible within the limits of this bacterial species.

Griffith found that mice injected subcutaneously with a small amount of a living R culture derived from Pneumococcus Type II together with a large inoculum of heat-killed Type III (S) cells frequently succumbed to infection, and that the heart's blood of these animals yielded Type III pneumococci in pure culture. The fact that the R strain was avirulent and incapable by itself of causing fatal bacteremia and the additional fact that the heated suspension of Type III cells contained no viable organisms brought convincing evidence that the R forms growing under these conditions had newly acquired the capsular structure and biological specificity of Type III pneumococci.

The original observations of Griffith were later confirmed by Neufeld and Levinthal (2), and by Baurhenn (3) abroad, and by Dawson (4) in this laboratory. Subsequently Dawson and Sia (5) succeeded in inducing transformation *in vitro*. This they accomplished by growing R cells in a fluid medium containing anti-R serum and heat-killed encapsulated S cells. They showed that in the test tube as in the animal body transformation can be selectively induced, depending on the type specificity of the S cells used in the reaction system. Later, Alloway (6) was able to cause

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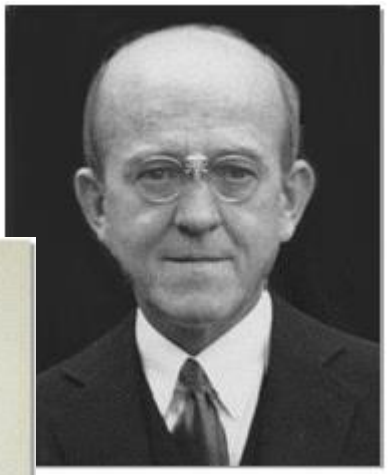
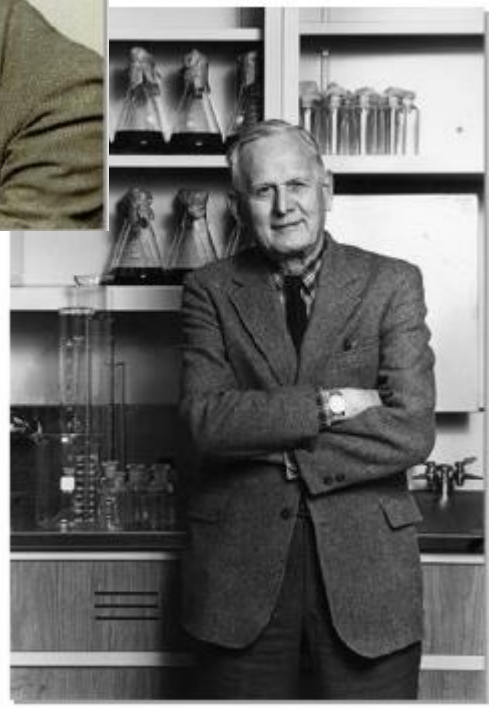
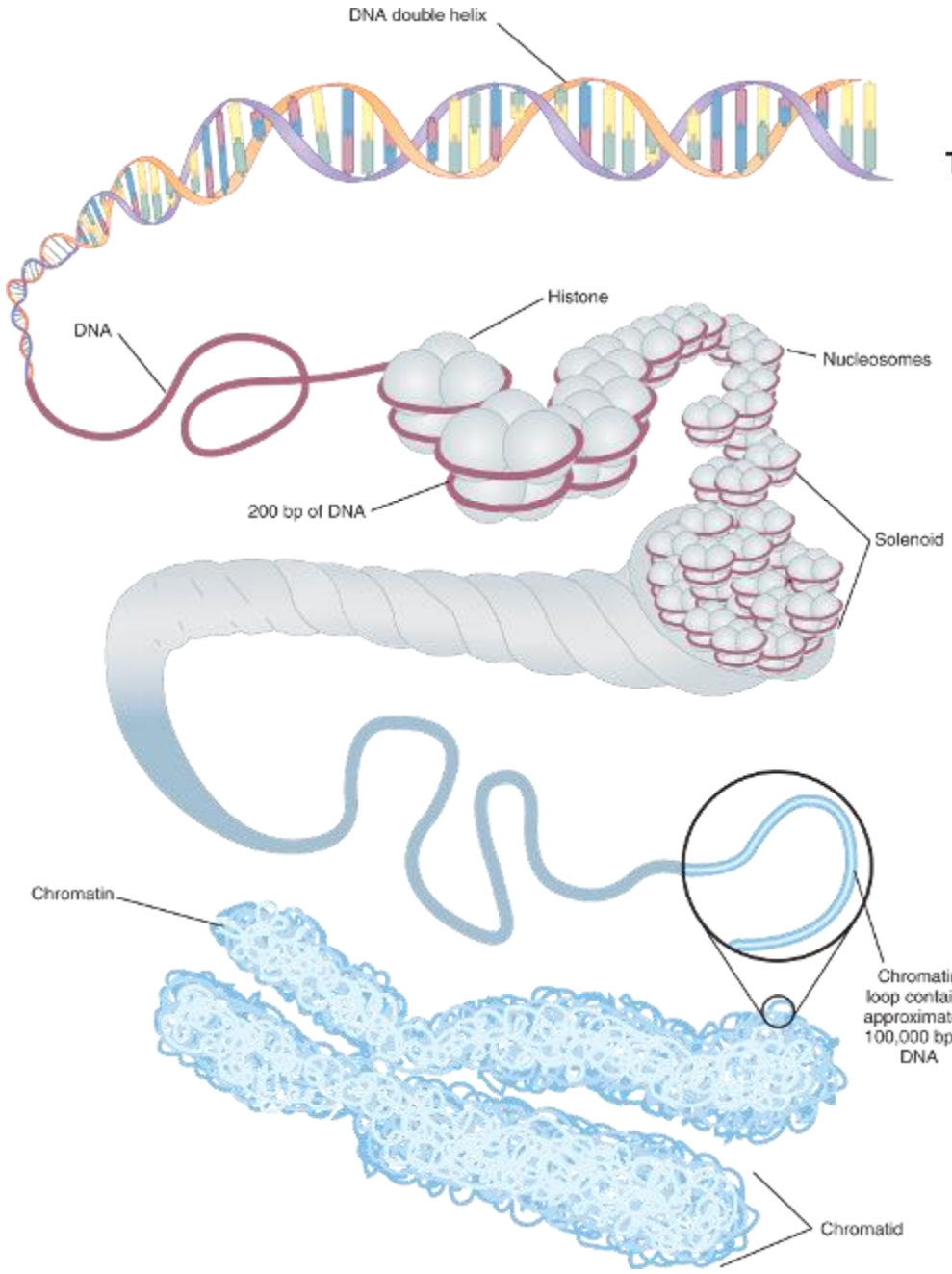
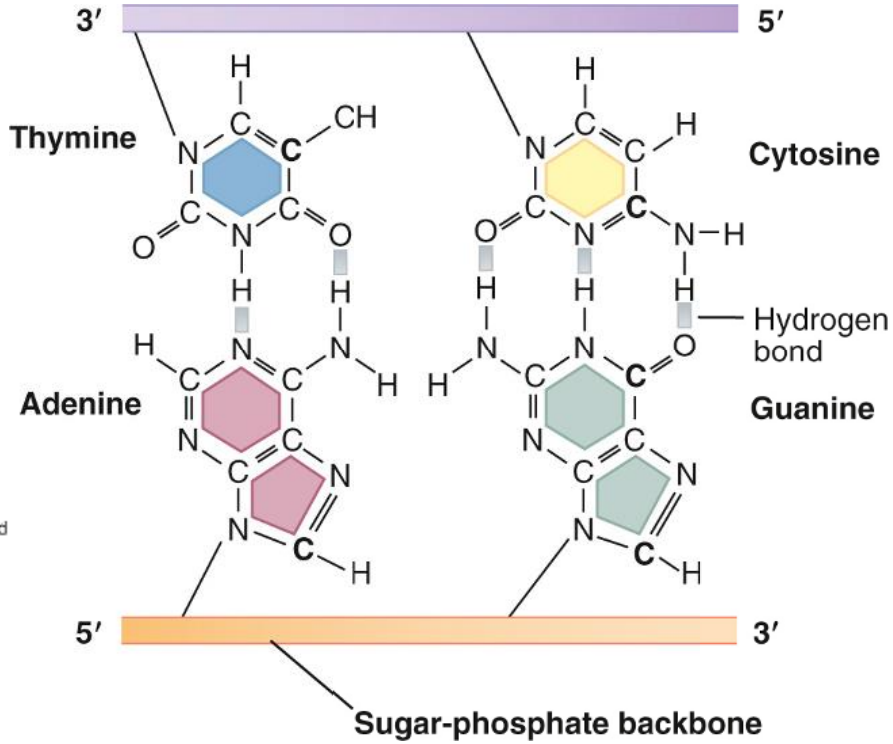
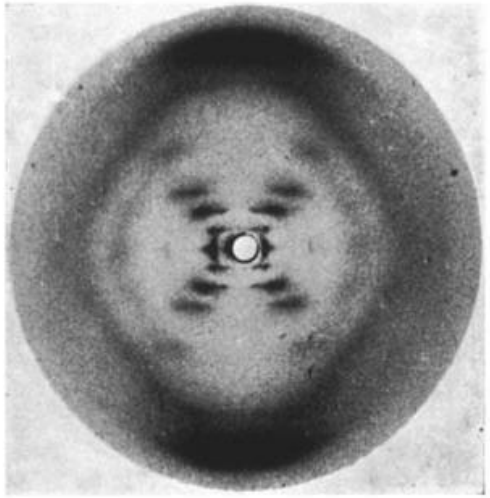
* Work done in part as Fellow in the Medical Sciences of the National Research Council.

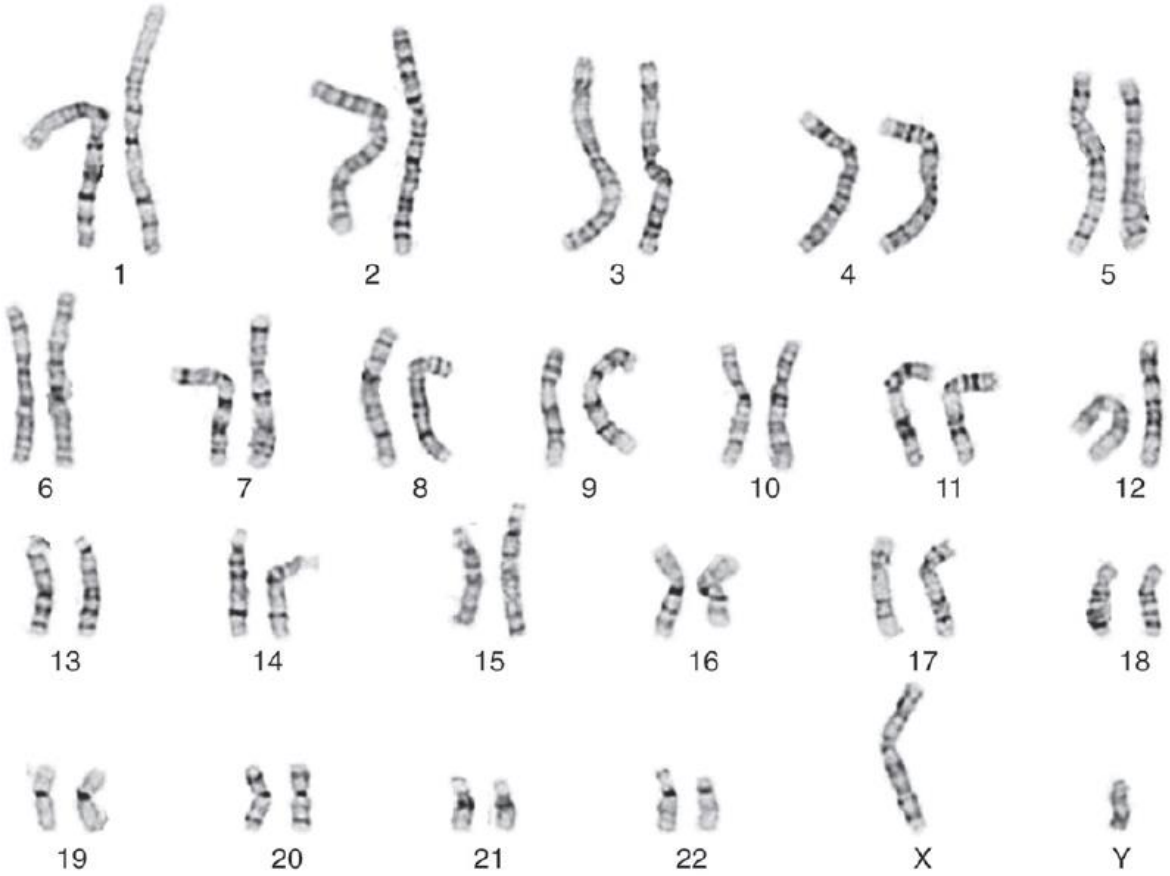





DNA double helix
DNA
Histone
Nucleosomes
200 bp of DNA
Solenoid
Chromatin
Chromatin loop contains approximately 100,000 bp of DNA
Chromatid


3′
5′
Thymine
Cytosine
Adenine
Guanine
Hydrogen bond
5′
3′
Sugar-phosphate backbone





Super Quick Review

Somatic/Gamete

Diploid/Haploid

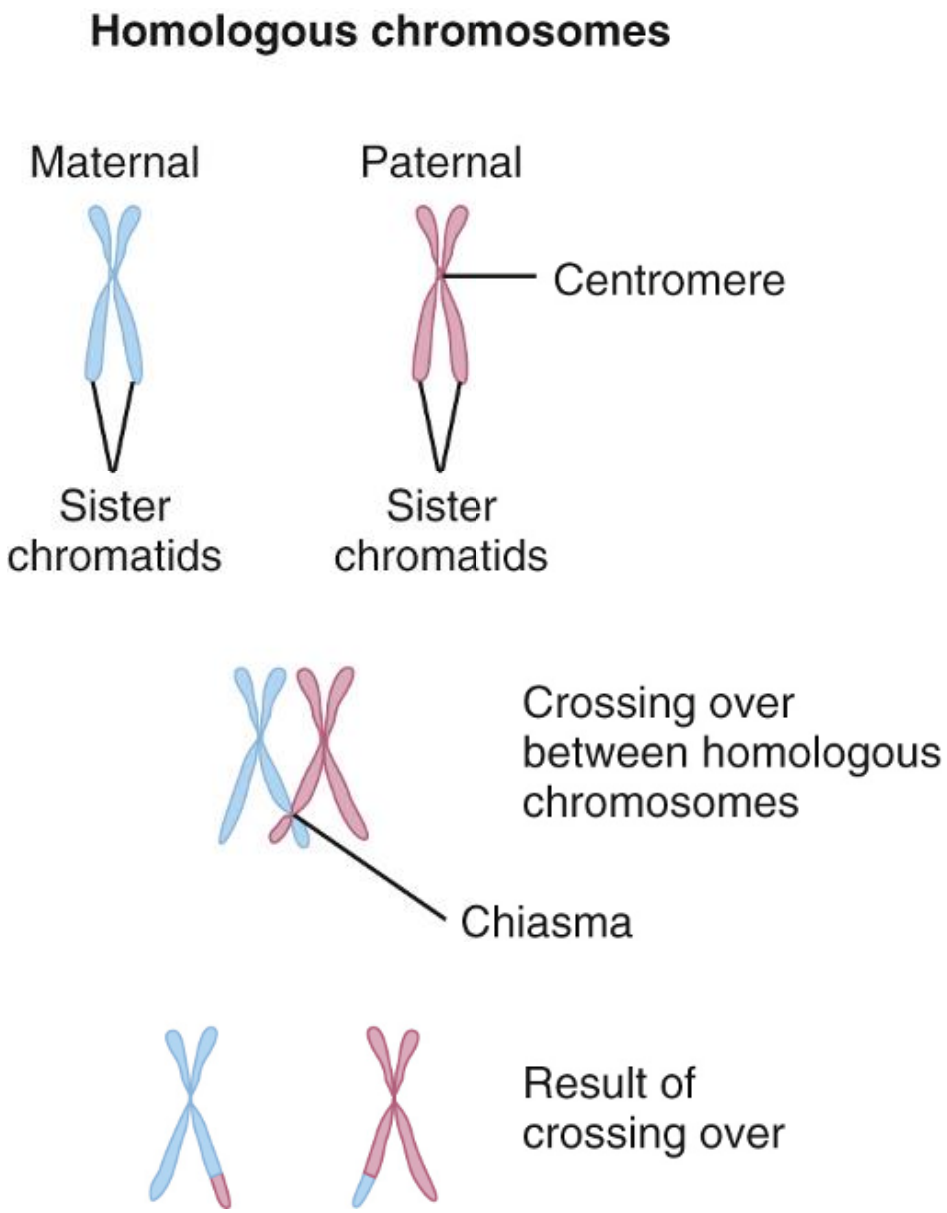
Autosome/sex chromosome

Homologues - cross over

Mitosis/Meiosis

Transcription/Translation

Exon/Intron - Splicing



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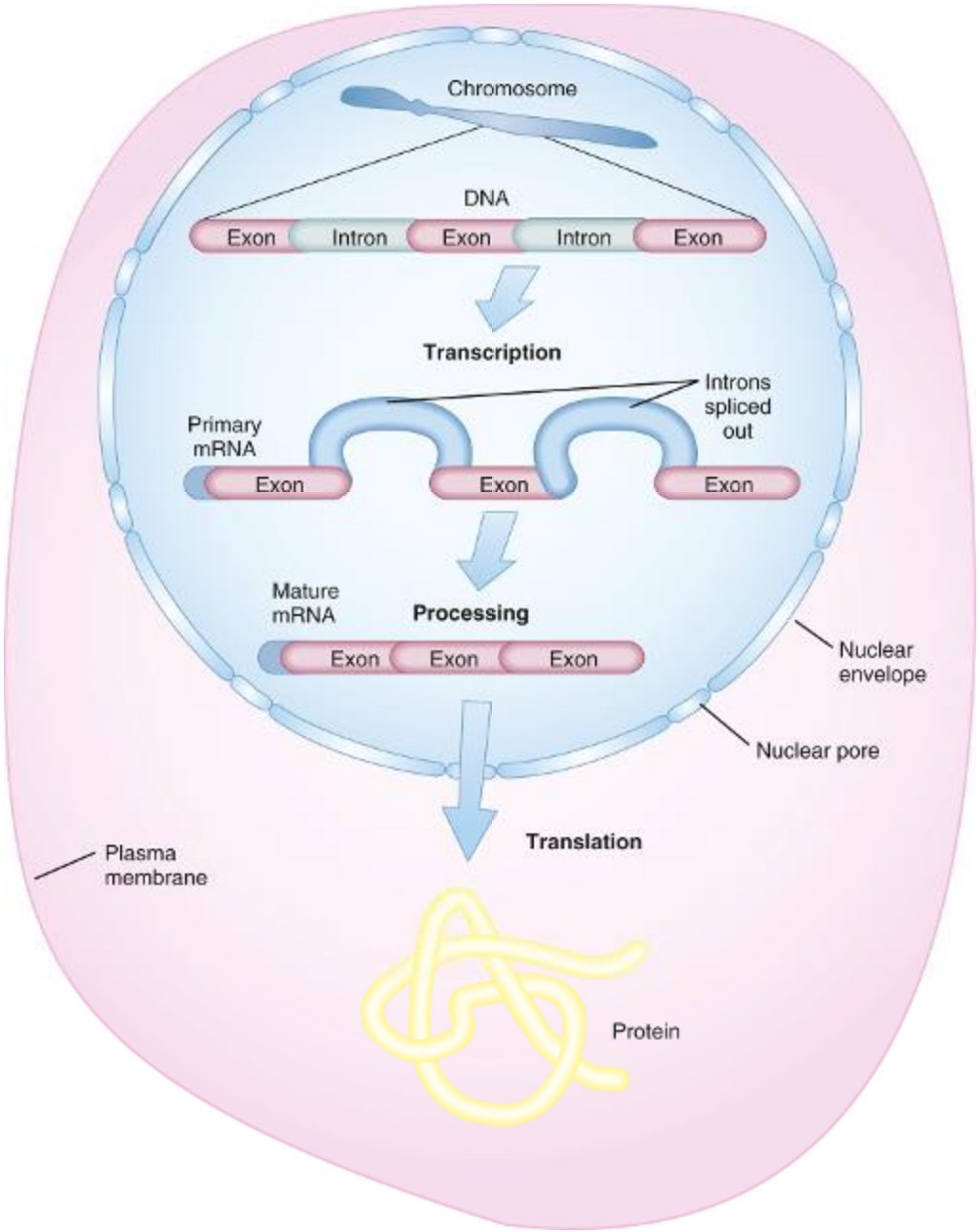

Super Quick Review

Somatic/Gamete

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Transcription/Translation

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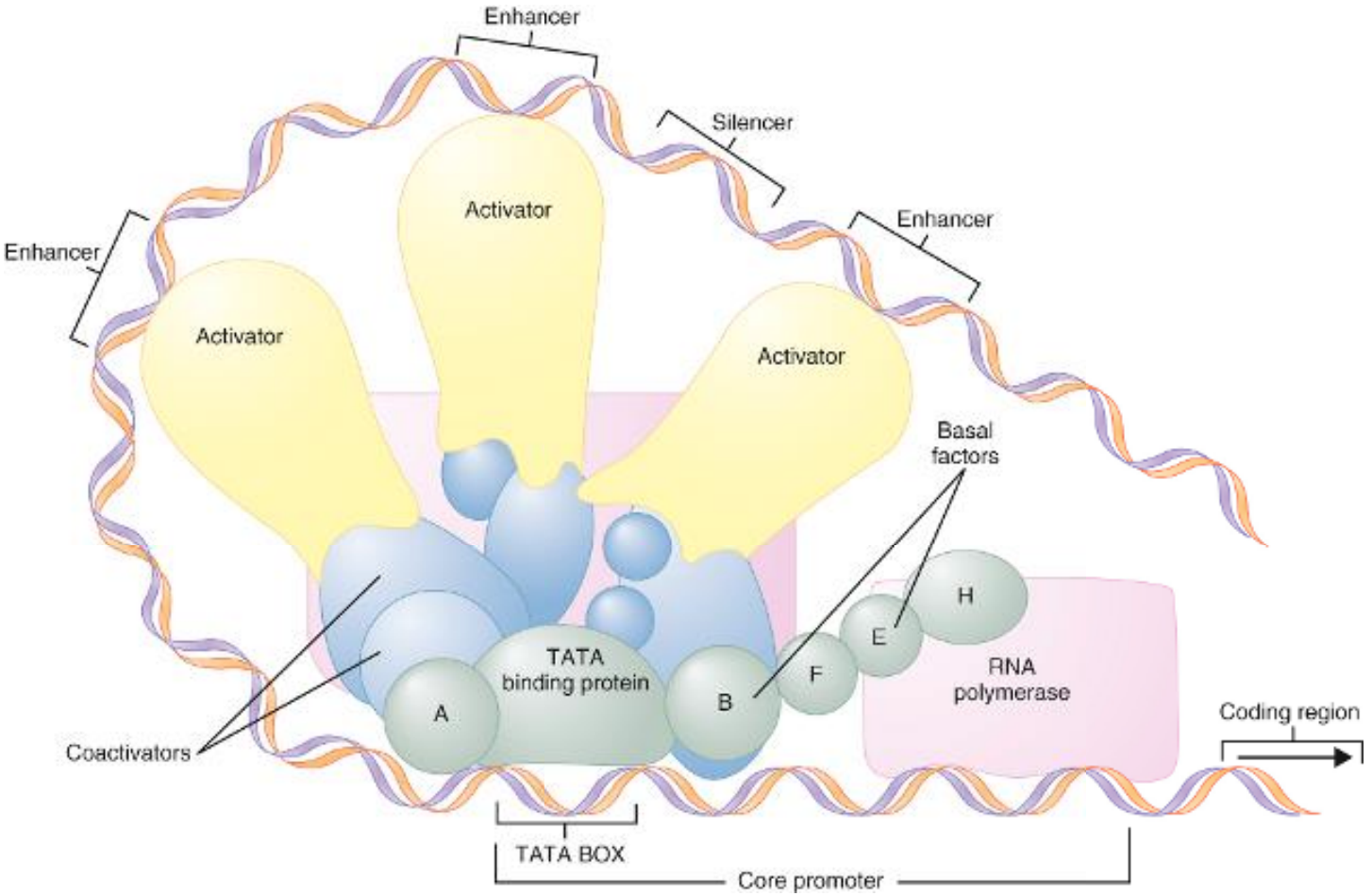
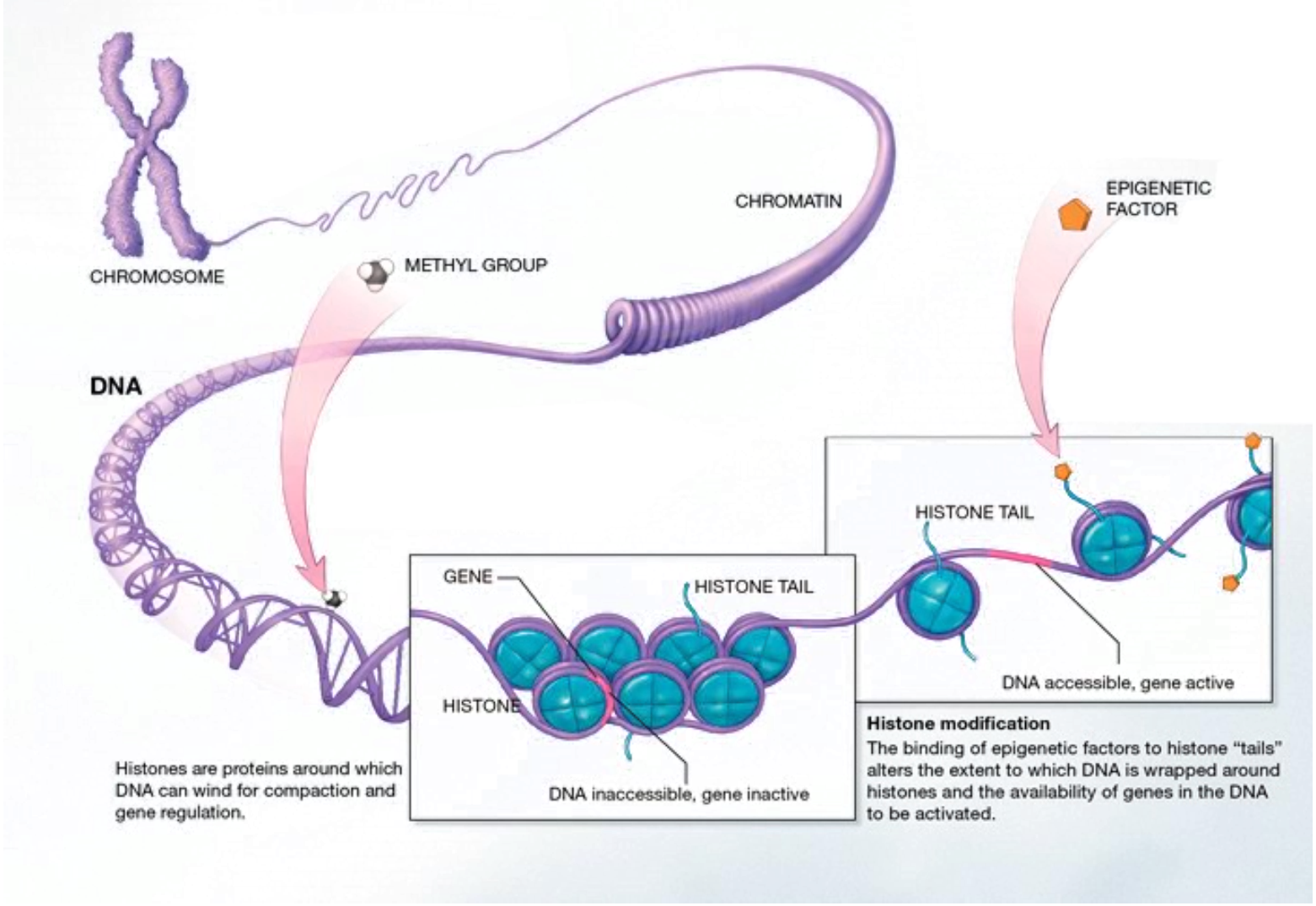
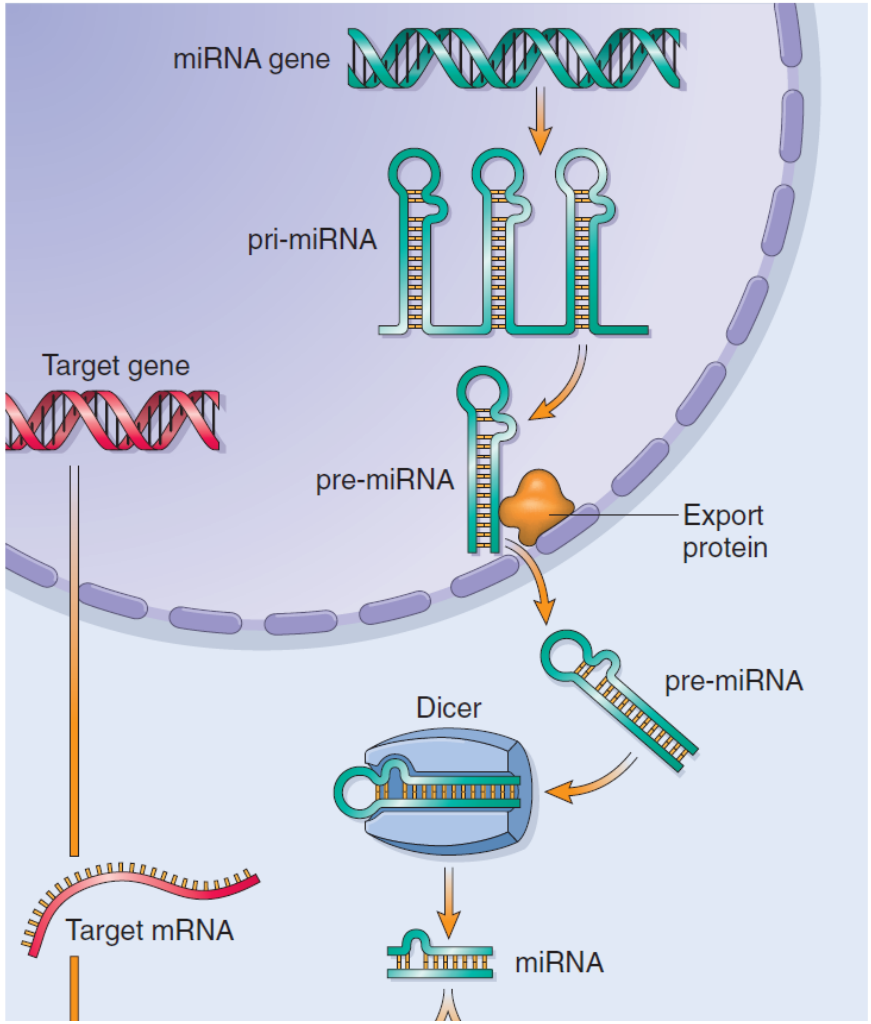
Transcription factors, Epigenetics, & miRNA

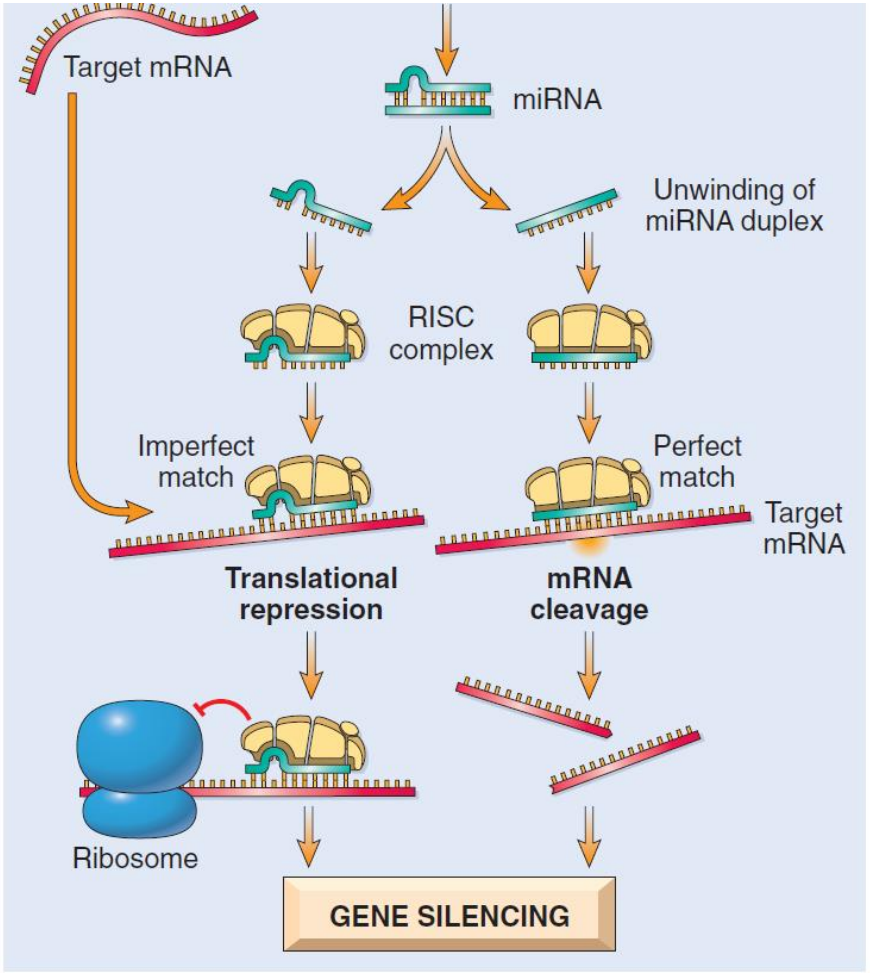


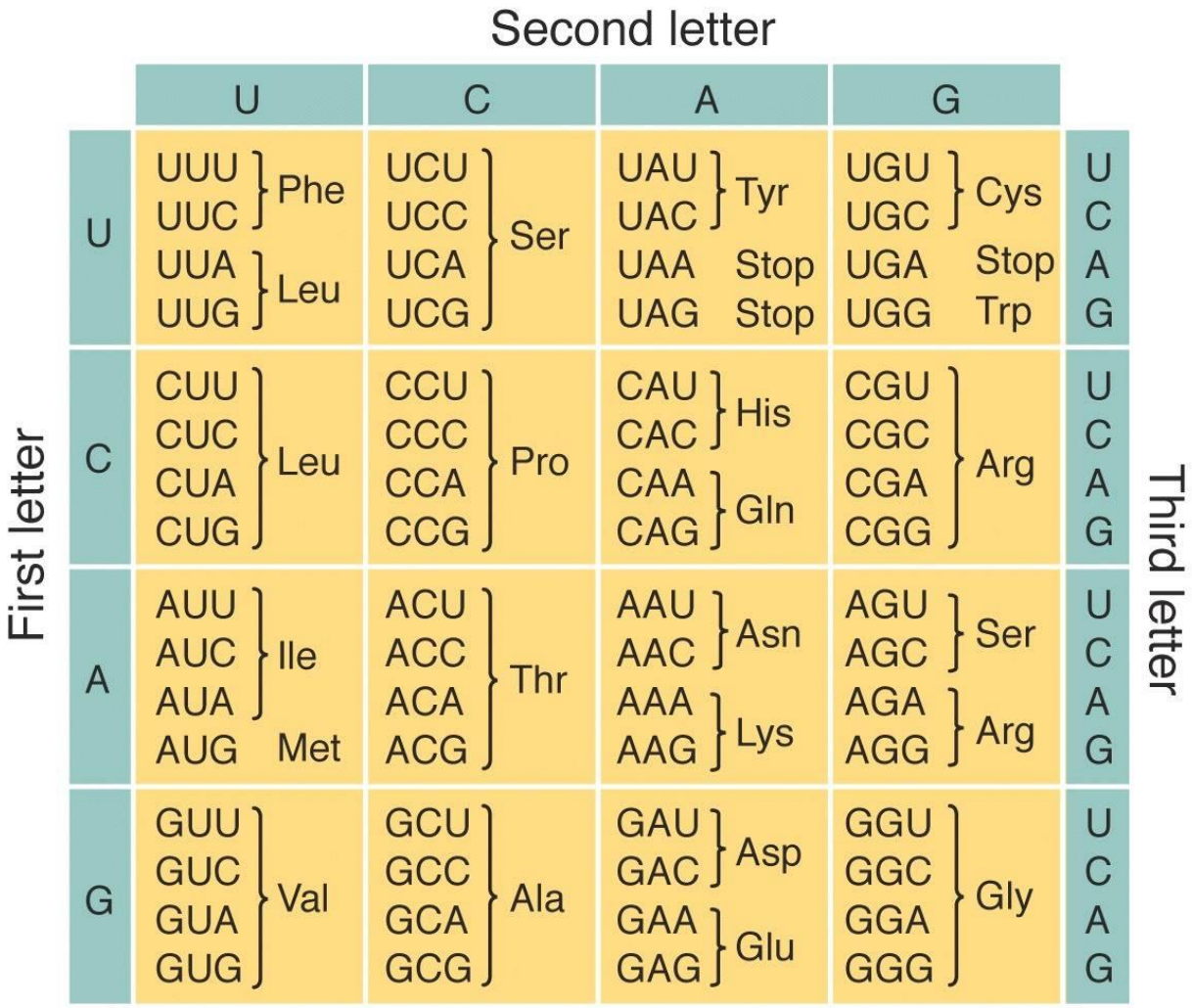
Transcription factors, Epigenetics, & miRNA



Transcription factors, Epigenetics, & miRNA







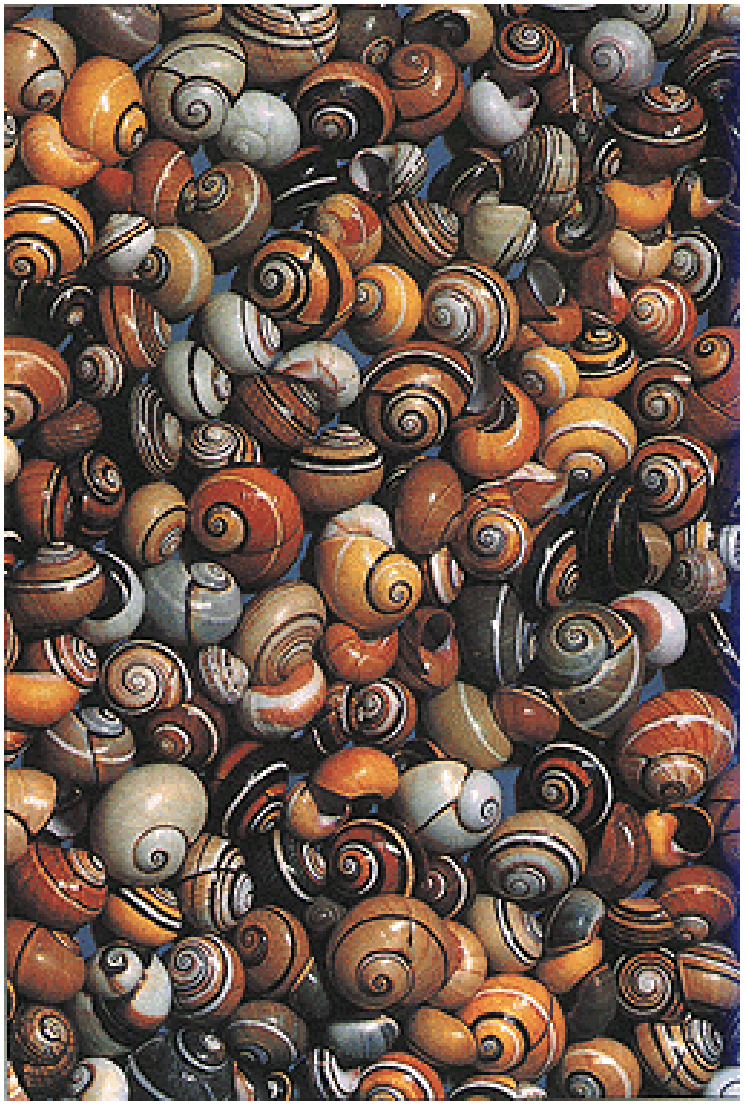
The genetic code

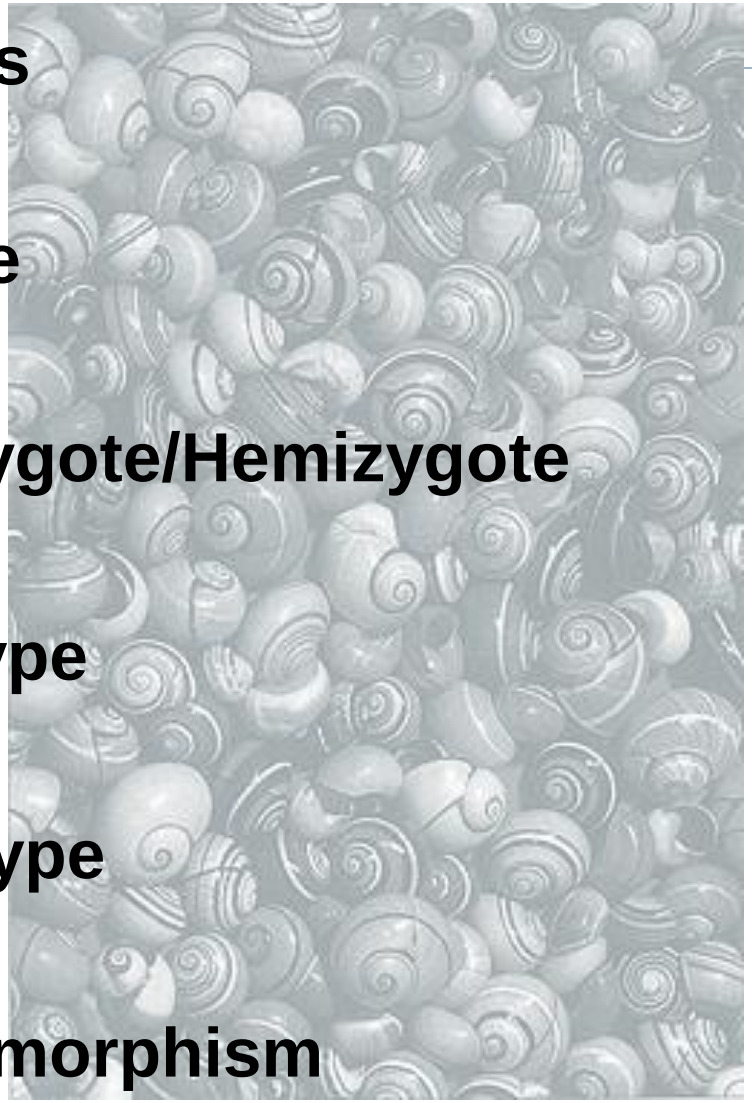
Codon
- aa
- stop

Degenerate

Universal (*mitochondria)

Genetic Variation & Mutation





Locus

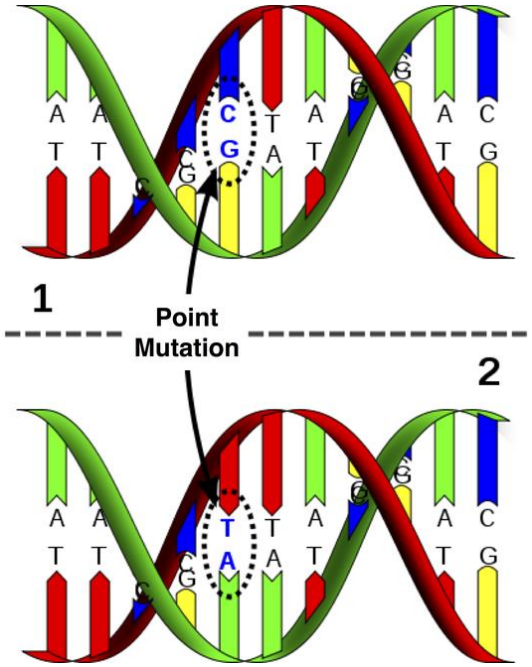
Allele

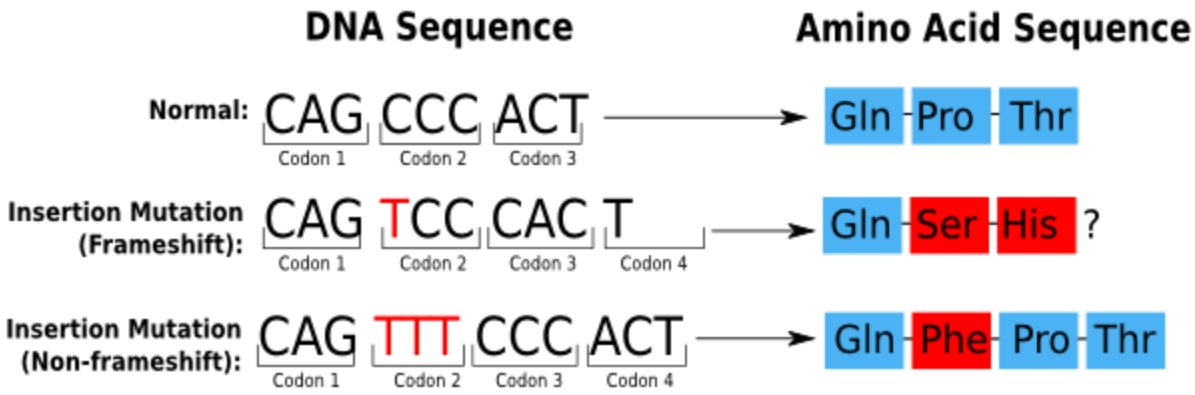
Homozygote/Heterozygote/Hemizygote

Genotype

Phenotype

Mutation/Polymorphism



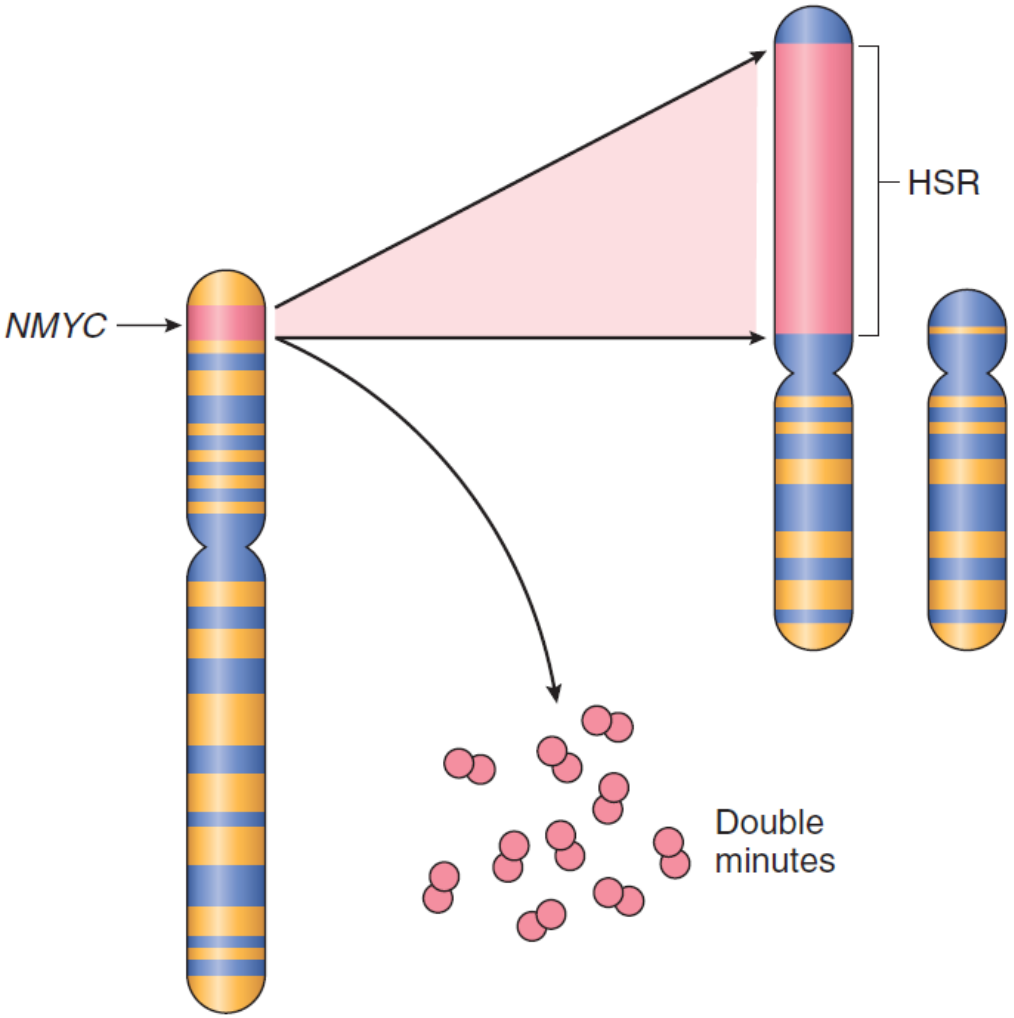


Mutations

Germ → Progeny
Somatic → Cancer

Point
- Silent
- Missense
- Nonsense (stop codon)
- Insertions
- Deletions

Frameshift
- Insertions
- Deletions

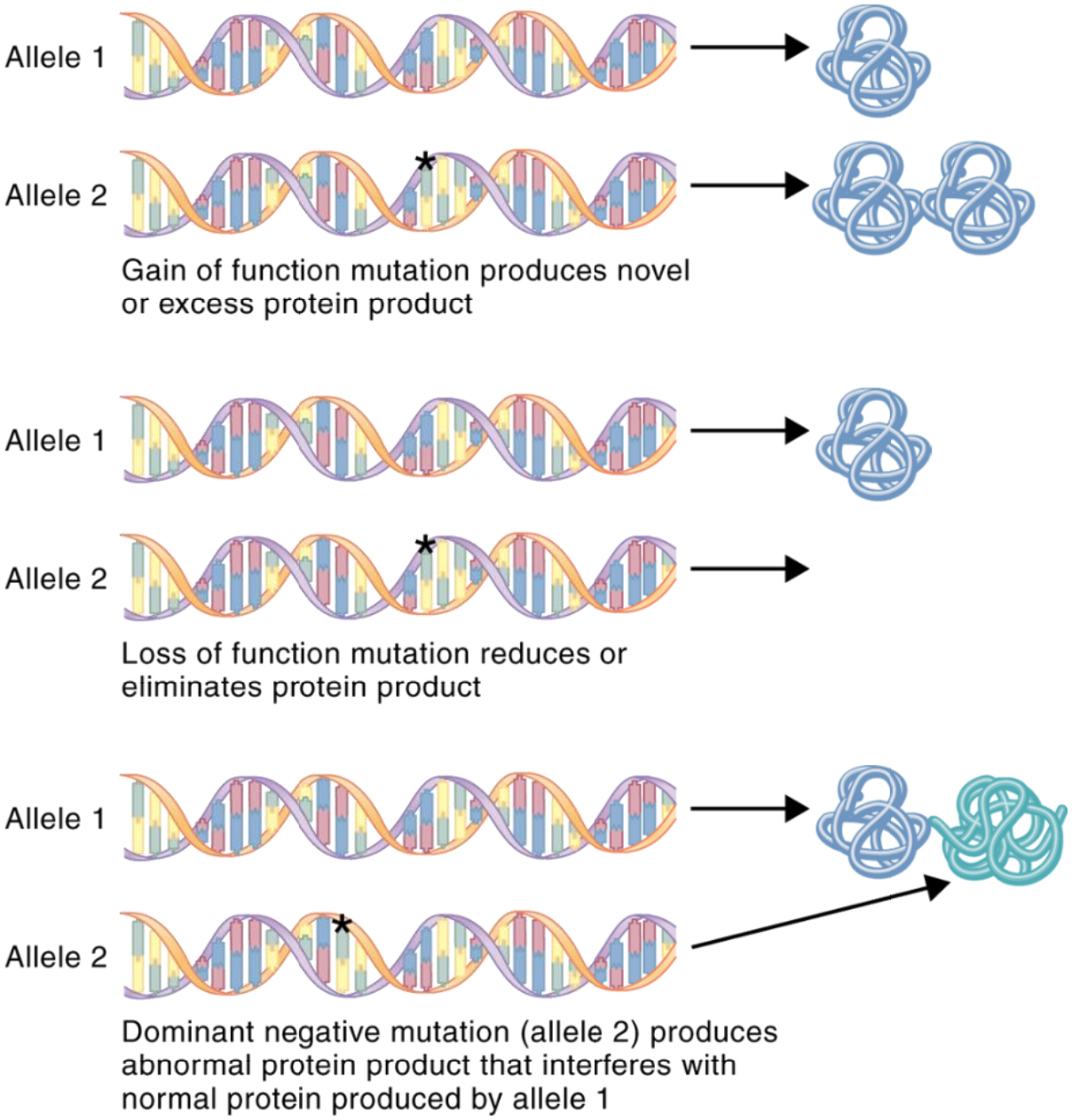


Larger Scale Changes

Duplication
(Amplification)

Homework:

- Charcot–Marie–Tooth
- Hereditary neuropathy
- Dejerine–Sottas syndrome
- PMP22
- Dosage sensitivity

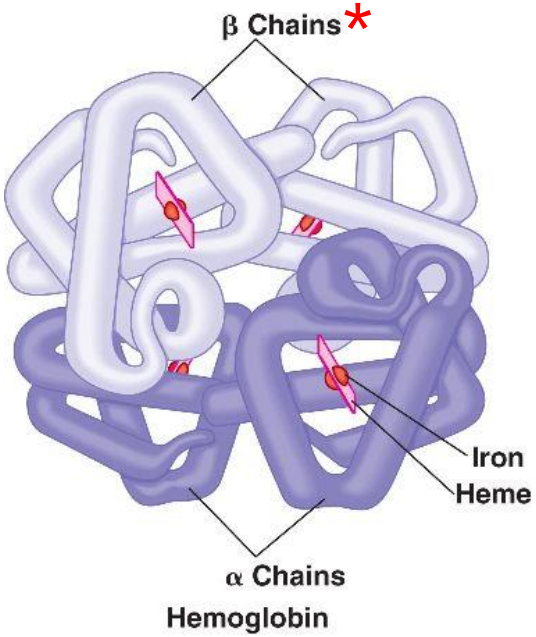


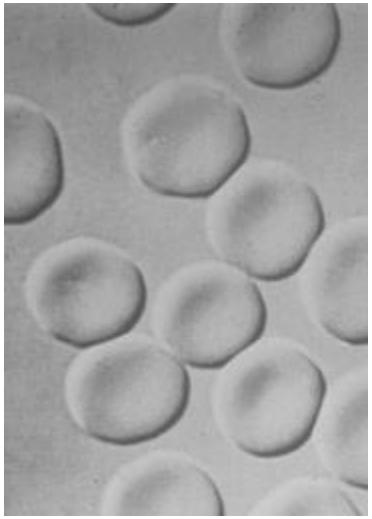
Molecular Consequences of Mutation

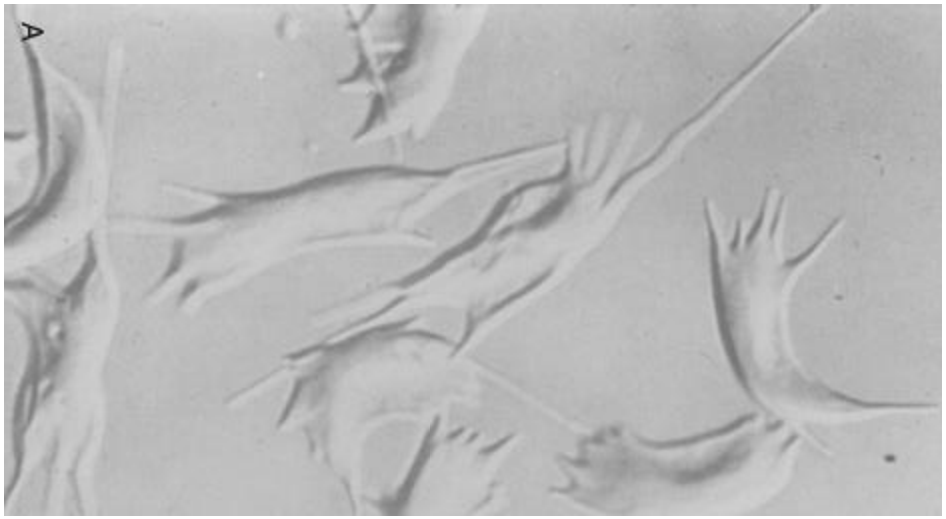
Gain of Function - Dominant

Loss of Function - Recessive/ Haploinsufficiency

Dominant Negative





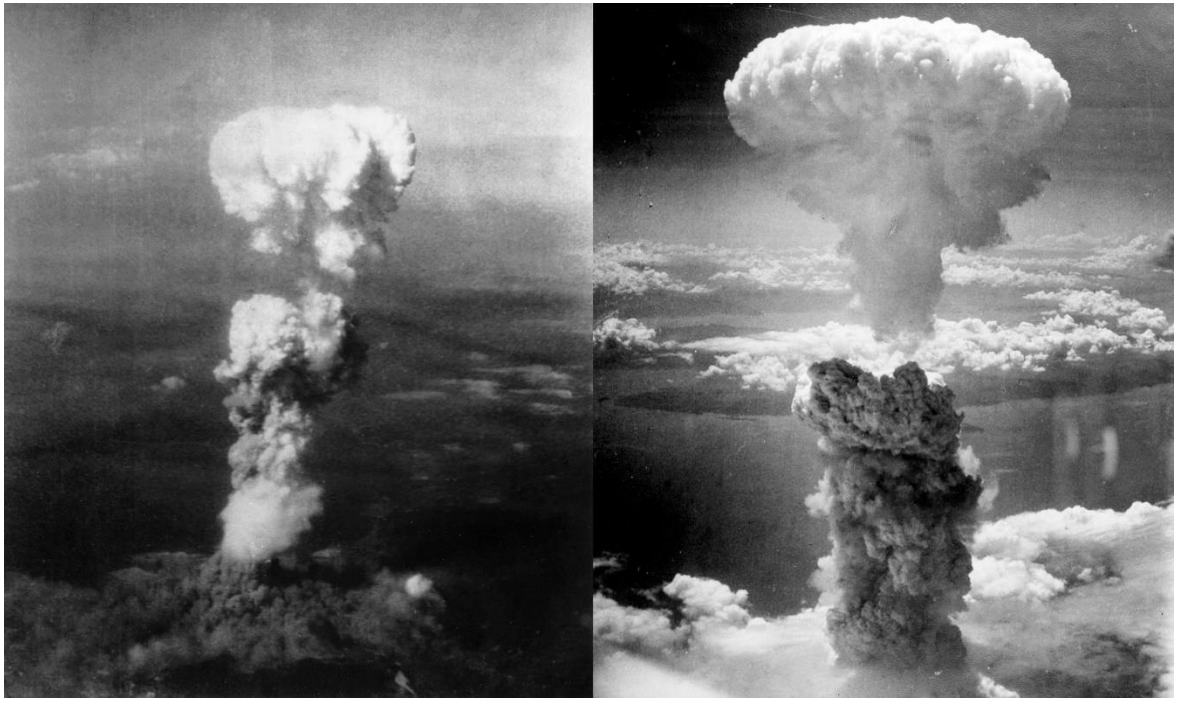


Clinical Consequences of Mutation (example)

Hb disorders as a nearly encompassing illustration

One example: sickle cell disease

- Missense mutation
- Homozygote disease
- Hb aggregates (low O_2)
- Vascular obstruction
- Anemia
- Splenomegaly
- Autosplenectomy

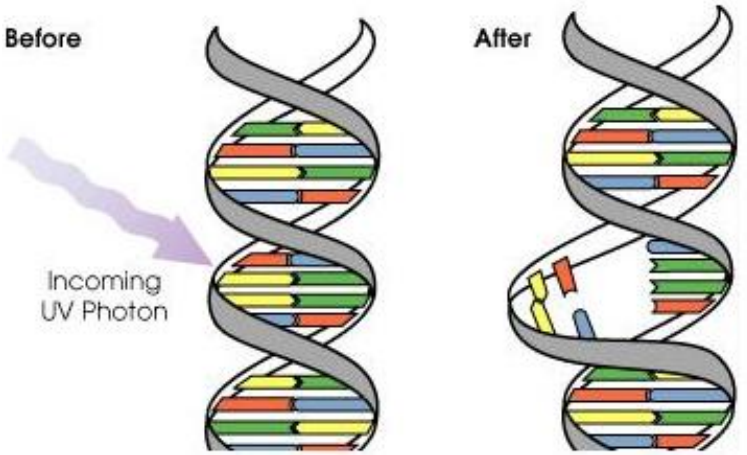


Causes of Mutation

Radiation
UV, X-rays, nuclear

- Chromosome breakage
- Translocations
- Point mutations
- Pyrimidine dimers

Chemicals



DNA damage and repair

Damaging agents

X-rays alkylating agents hydrolysis O_2 radicals	UV irradiation chemical mutagens	X-rays anti-tumor agent	replication errors

abnormal bases base adducts single-strand break abasic site	bulky adducts thymidine dimers	double-strand break interstrand crosslink	A-G mismatch T-C mismatch base insertion base deletion

Repair processes

base-excision repair (BER)	nucleotide-excision repair (NER)	recombination repair (HR, EJ)	mismatch repair

Spontaneous Mutation…

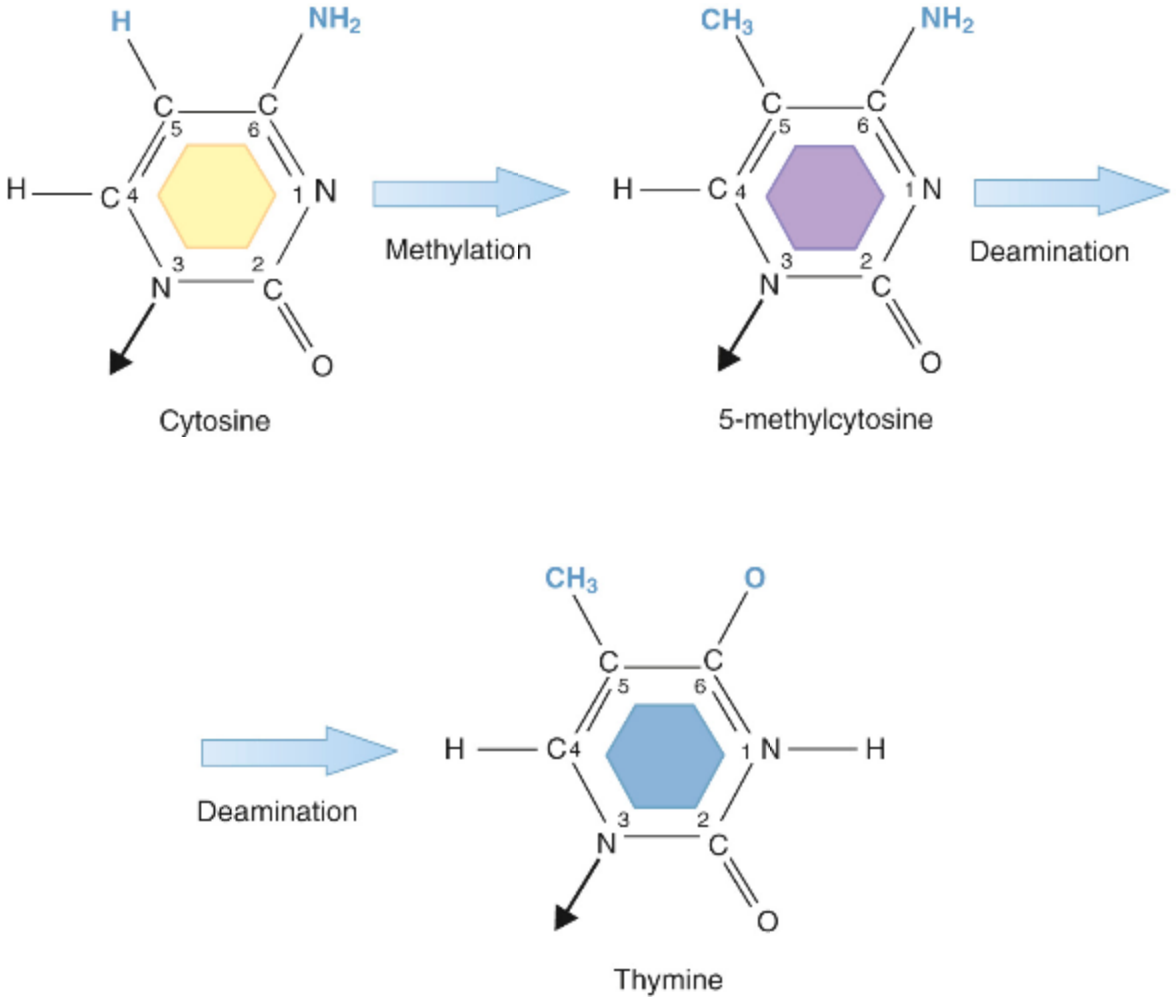
…or why are we not all superheroes already?!

30 new mutations per gamete

Percent of DNA encoding proteins

Gene size

Mutational hotspots



Spontaneous Mutation…

…or why are we not all superheroes already?!

30 new mutations per gamete

Percent of DNA encoding proteins

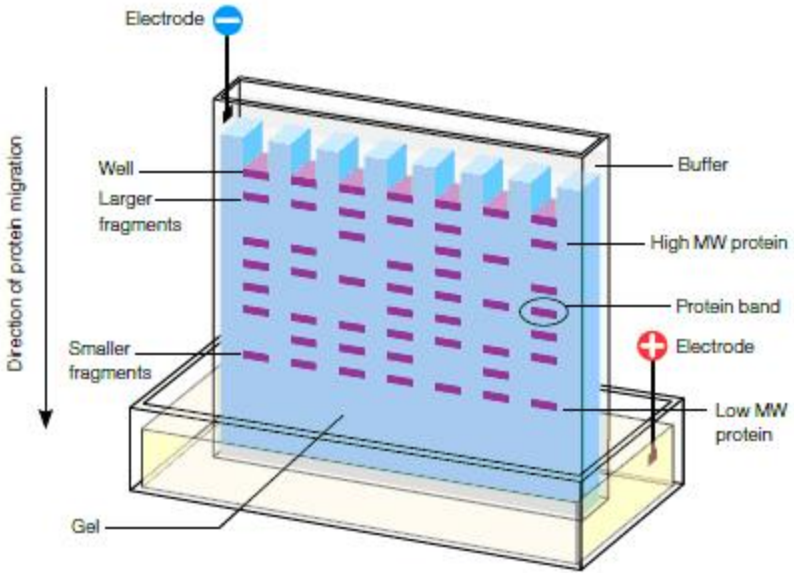
Gene size

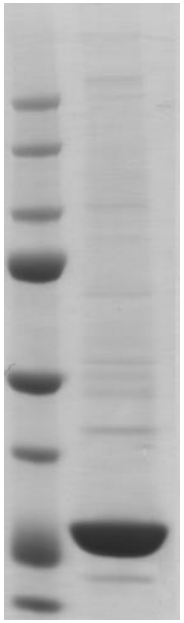
Mutational hotspots (e.g. CpG)

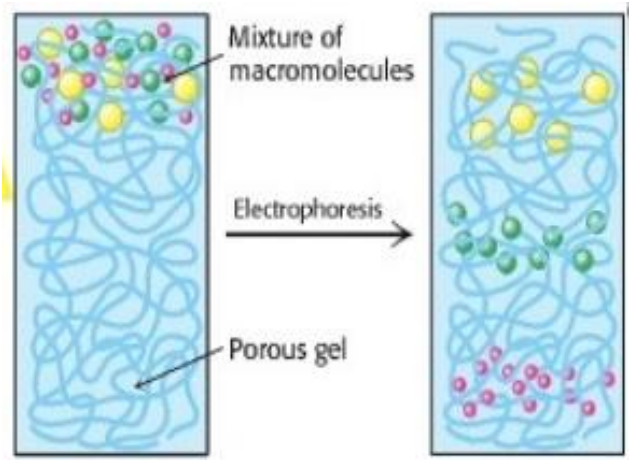
Detection & Measurement of Genetic Variation

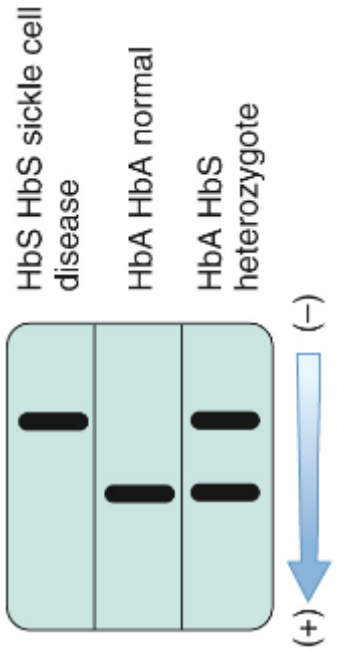
Protein Electrophoresis

Separate by size and/or charge

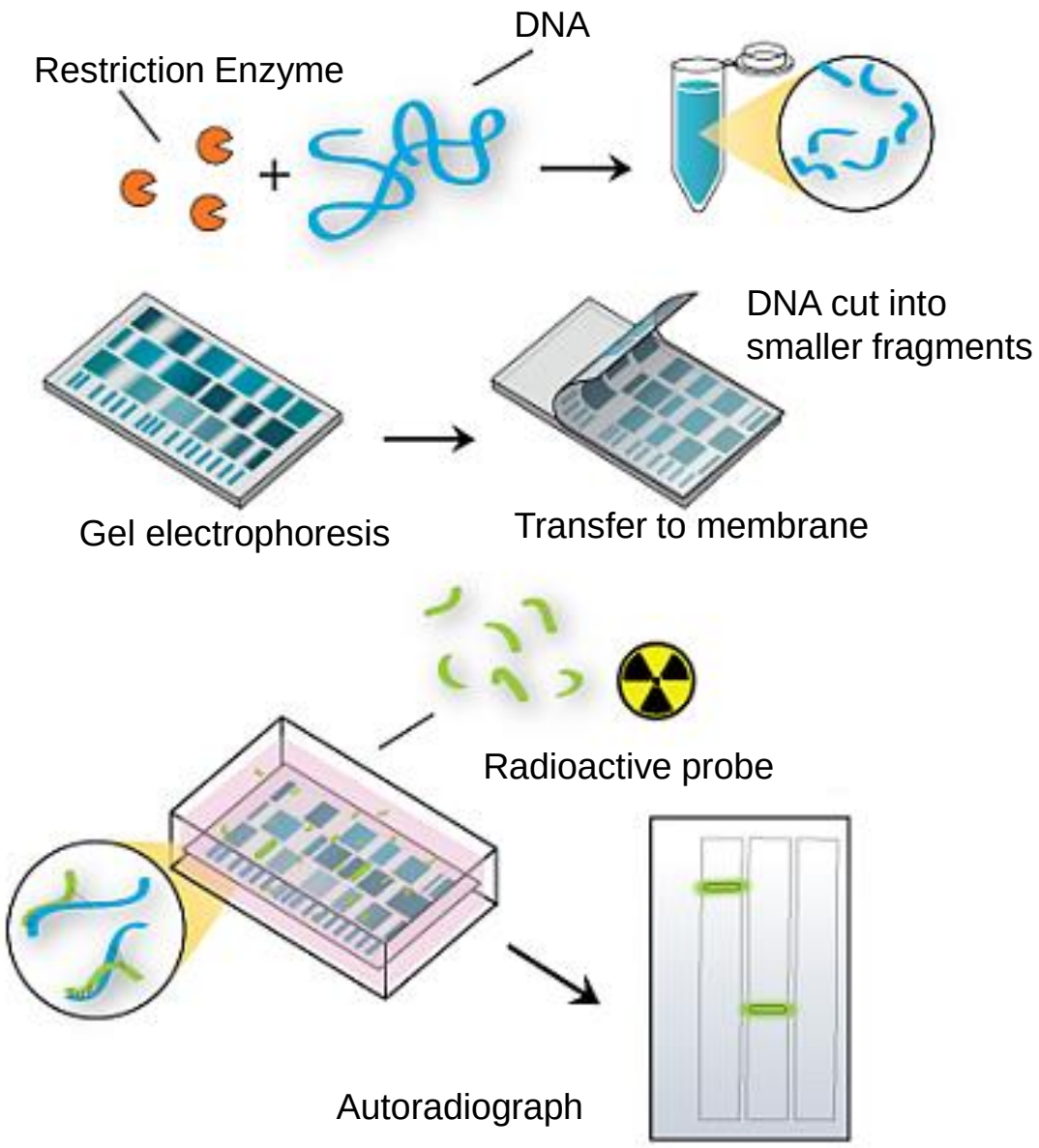








Southern Blotting & Restriction Fragment Analysis

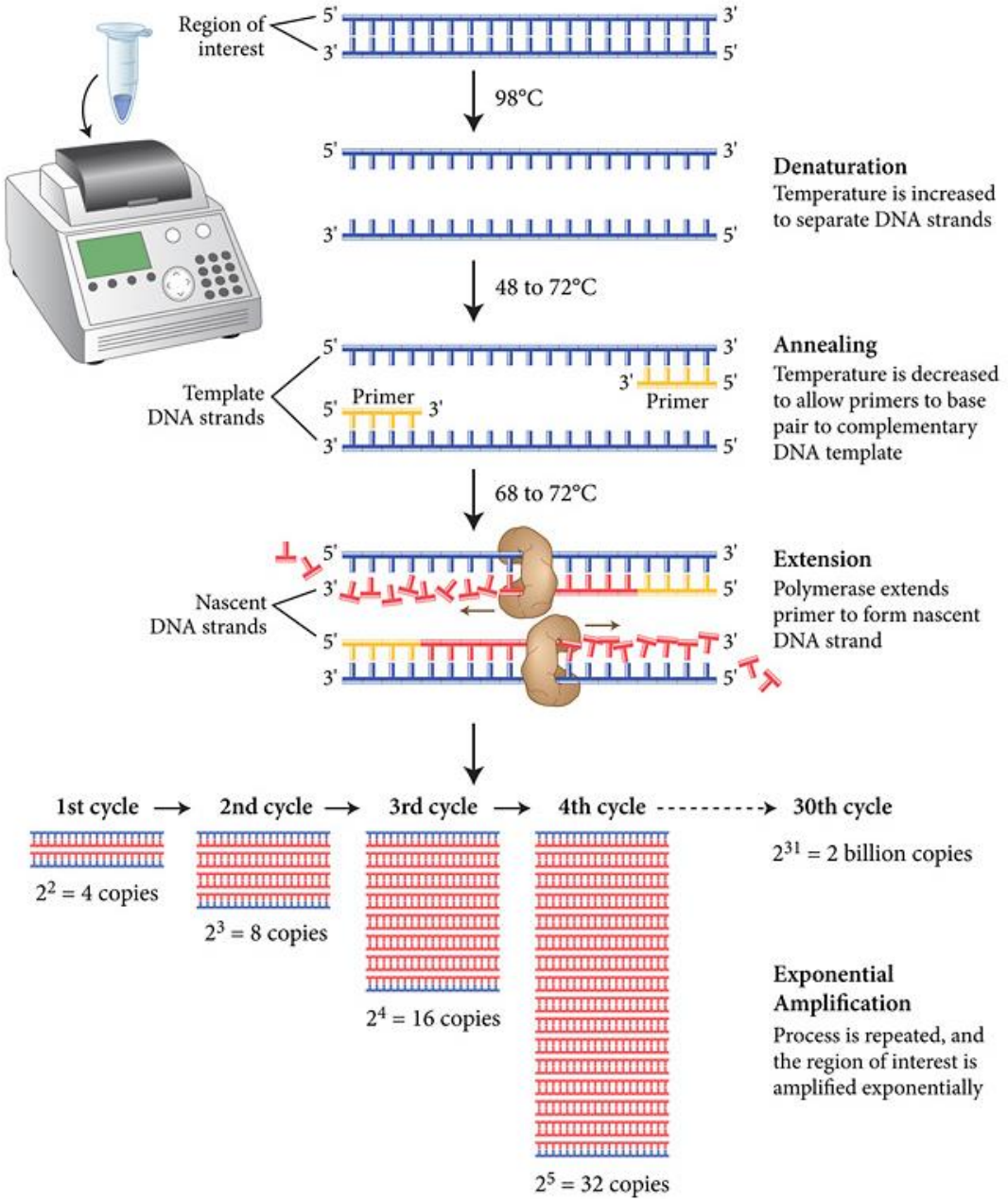


Restriction enzymes cleave human DNA at specific sequences (restriction sites).

Restriction digest → Restriction fragments

You can detect:

- Insertions
- Deletions
- Mutations affecting restriction sites (e.g. sickle cell disease)



Polymerase Chain Reaction

Advantages:

Can be used with extremely small quantities of DNA

Faster than cloning

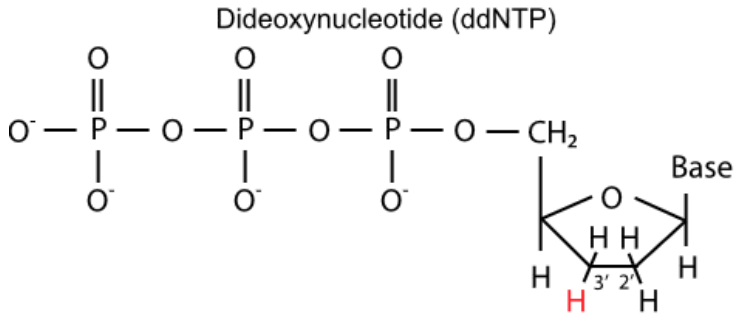
No radioactive probes required

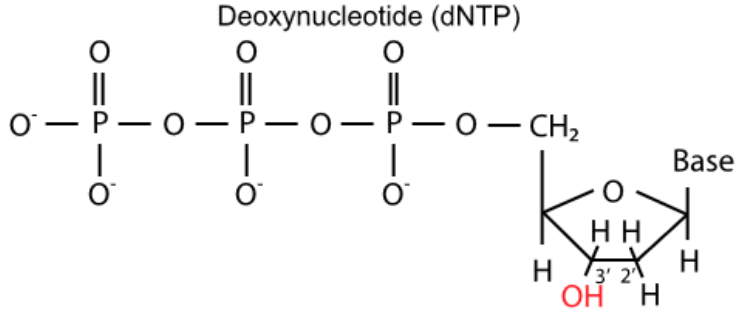
Disadvantages:

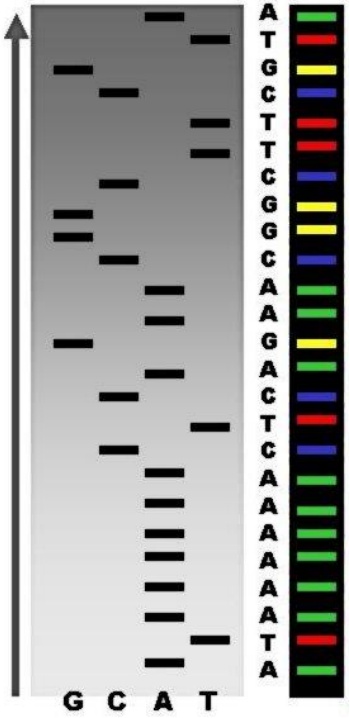
Known sequence required

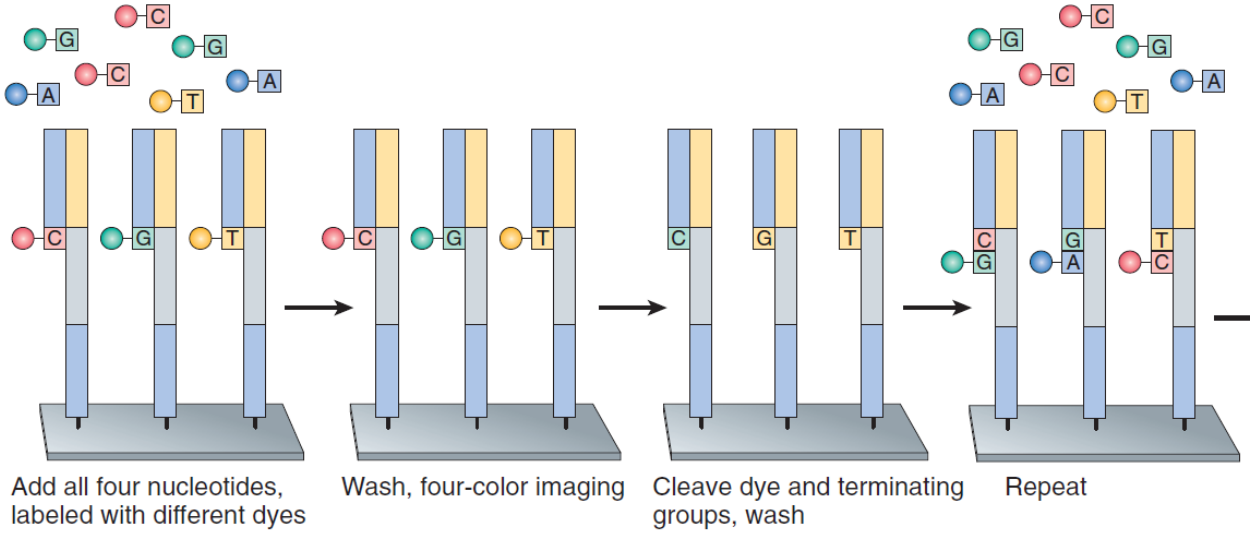
Contamination

Limited to a few Kb







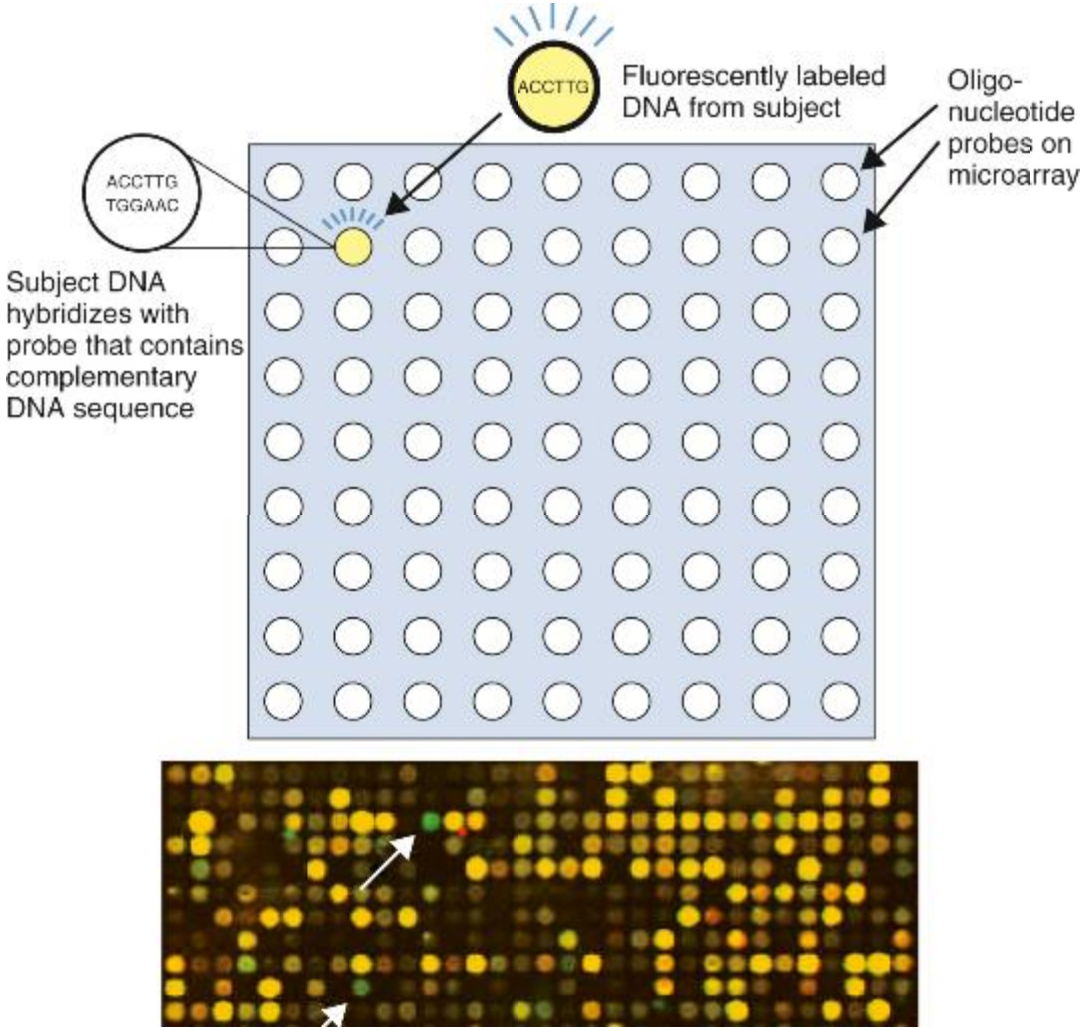


DNA sequencing

Sanger sequencing (dideoxynucleotides)

Automated sequencing using 4 flourochromes

High throughput DNA sequencing

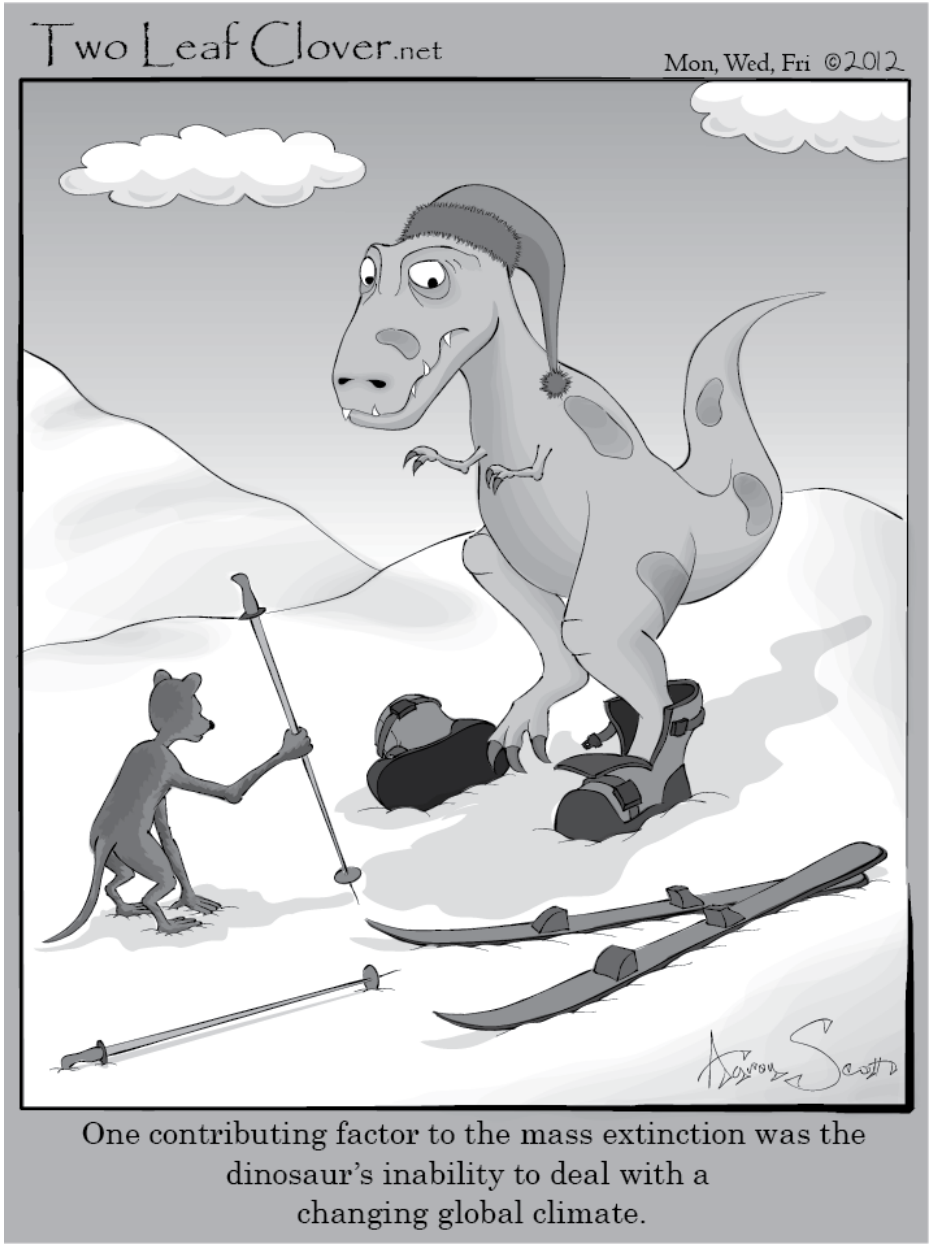


Microarrays

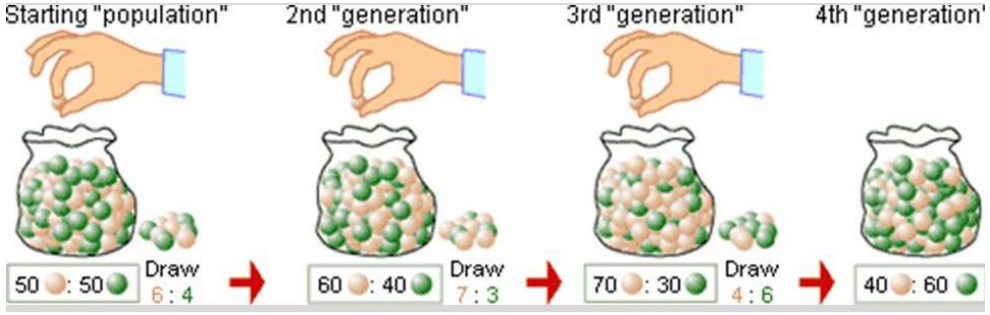
DNA
Known mutations only

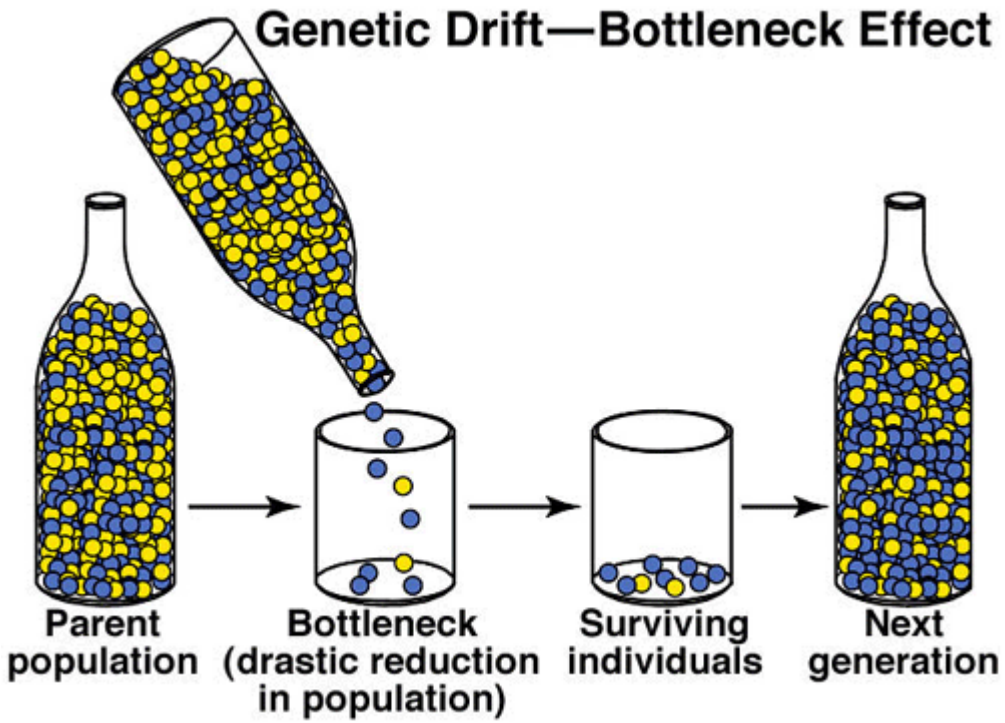
mRNA
Expression

Non-mutational Genetic Variation



Natural selection





Genetic Drift

& the bottleneck effect

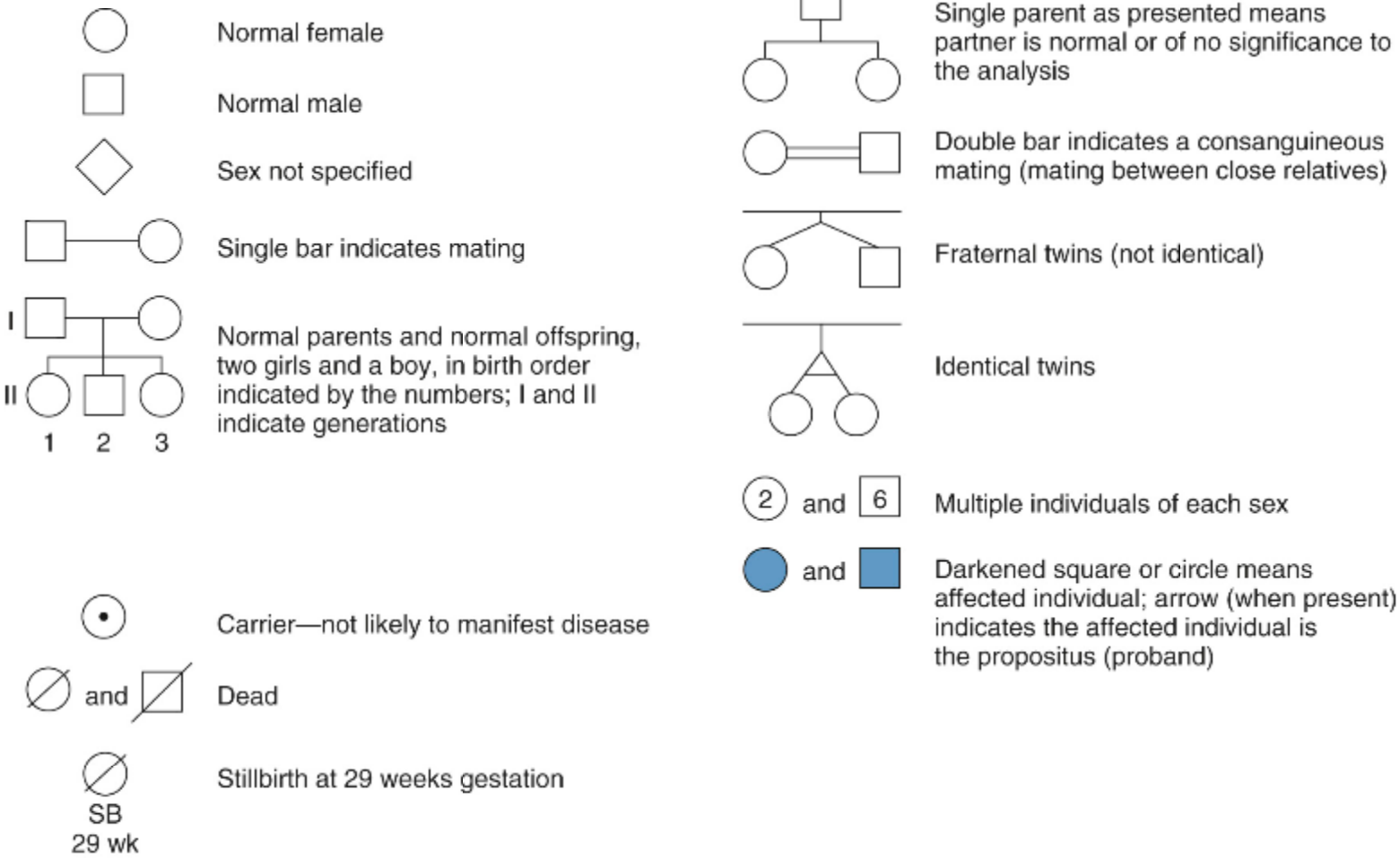
& the founder effect

Gene flow

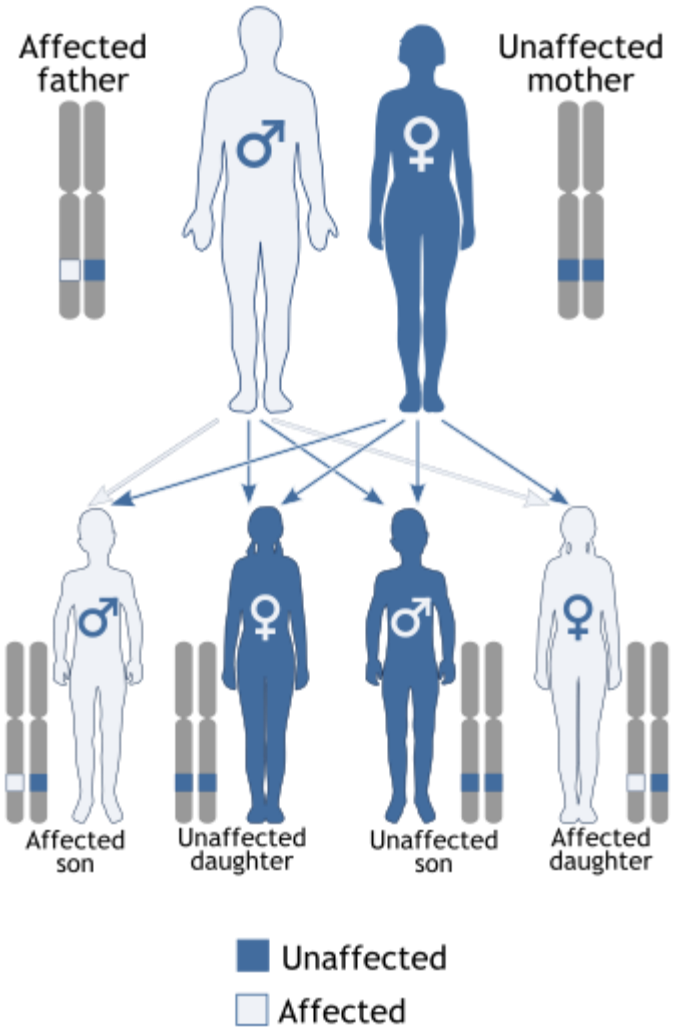

LAND OF
THE FREE
NO TRESPASSING
Chattanooga Times Free Press
Bennett

Single Gene Disorders
(AD,AR)

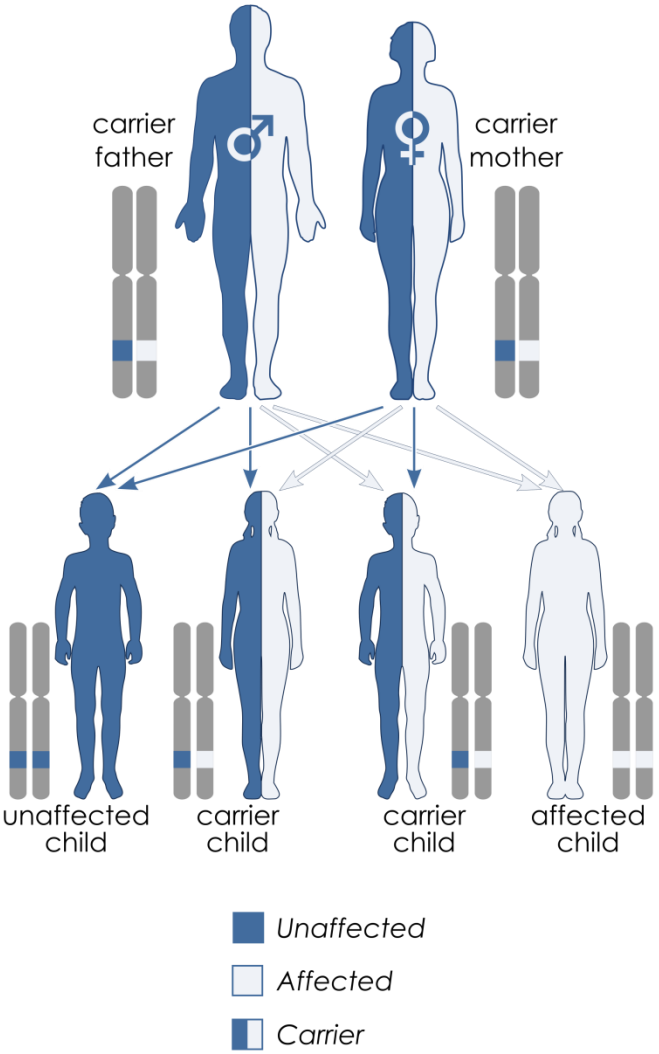
Basic Pedigree



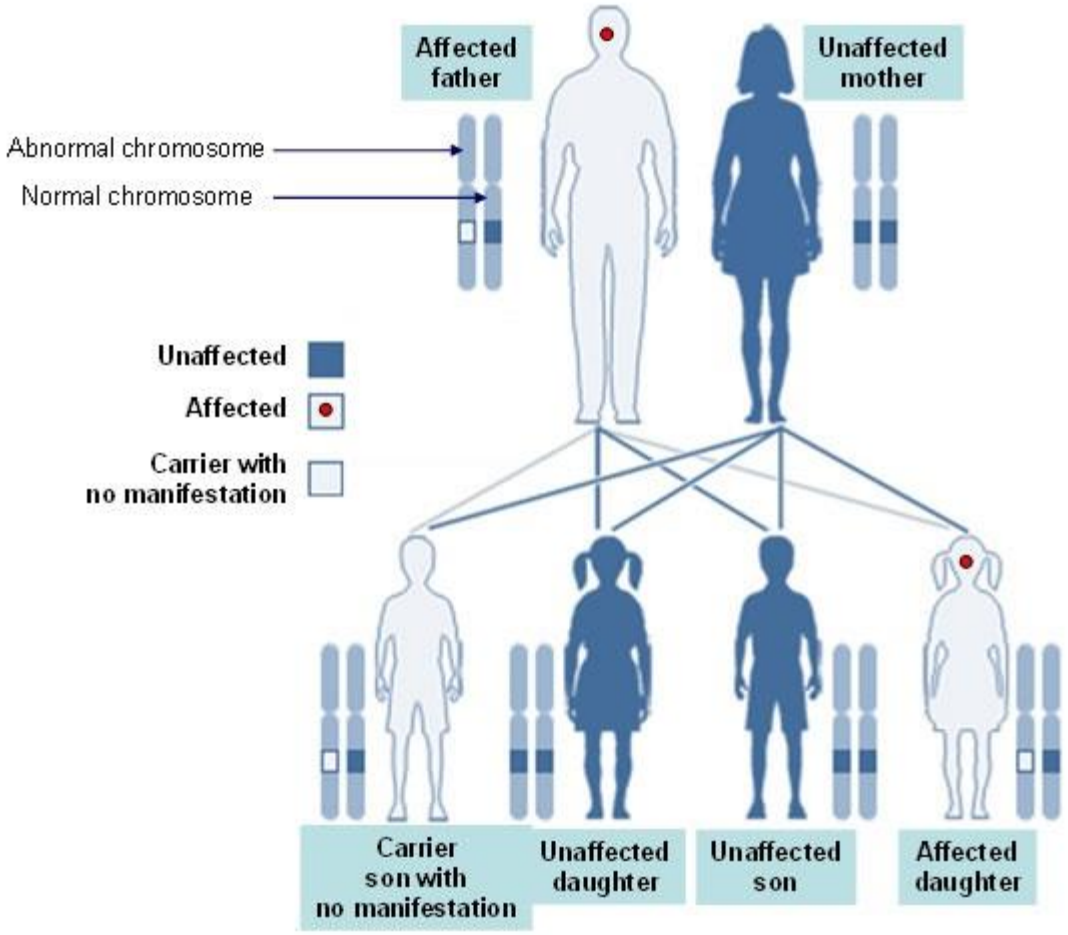
Autosomal dominant

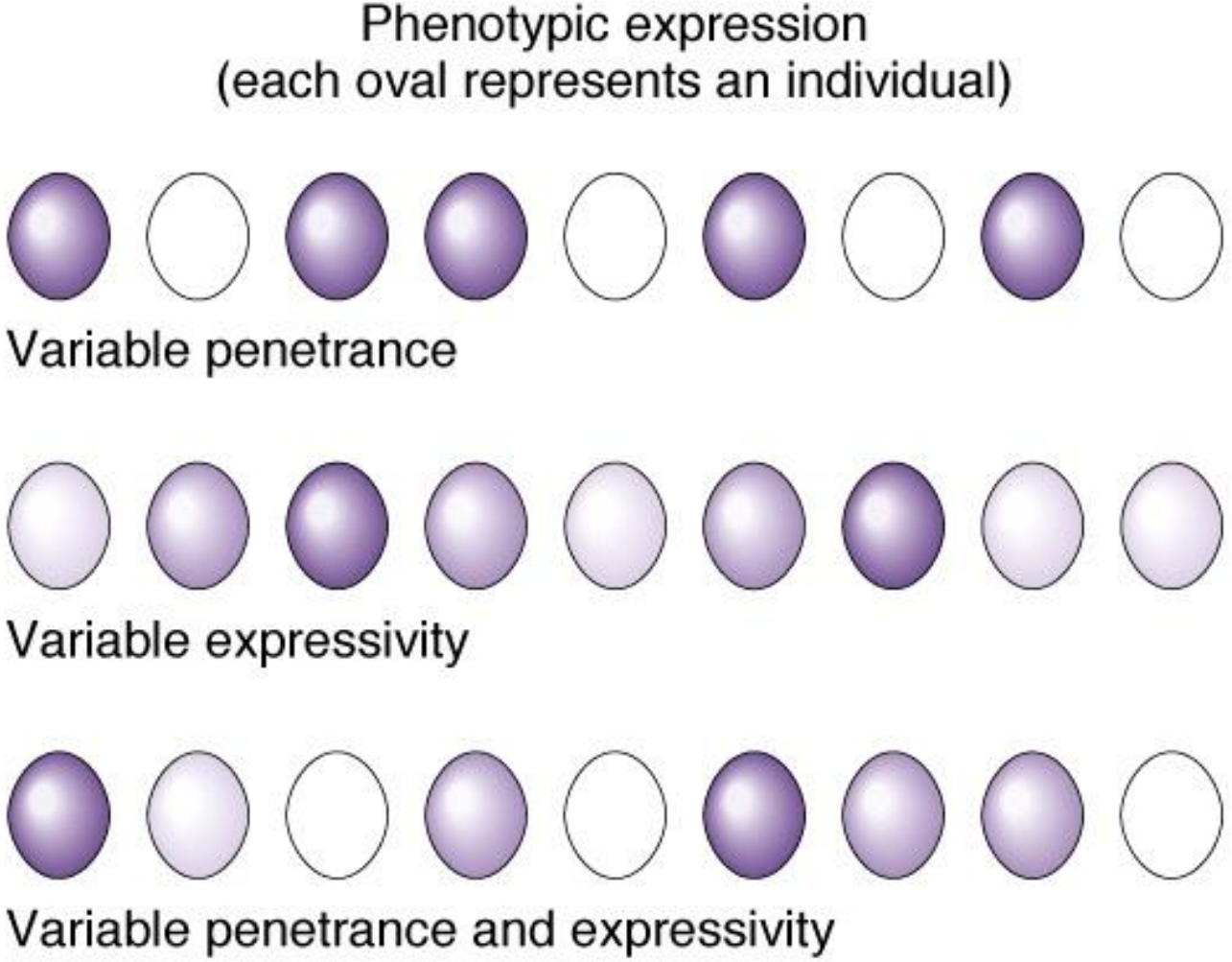


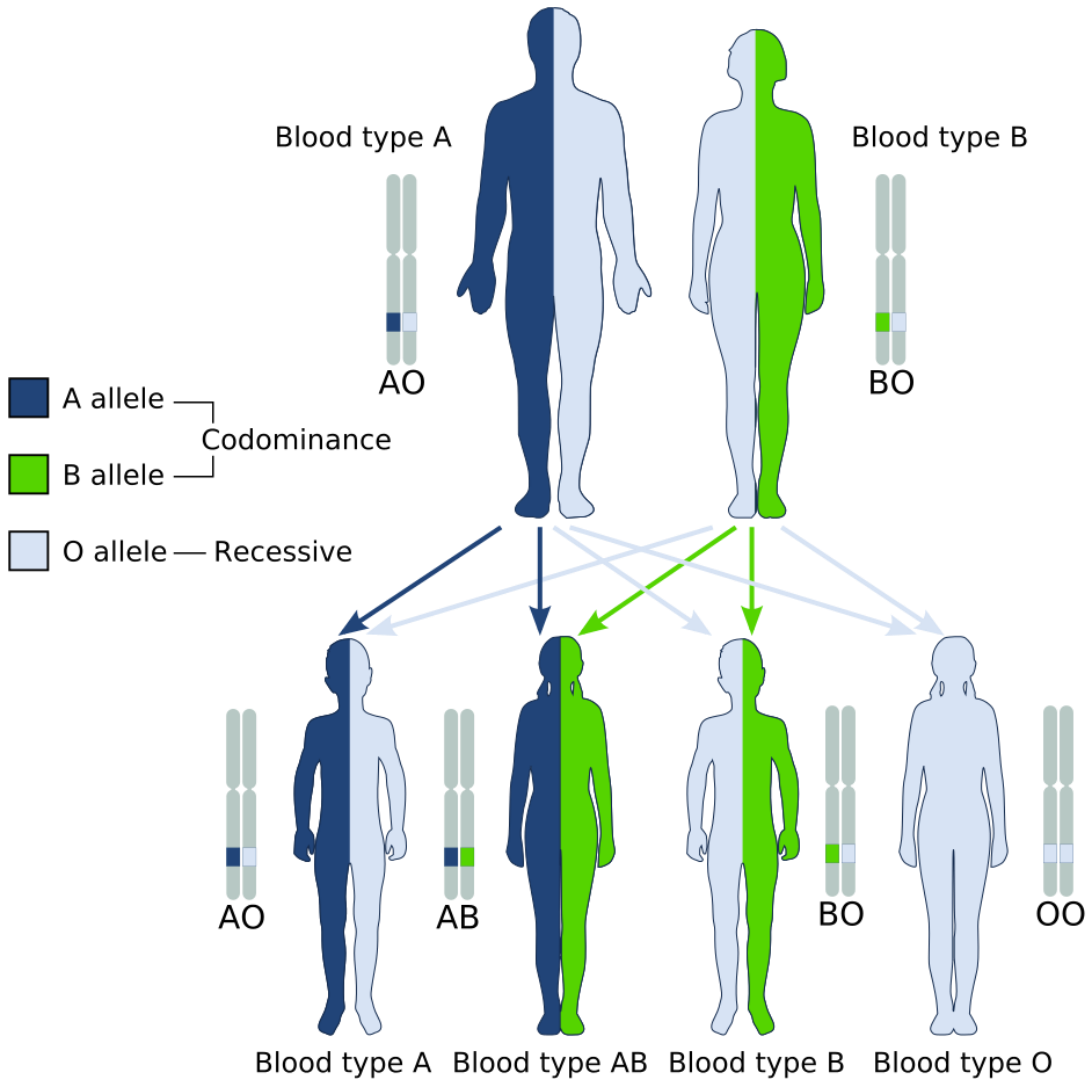
Autosomal recessive inheritance



Autosomal dominant disease with incomplete penetrance




Phenotypic expression
(each oval represents an individual)
Variable penetrance
Variable expressivity
Variable penetrance and expressivity


Blood type A
Blood type B
AO
BO
A allele
B allele
Codominance
O allele
Recessive
AO
AB
BO
OO
Blood type A
Blood type AB
Blood type B
Blood type O

Dominant Negative

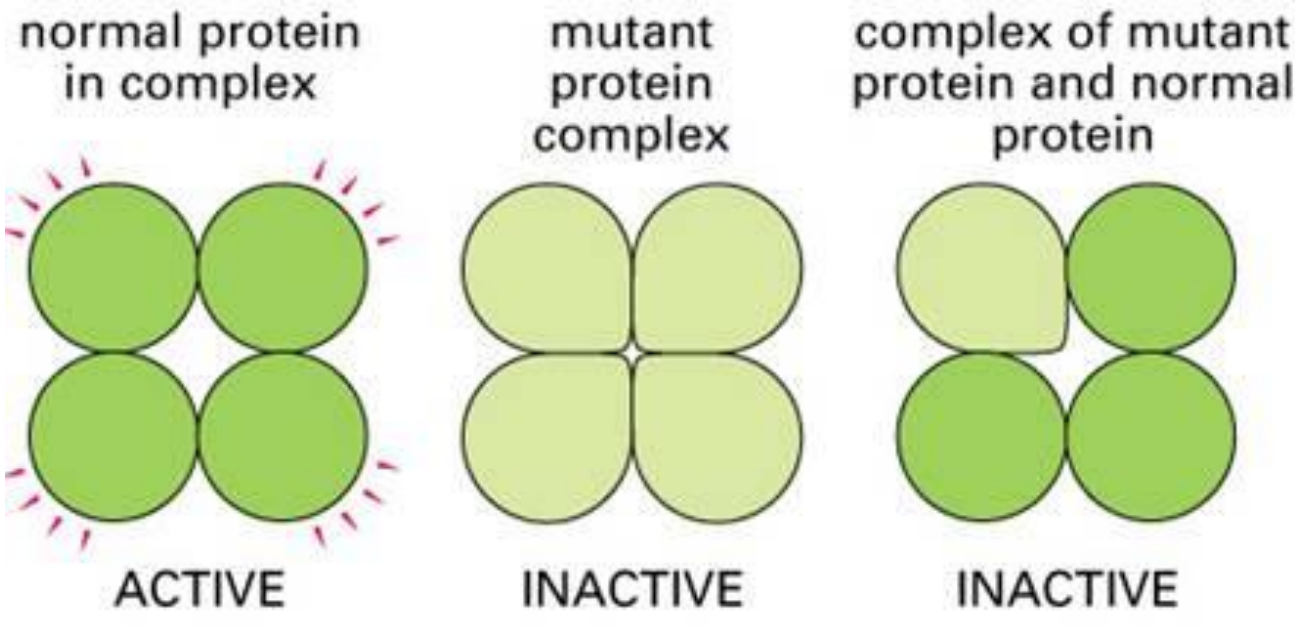
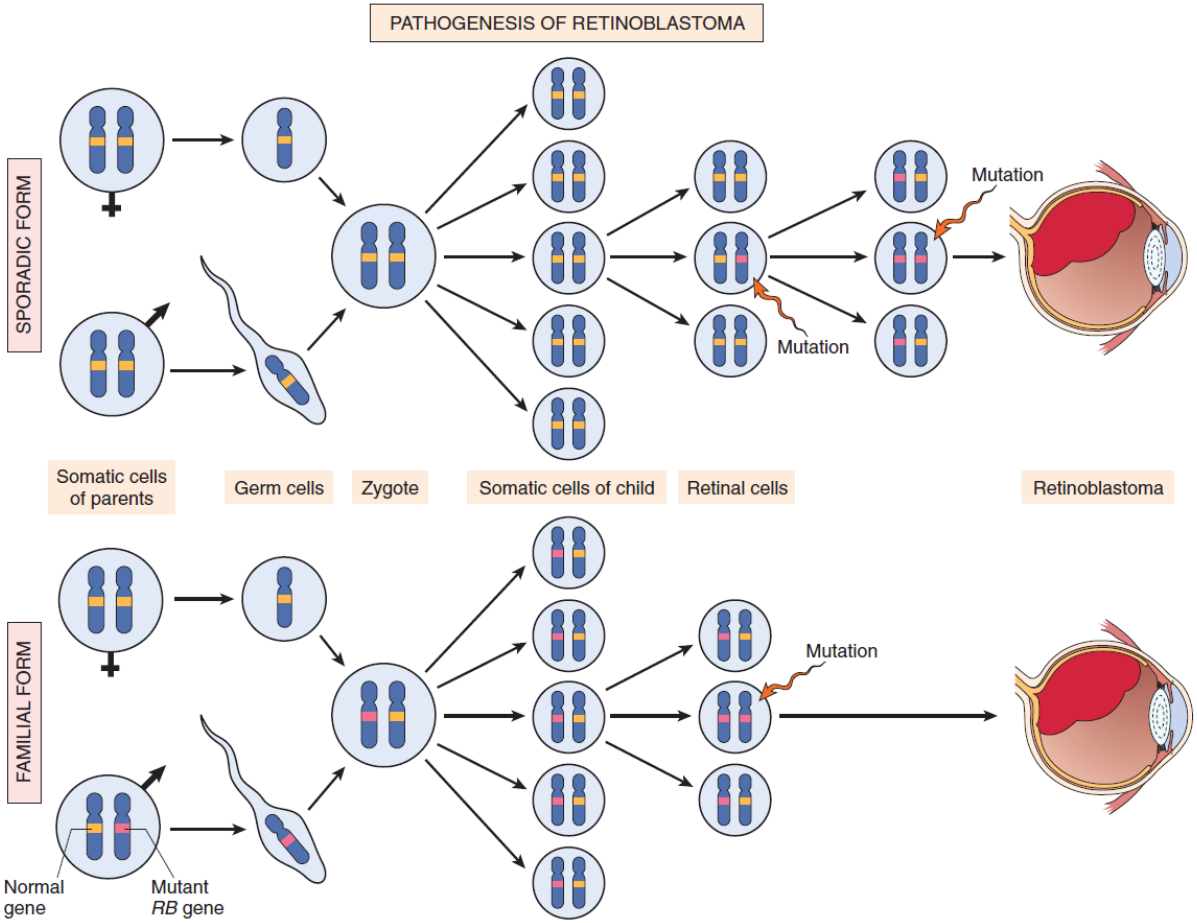


Figure 8–67. Molecular Biology of the Cell, 4th Edition.

RB (Reduced Penetrance)

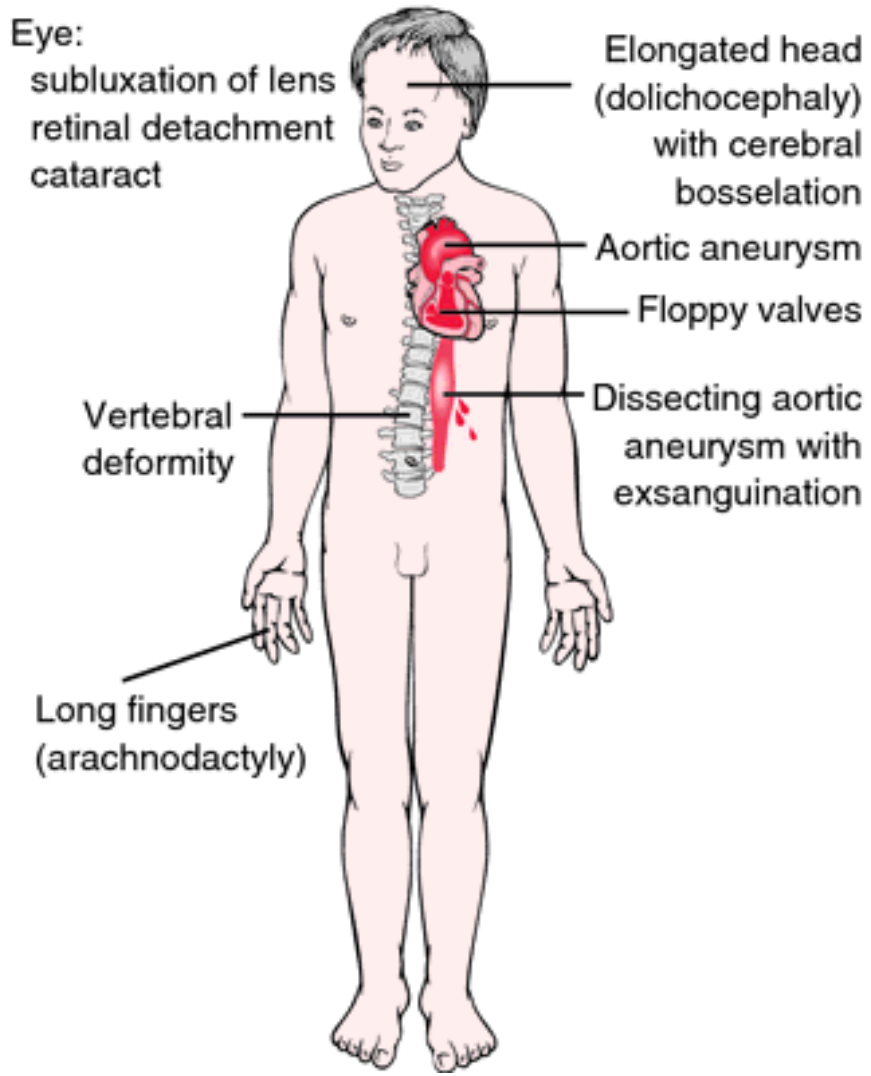


Knudson “two-hit” hypothesis

Two defective copies needed

Familial: -inherited
-somatic mutation

Sporadic: 2 somatic mutations



Marfan Syndrome (pleiotropy & locus heterogeneity)

AD

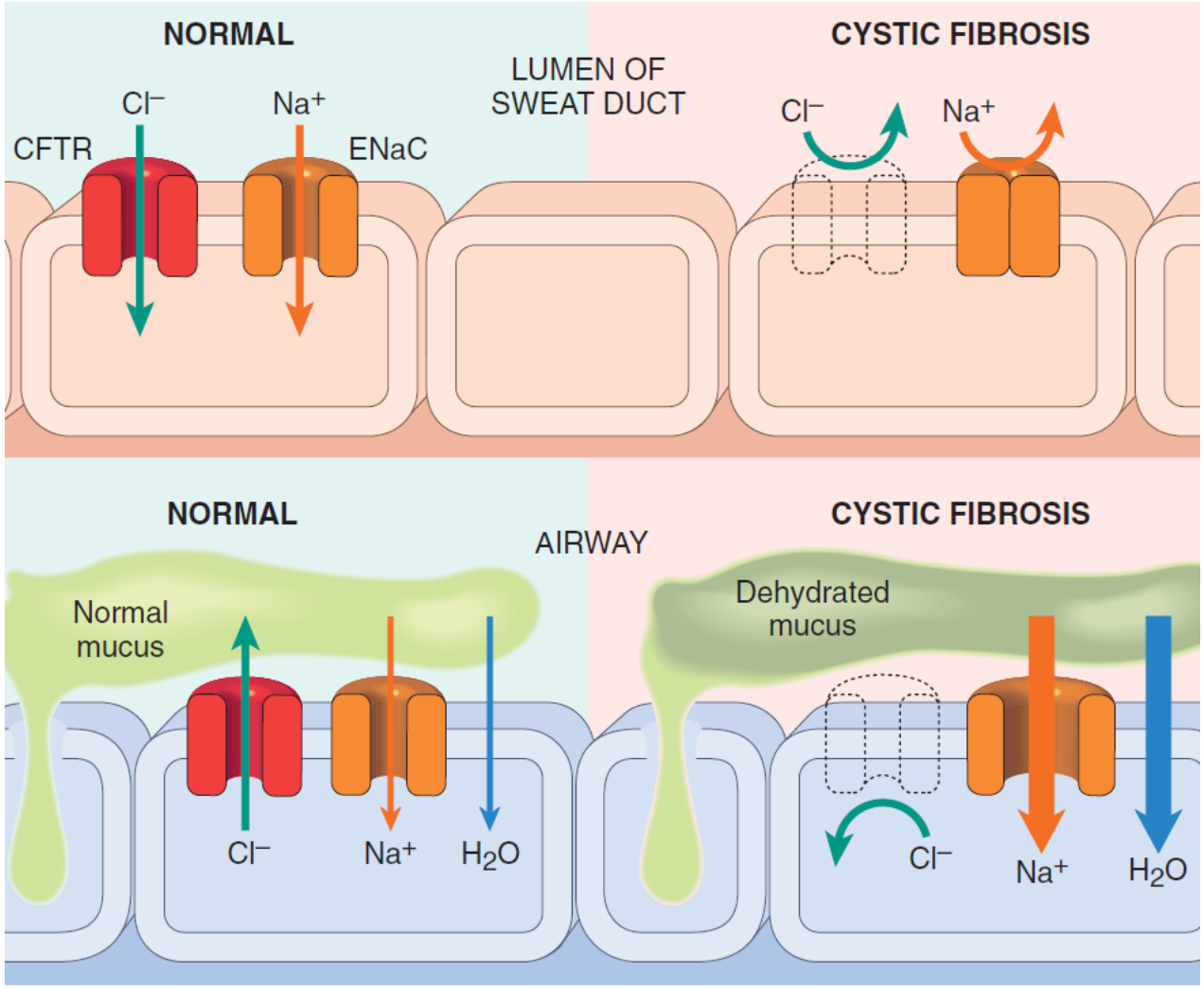
FBN1 Fibrillin (ECM)

Dominant negative

Effect on TGFβ sequestration in the ECM

TGF receptor type II (Marfan Syndrome type 2)

Clinical trials on angiotensin receptor blockers



Cystic Fibrosis
(modifiers & allelic heterogeneity)

AR

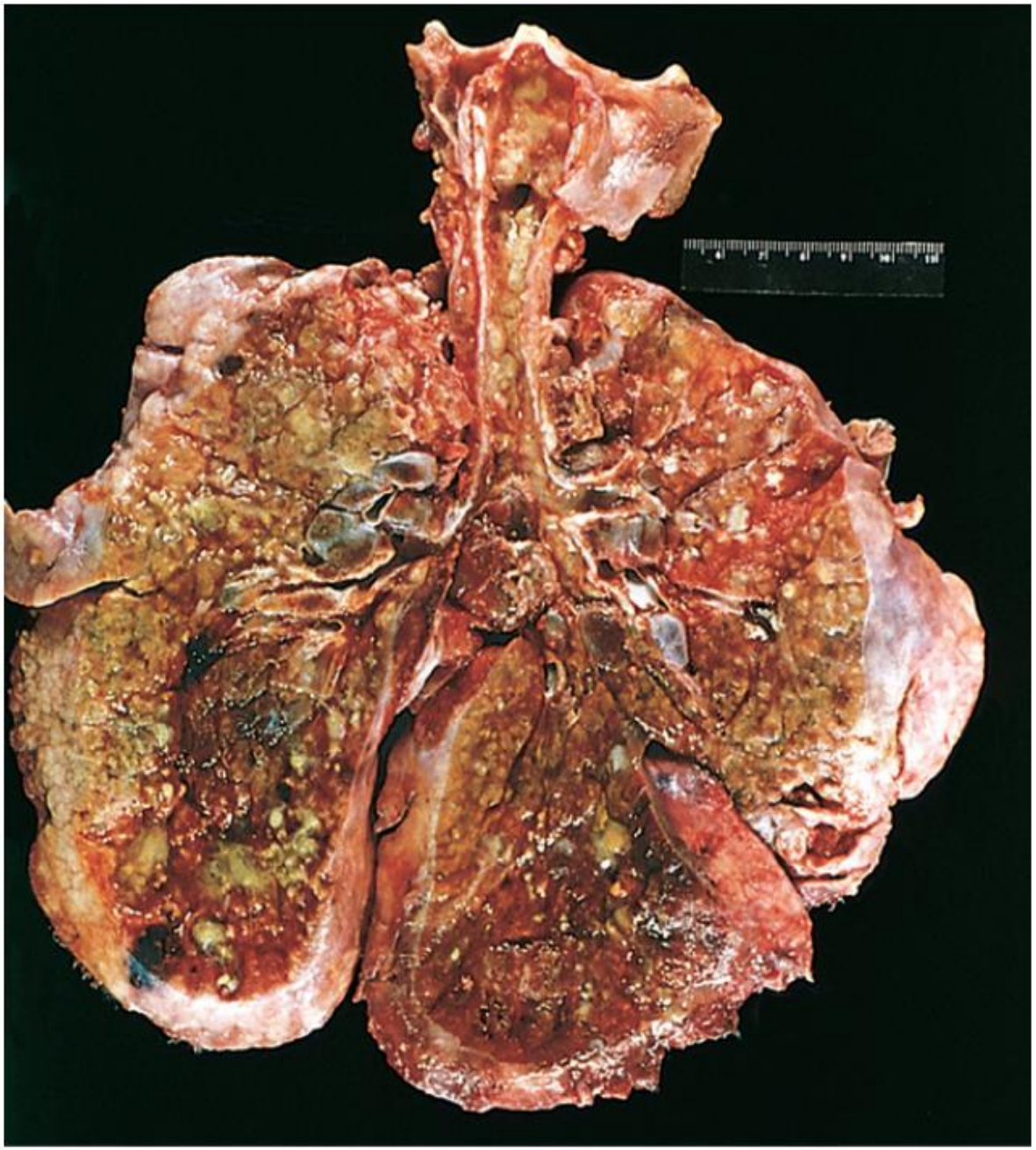
CFTR Chloride channel

>1300 mutations (mild-severe)

Tissue specific effects

Viscid mucous secretions
- Chronic pulmonary infections
- Pancreatic insufficiency

Innate immunity polymorphism modifiers



Cystic Fibrosis
(modifiers & allelic heterogeneity)

AR

CFTR Chloride channel

>1300 mutations (mild-severe)

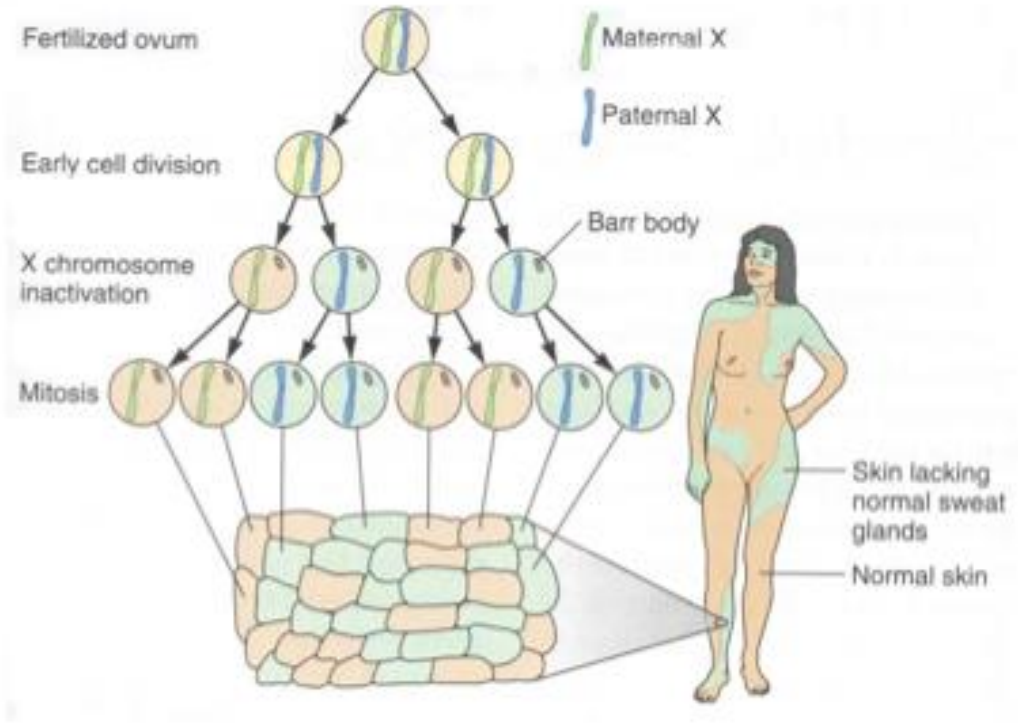
Tissue specific effects

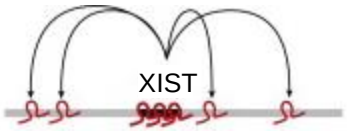
Viscid mucous secretions
- Chronic pulmonary infections
- Pancreatic insufficiency

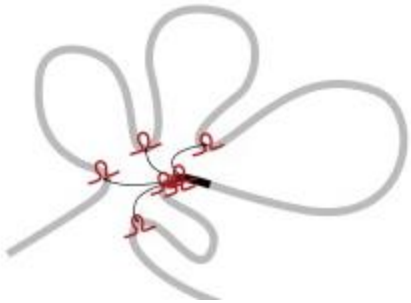
Innate immunity polymorphism modifiers

Consanguinity

Single Gene Disorders
(Sex chromosomes & nontraditional inheritance)







Lyonization

X chromosome inactivation early in fetal life

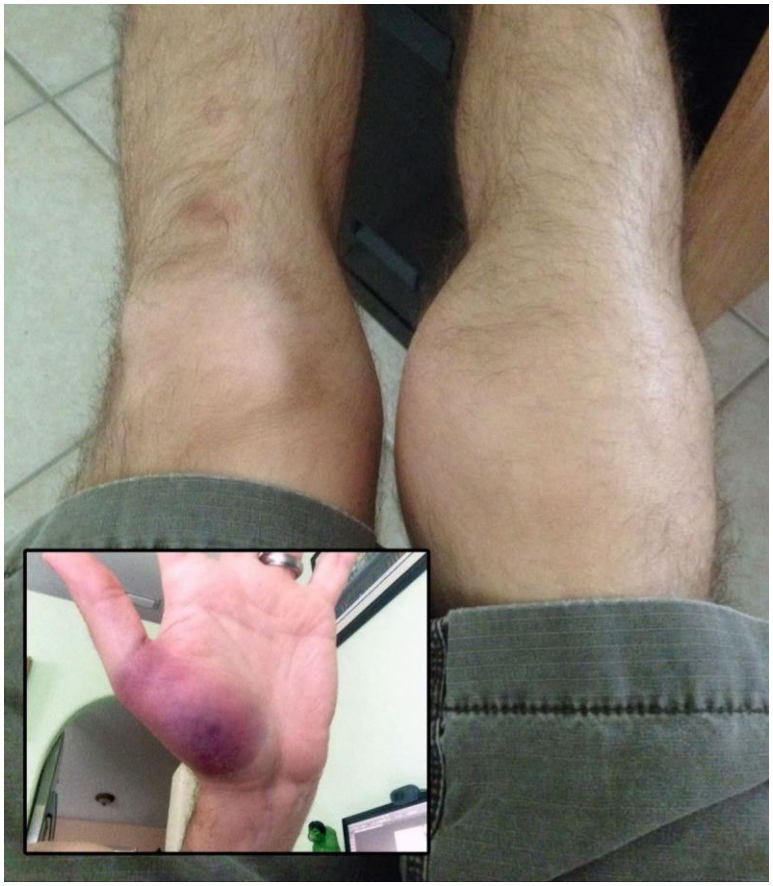
Random

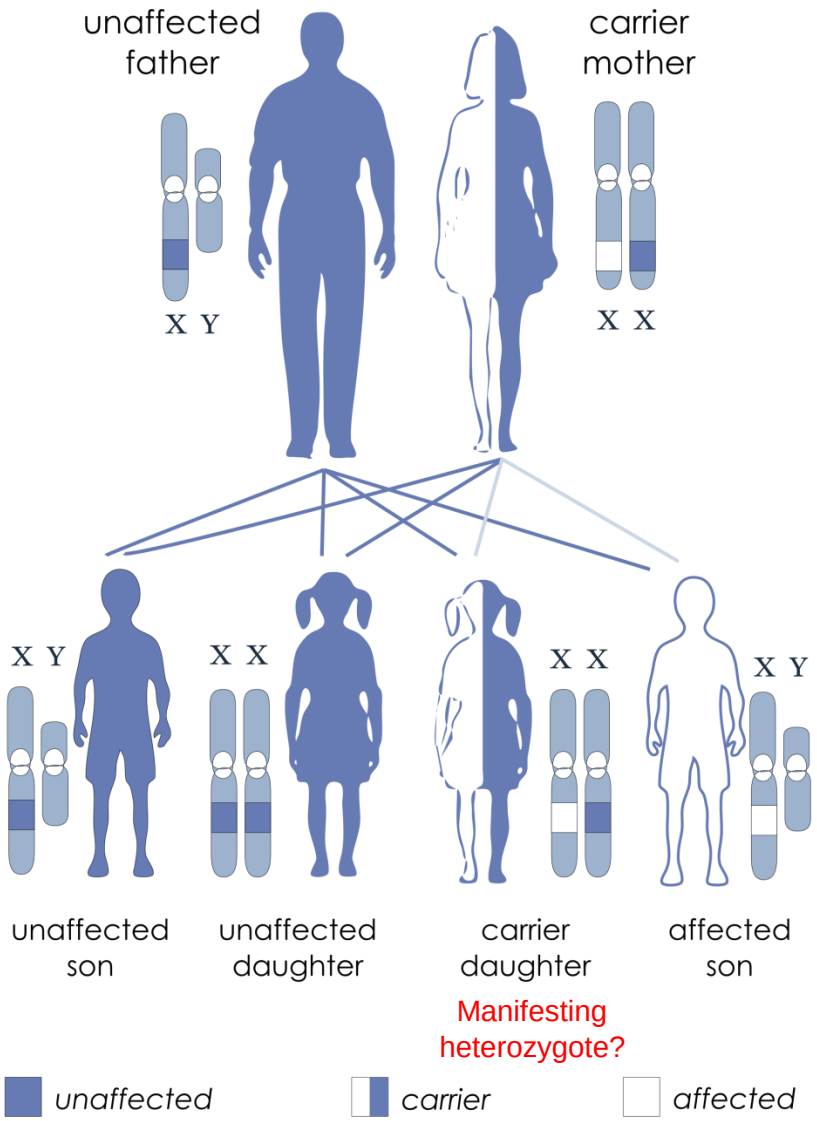
Normal females are mosiacs

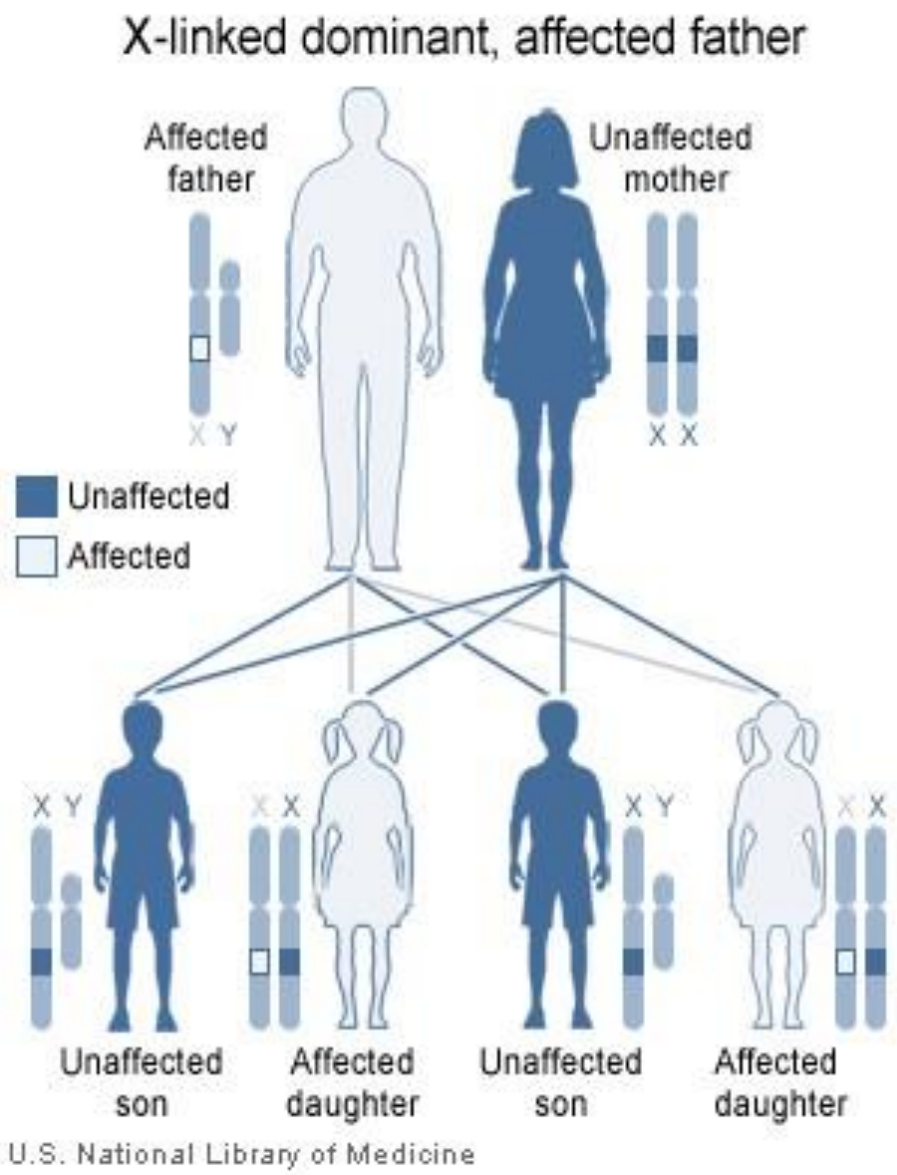
Small percentage of genes do escape inactivation

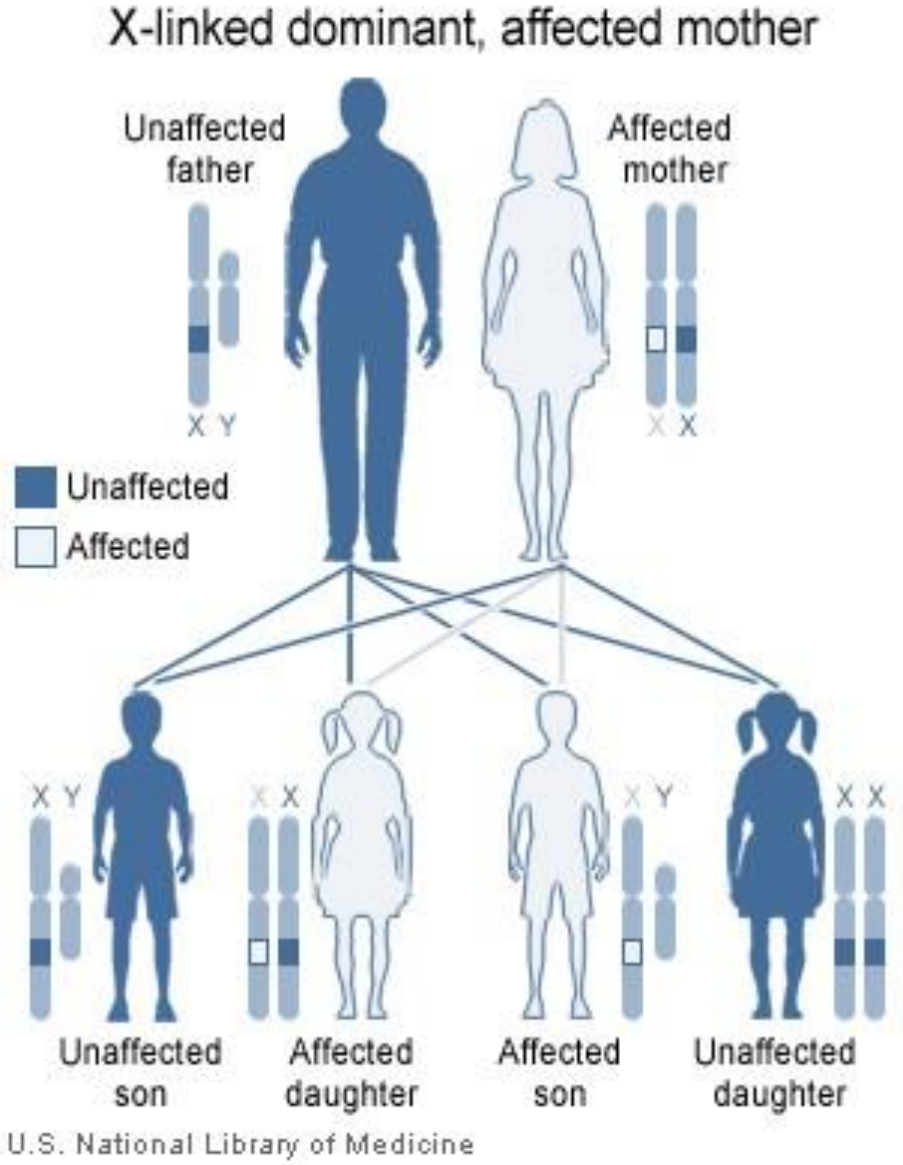
XIST (lncRNA)

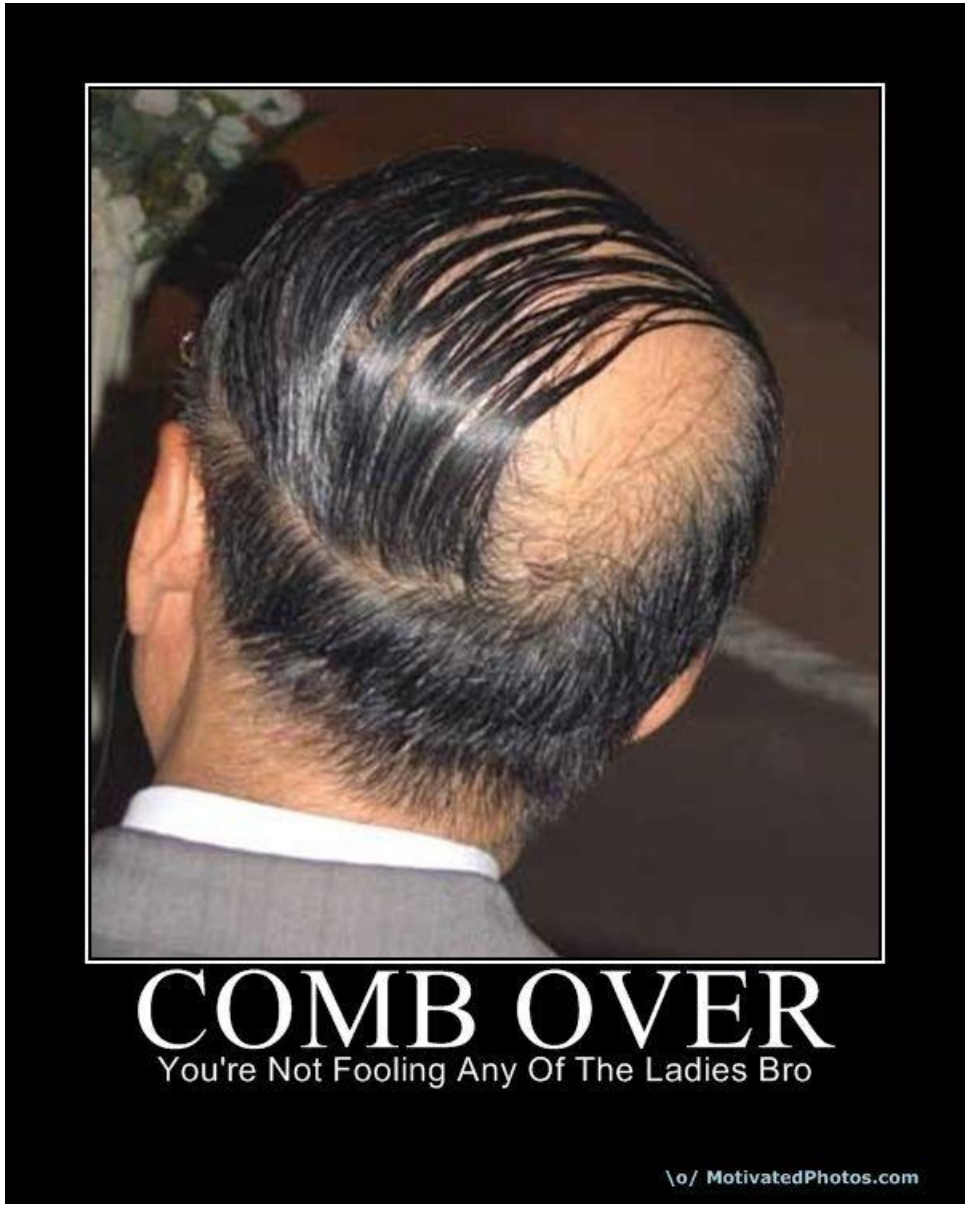
X-linked recessive inheritance



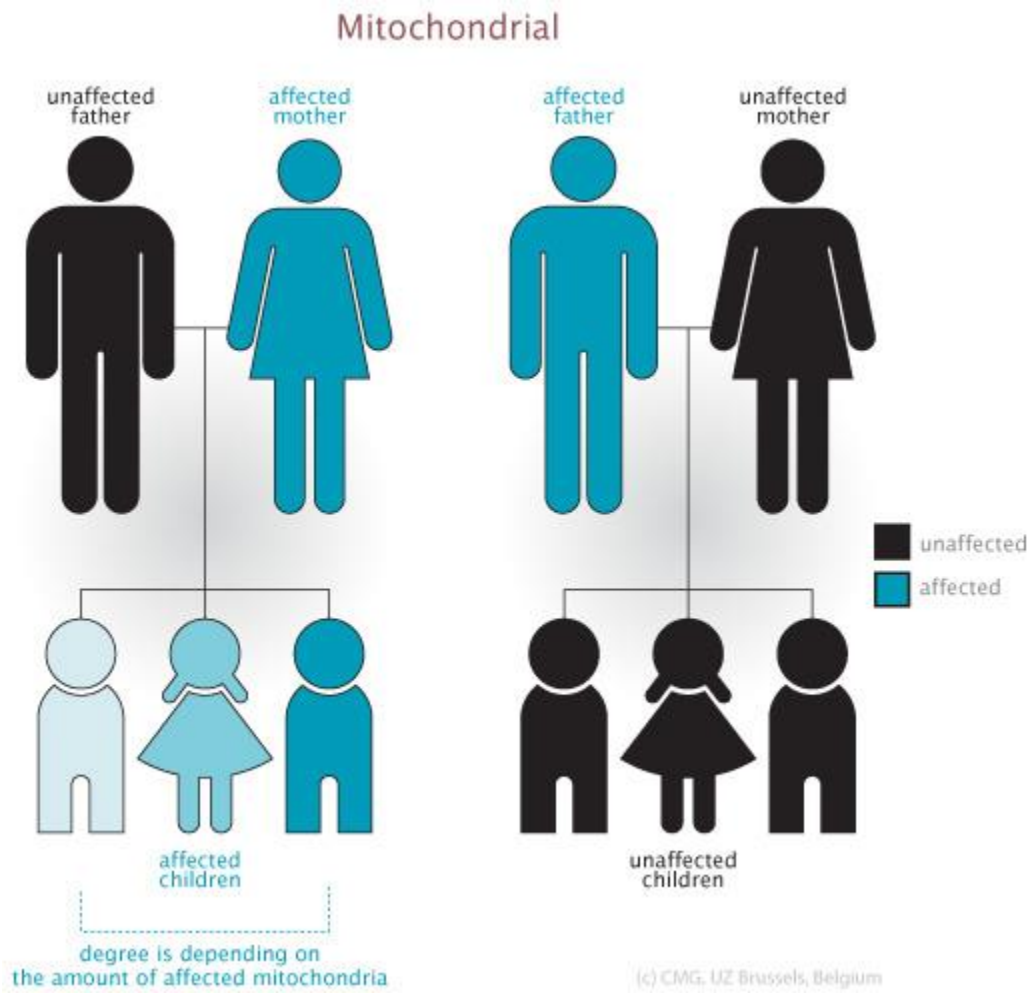



X-linked dominant, affected father
Affected father
Unaffected mother
X Y
X X
Unaffected
Affected
X Y
X X
X Y
X X
Unaffected son
Affected daughter
Unaffected son
Affected daughter
U.S. National Library of Medicine


X-linked dominant, affected mother
Unaffected father
Affected mother
X Y
X X
Unaffected
Affected
X Y
X X
X Y
X X
Unaffected son
Affected daughter
Affected son
Unaffected daughter
U.S. National Library of Medicine



Sex-Limited and Sex-Influenced Traits



Mitochondrial Inheritance

Circular DNA

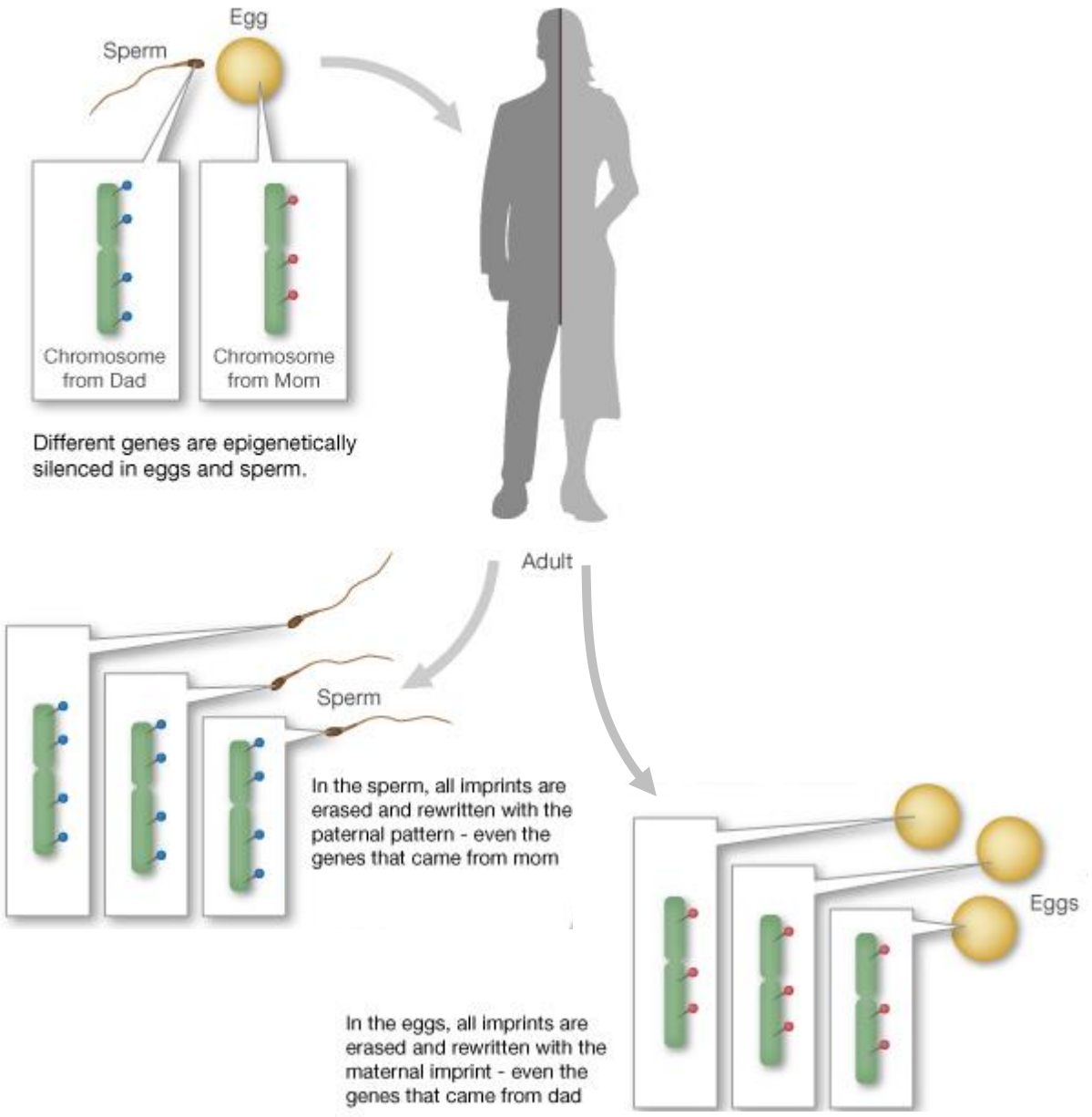
Higher mutation rates (heteroplasmy)

Maternal inheritance

Genes involved in oxidative phosphorylation

Affect organs most dependent on oxidative phosphorylation (skeletal muscle, heart, brain)

e.g. Leber hereditary optic neuropathy



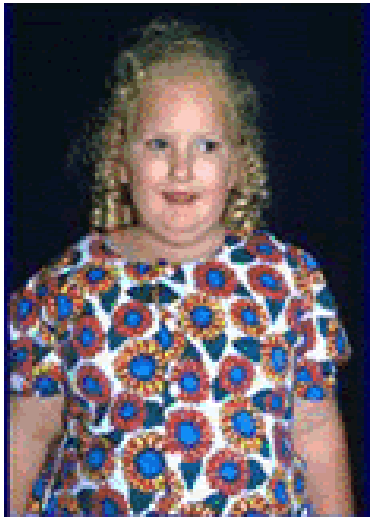
Genomic Imprinting

Transcriptionally inactive allele inherited from one of the parents

Methylation/histone deacetylation silencing

PWS

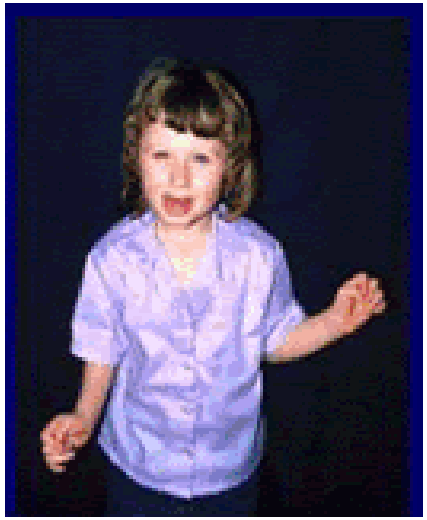
Paternal



moderate intellectual disability, short stature, hypotonia, obesity, small hands and feet, and hypogonadism

AS

Maternal



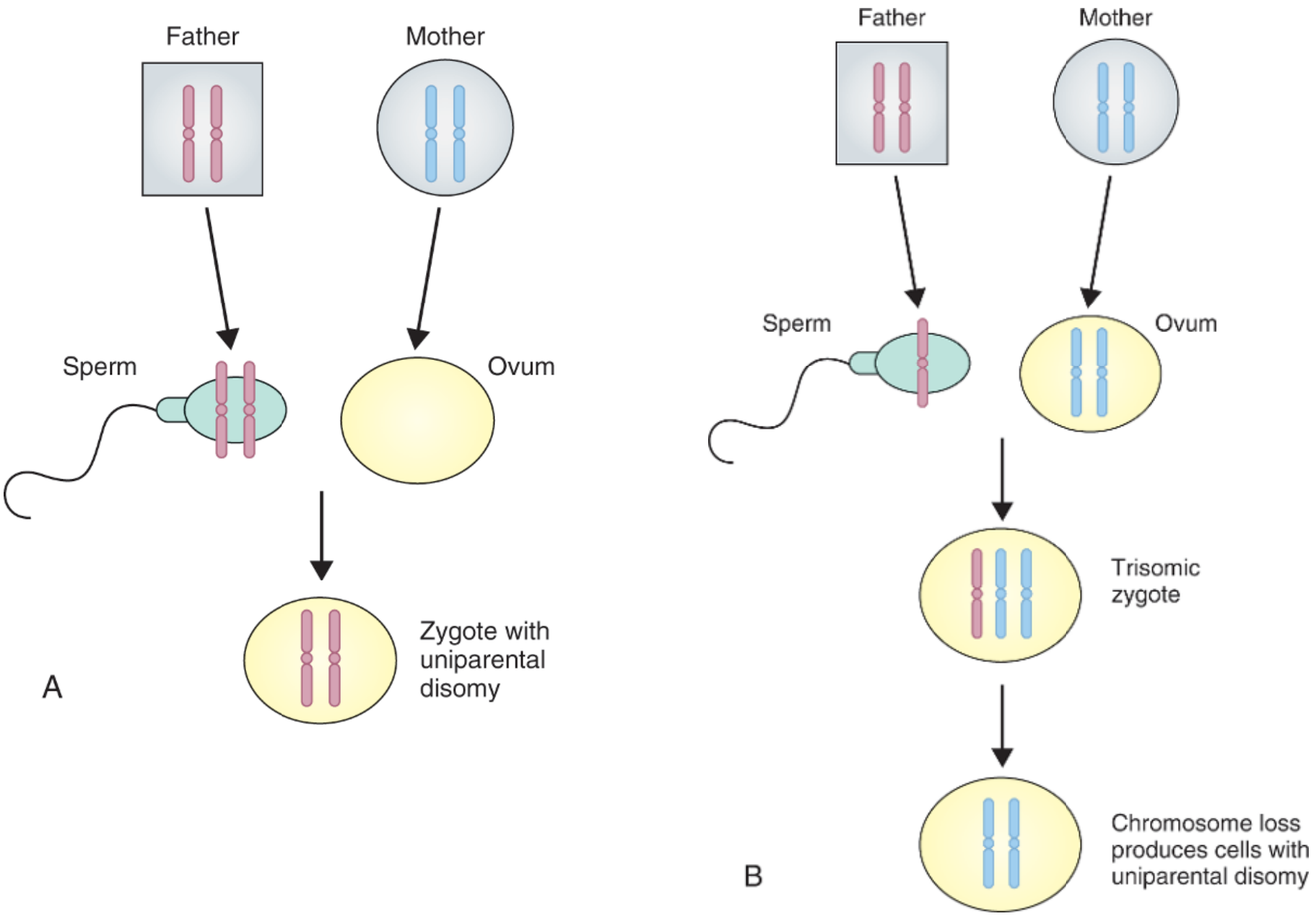
severe intellectual disability, ataxic gait, seizures, and inappropriate laughter

Prader-Willi and Angelman Syndromes

Both result from deletion of the same region on chromosome 15, but are distinct diseases??

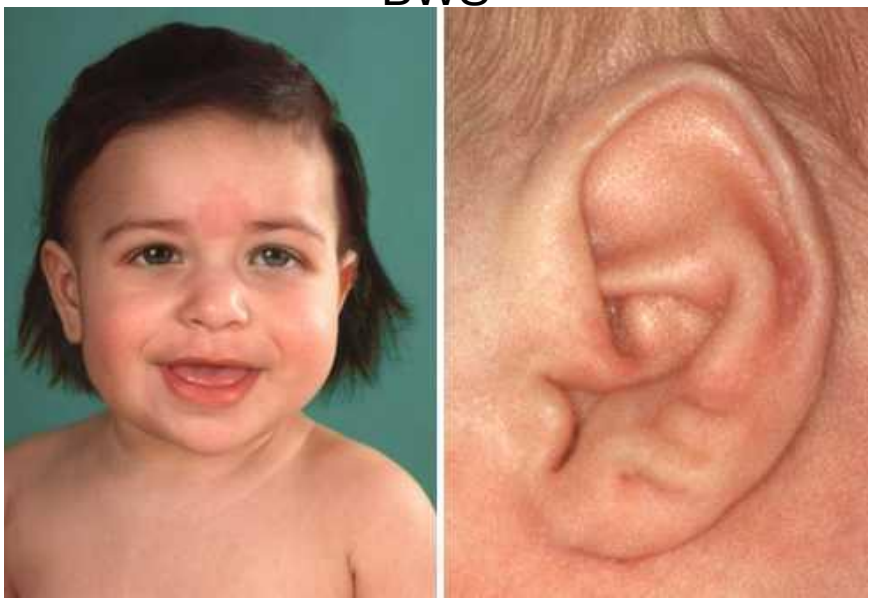
One is from a deletion of the paternal copy and the other the maternal.

Can also result from uniparental disomy


Father
Mother
Sperm
Ovum
Zygote with uniparental disomy
A
Father
Mother
Sperm
Ovum
Trisomic zygote
Chromosome loss produces cells with uniparental disomy
B

BWS

Increased IGF2 expression



overgrowth, predisposition to cancer, enlarged tongue, ear lobe creases

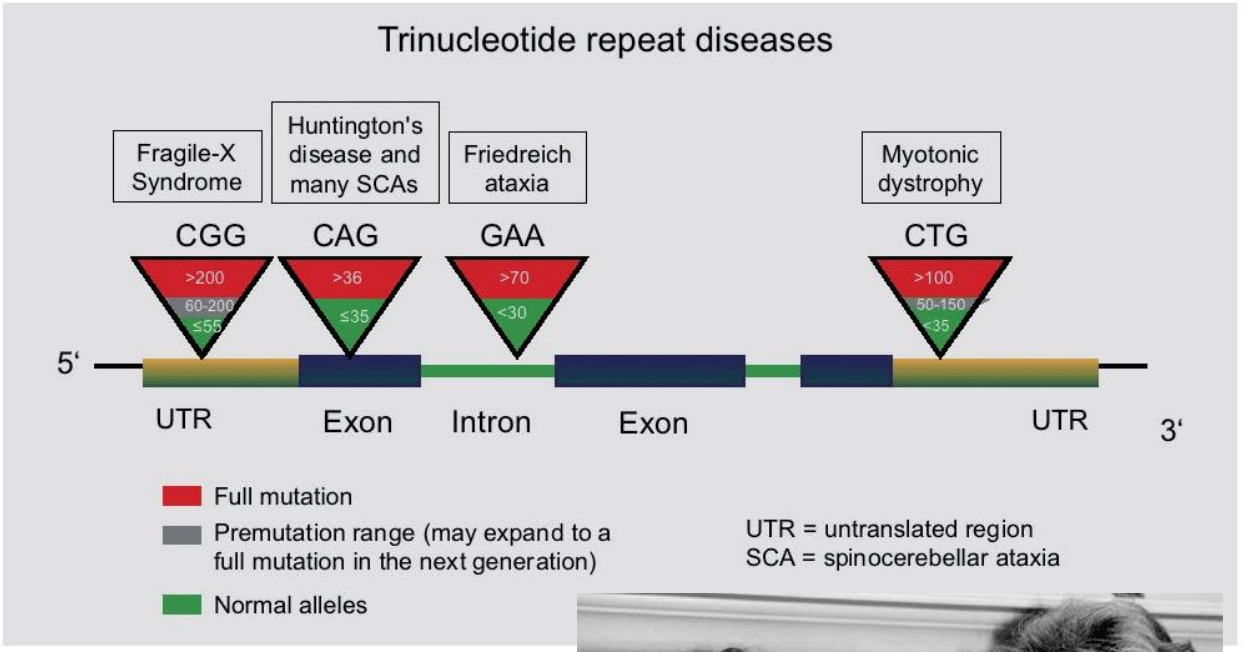
SRS

Reduced IGF2 expression

growth retardation, proportionate short stature, leg length discrepancy, and a small, triangular-shaped face

Beckwith–Wiedemann & Silver–Russell Syndromes

Uniparental disomy (paternal vs maternal respectively), or changes in methylation status of a region containing IGF2 changing its expression



Anticipation & repeat expansion

More severe and earlier presentation with each passing generation

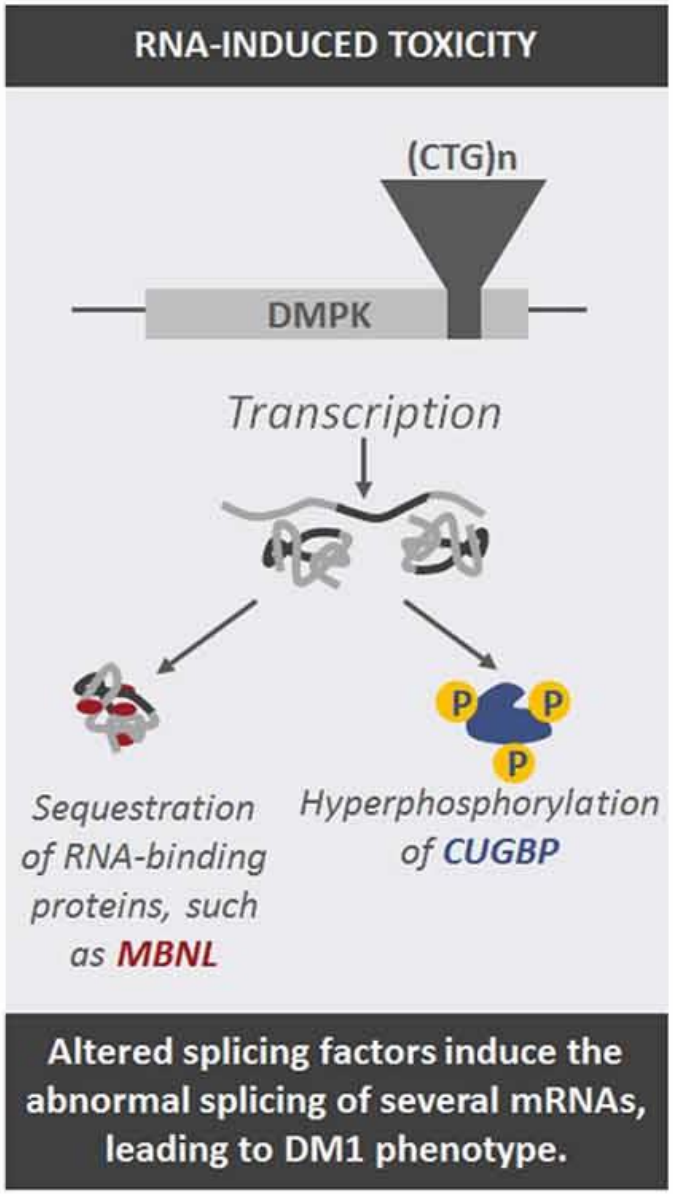
Better diagnosis?
Biological phenomenon?

Myotonic Dystrophy

AD

DMPK trinucleotide repeat

Muscle degeneration
Myotonia
Cardiac arrythmias
Testicular atrophy
Insulin resistance
Catracts



- **Aberrant protein expression**

ClC-1	MBNL
SERCA	CUGBP1
IR	DMPK
Tnnt	SIX5
Tau	ZNF9
NMDAR1	NKX2-5
etc.	Sp1
	etc.

- **Loss of cell function and viability**

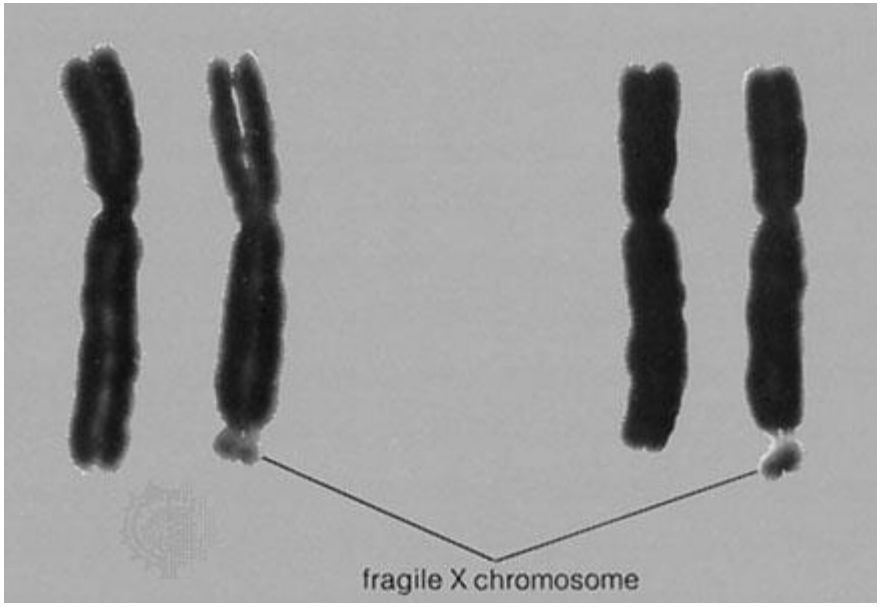
Myotonic Dystrophy (Anticipation, pleiotropy, & locus heterogeneity)

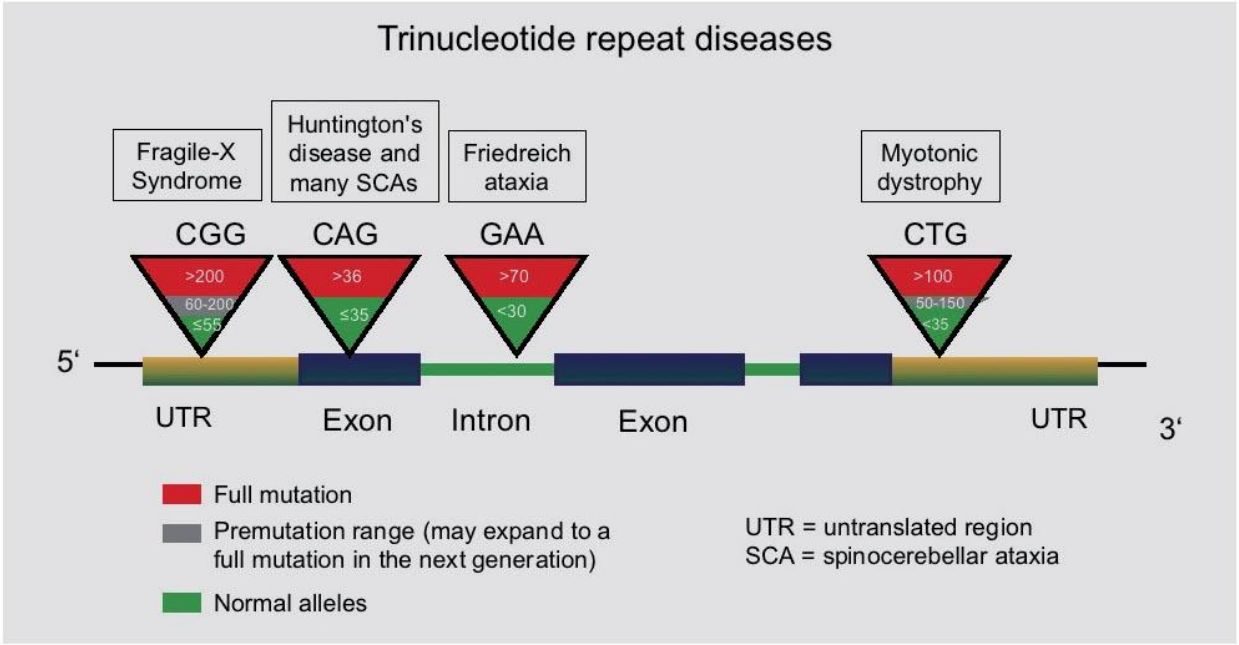
Second type on chromosome 3 vs type 1 on chromosome 19

Same molecular mechanism

Similar features

Sometimes less severe





Fragile X Syndrome

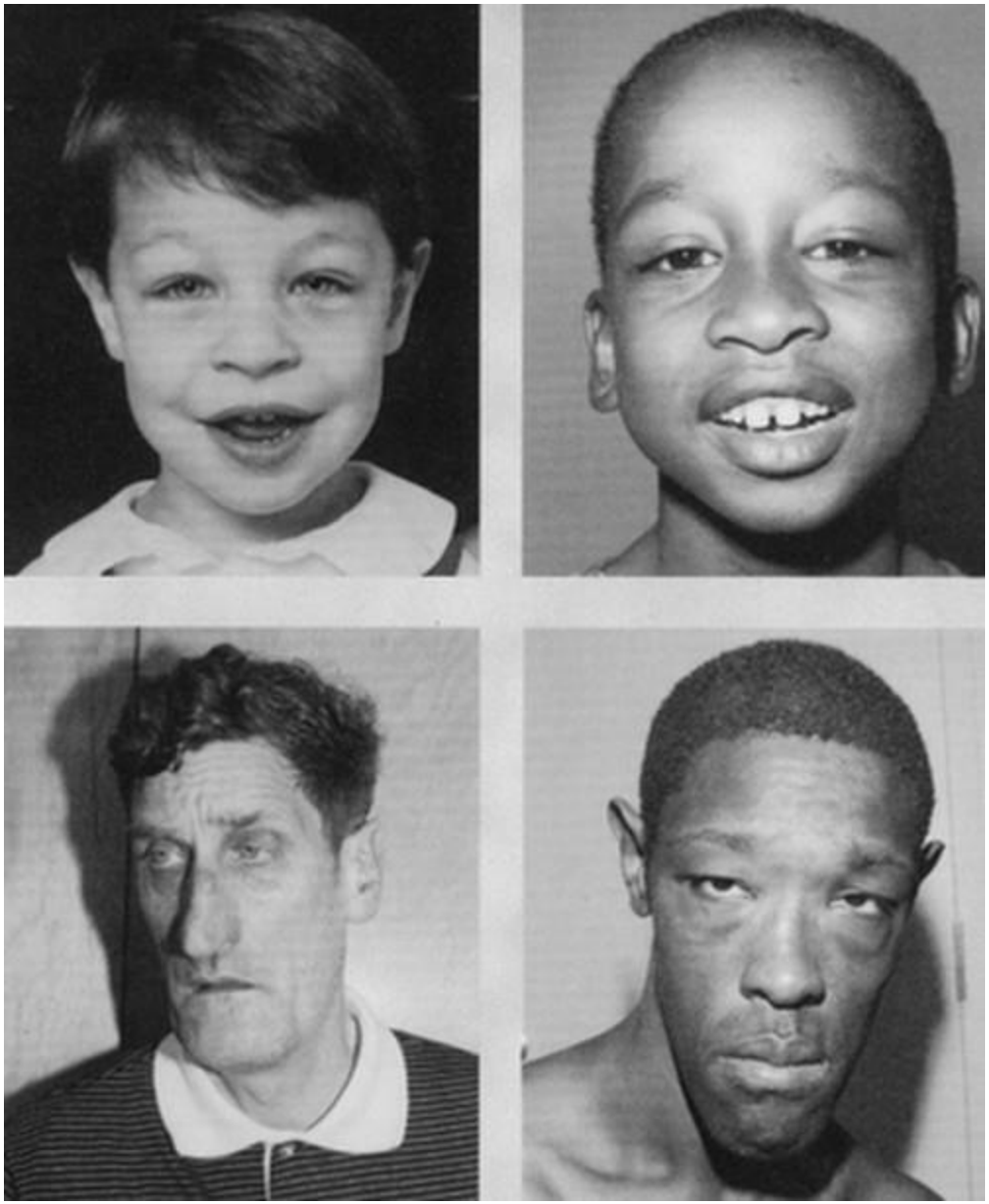
Fragile X mental retardation 1 gene mutation (*FMR1)*

More common in males (X inactivation)

Second most common genetic cause of mental retardation, after Down syndrome

Anticipation & the Sherman paradox

Homework



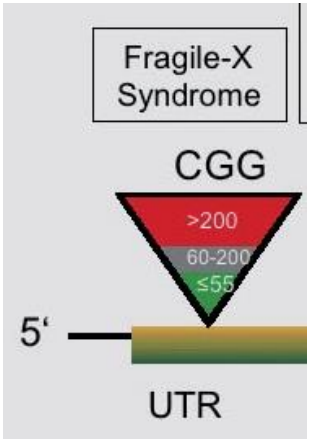
Fragile X Syndrome

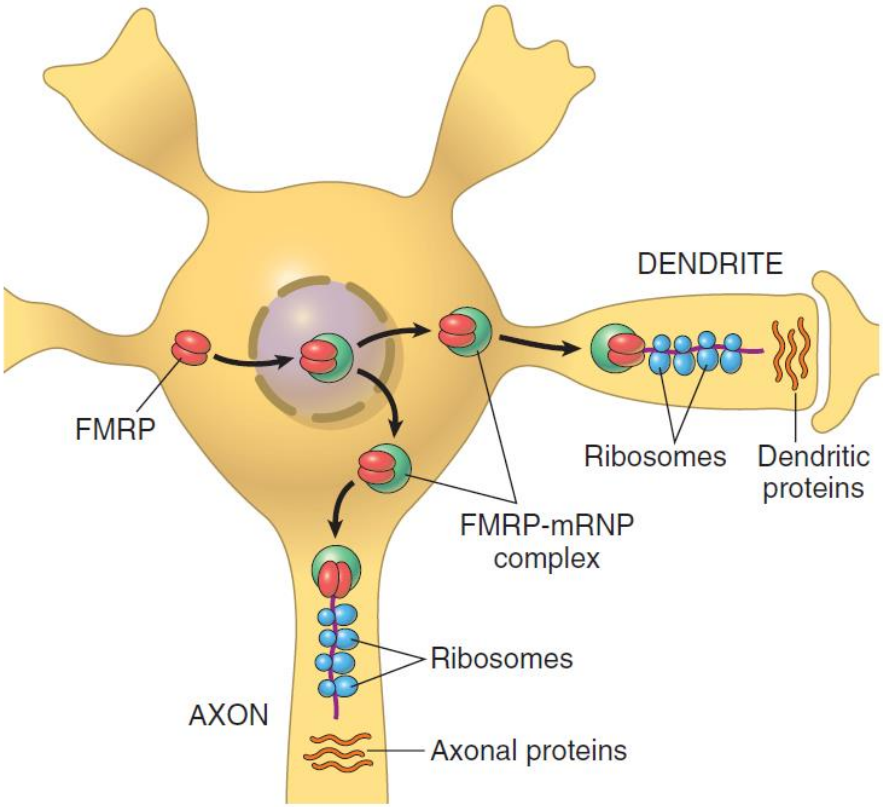
Moderate to severe mental retardation

long face with a large mandible

large everted ears

large testicles (macroorchidism)





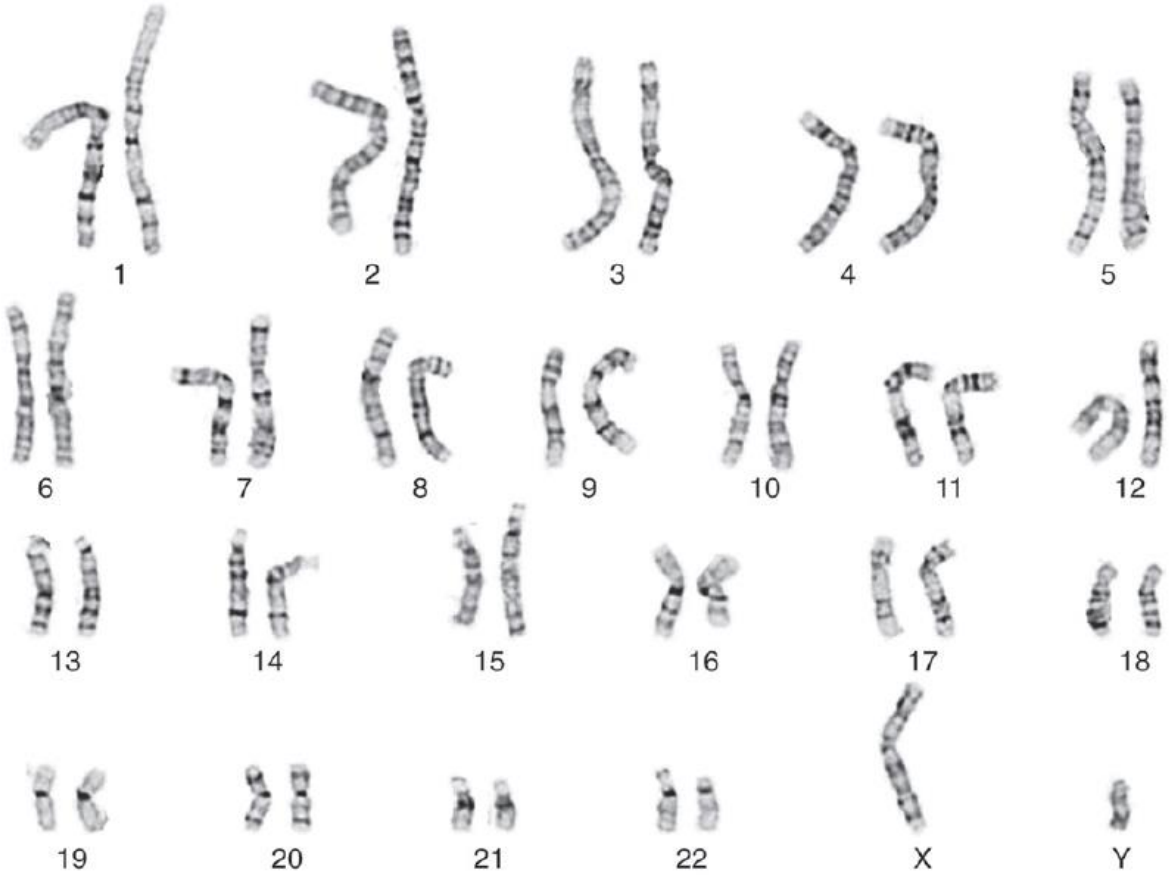
Fragile X Syndrome

Methylation (silencing) of the promoter

mRNA shuttle

Translation regulator

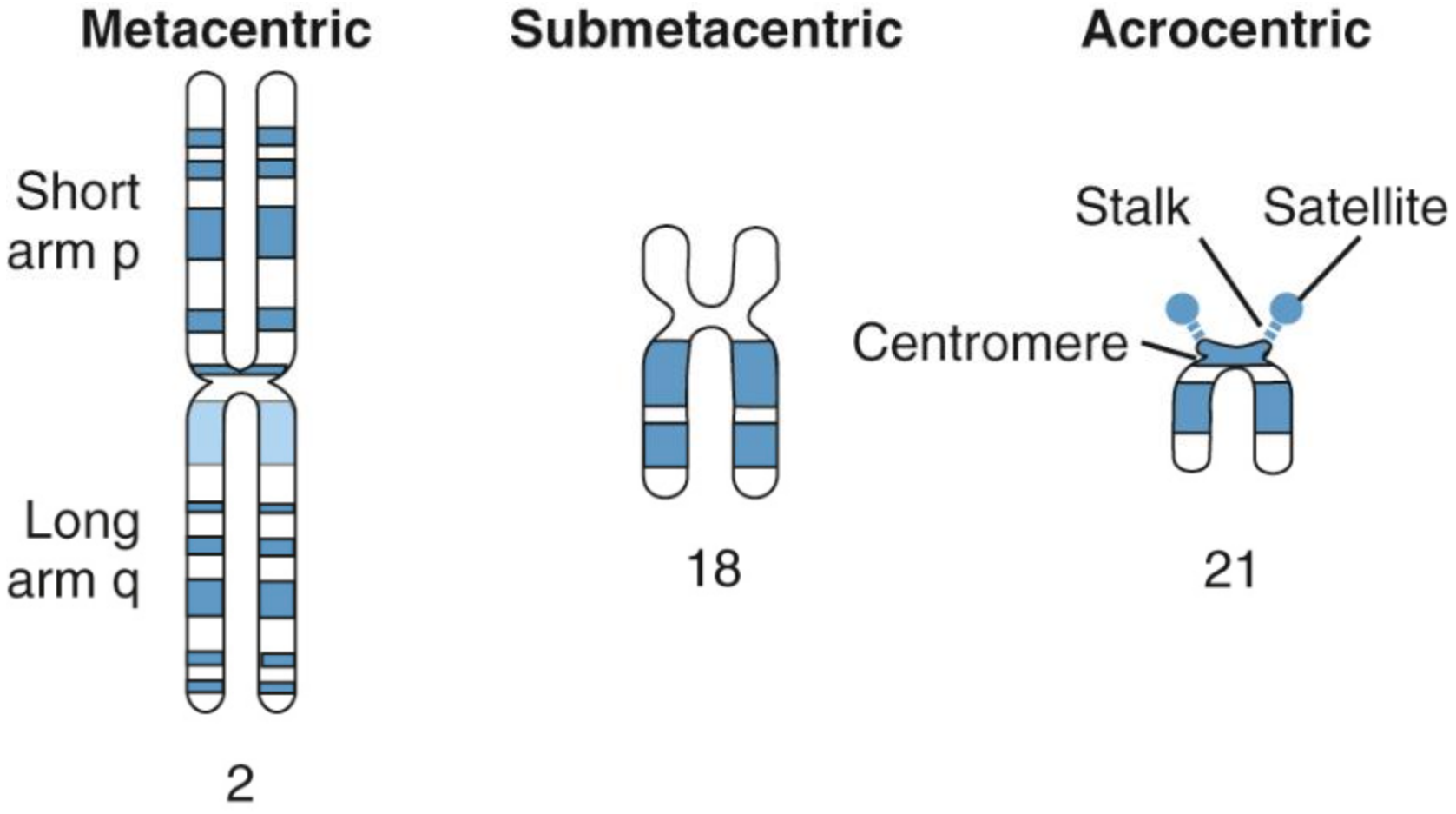
Clinical Cytogenetics

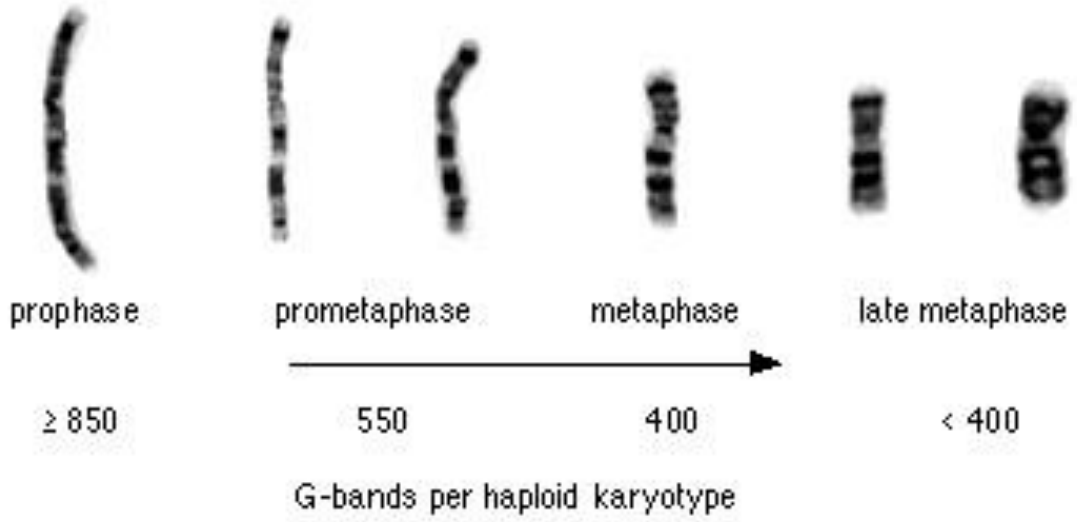


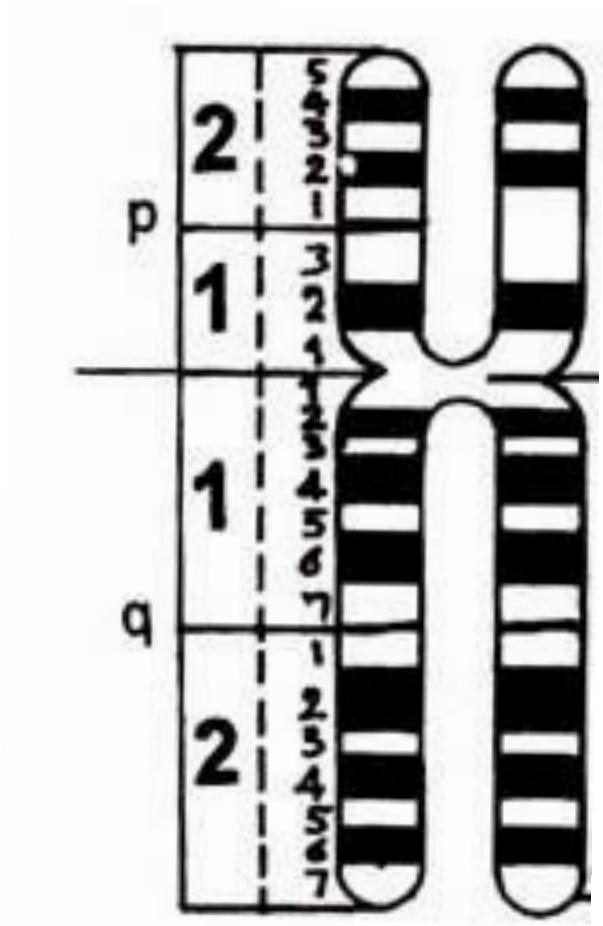
Karyotype

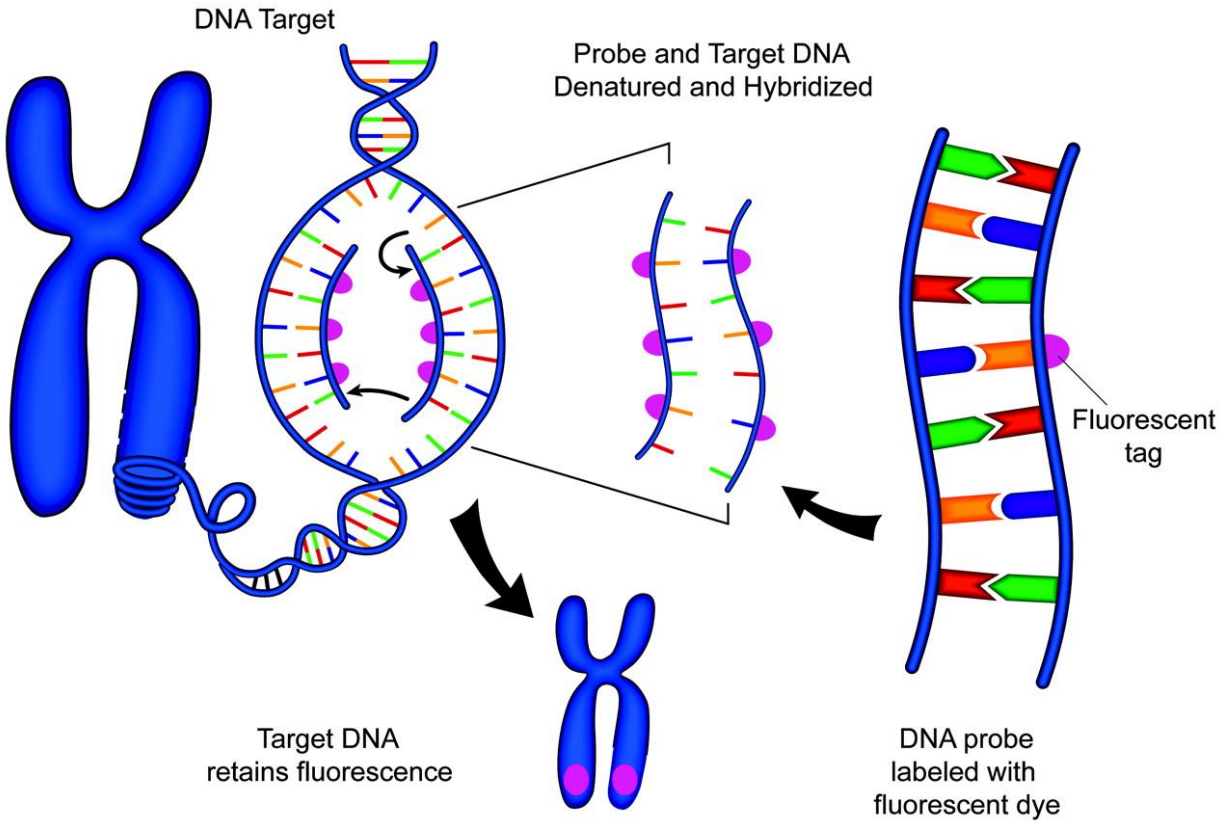
A karyotype is a photographic representation of a stained metaphase spread in which the chromosomes are arranged in order of decreasing length.

Various staining techniques, commonly used as seen here is the Giemsa staining (G banding)


Metacentric
Submetacentric
Acrocentric
Short arm p
Long arm q
2
18
Stalk
Satellite
Centromere
21


prophase
prometaphase
metaphase
late metaphase
≥ 850
550
400
< 400
G-bands per haploid karyotype


p
q
2
1
1
2

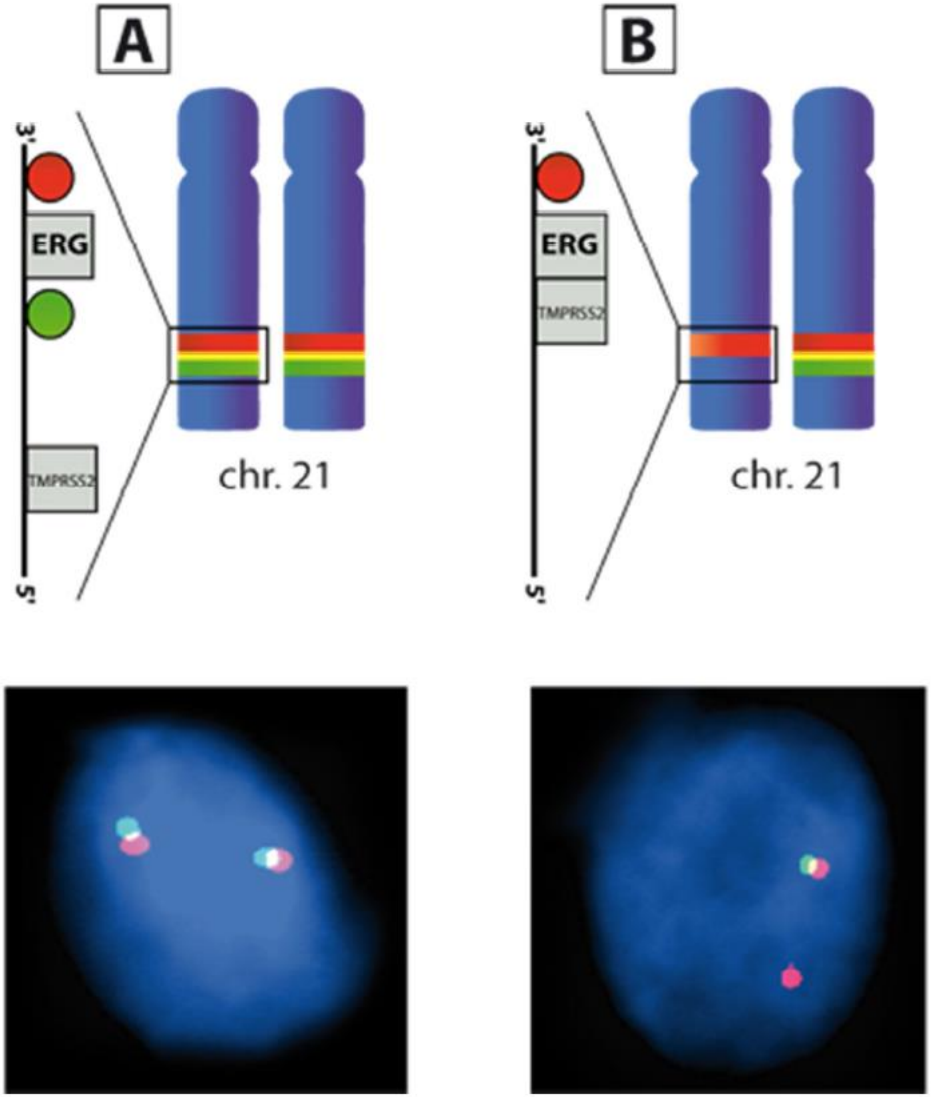


F.I.S.H.

Can be carried out with interphase chromosomes

Single or multiple probes

Detects deletion or addition of genetic material as well as translocations



F.I.S.H.

Can be carried out with interphase chromosomes

Single or multiple probes

Here we're detecting deletion.

The Process of Array CGH

CANCER GENETICS

CONTROL DNA

PATIENT DNA

1

Patient and control DNA labeled with fluorescent dyes are applied to the microarray.

2

Patient and control DNA are hybridized to the microarray.

HYBRIDIZATION

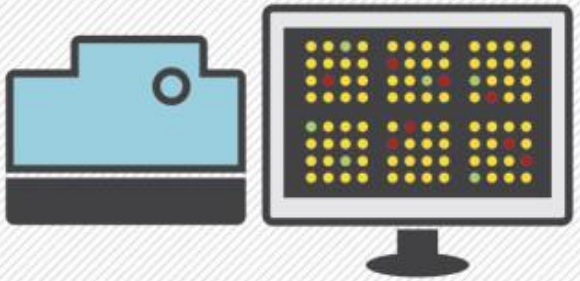
DNA GAIN

DNA LOSS

NO CHANGE

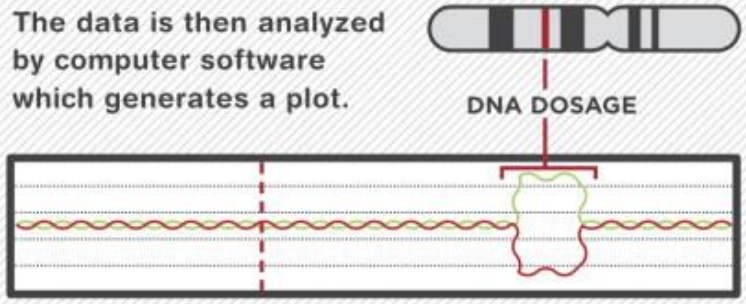
3

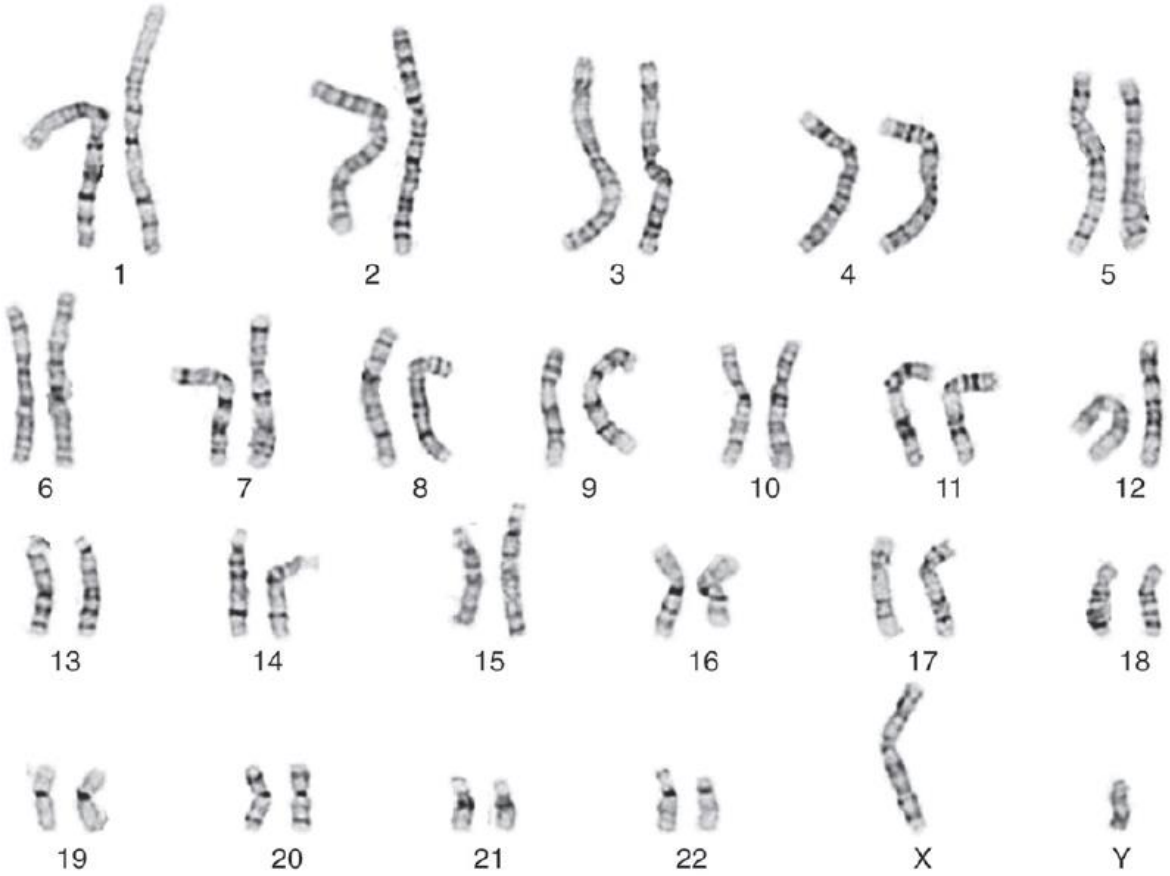
The fluorescent signals are measured by the microarray scanner.



4

The data is then analyzed by computer software which generates a plot.





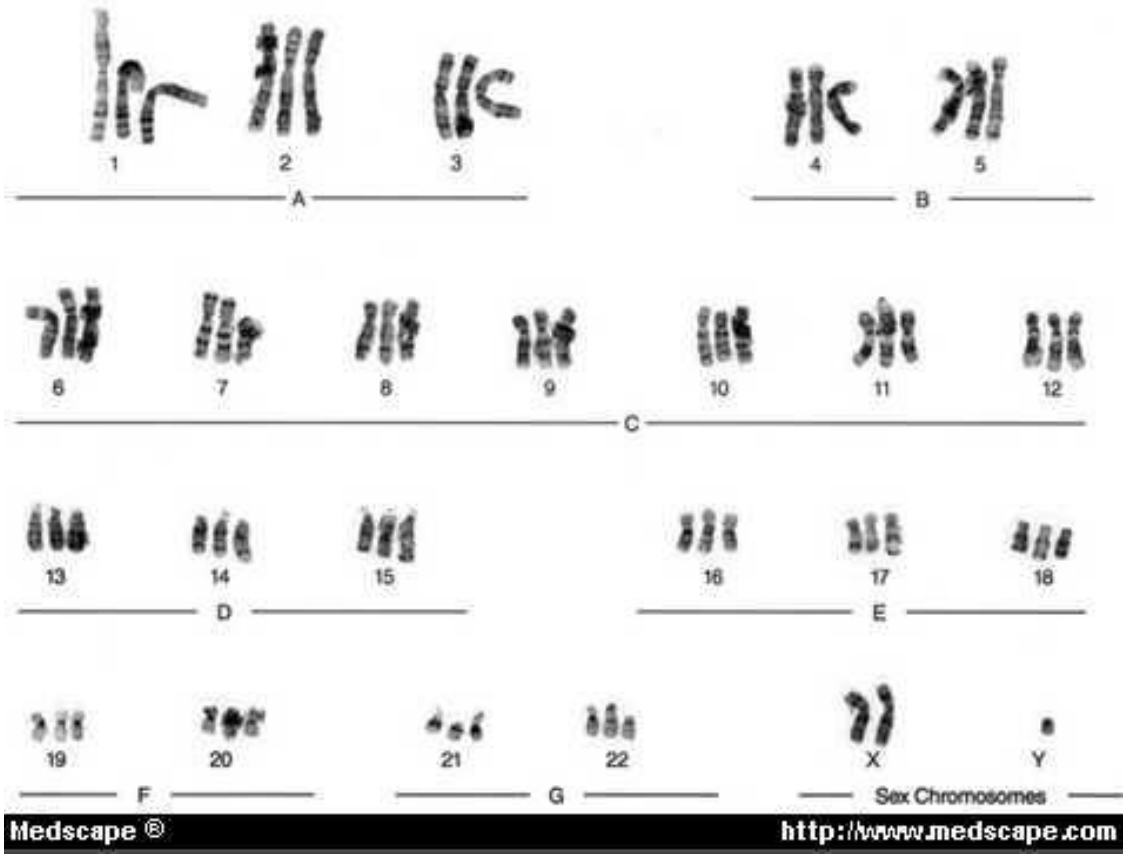
Numeric Abnormalities

2n=46

Euploid

Polyploid

Aneuploid



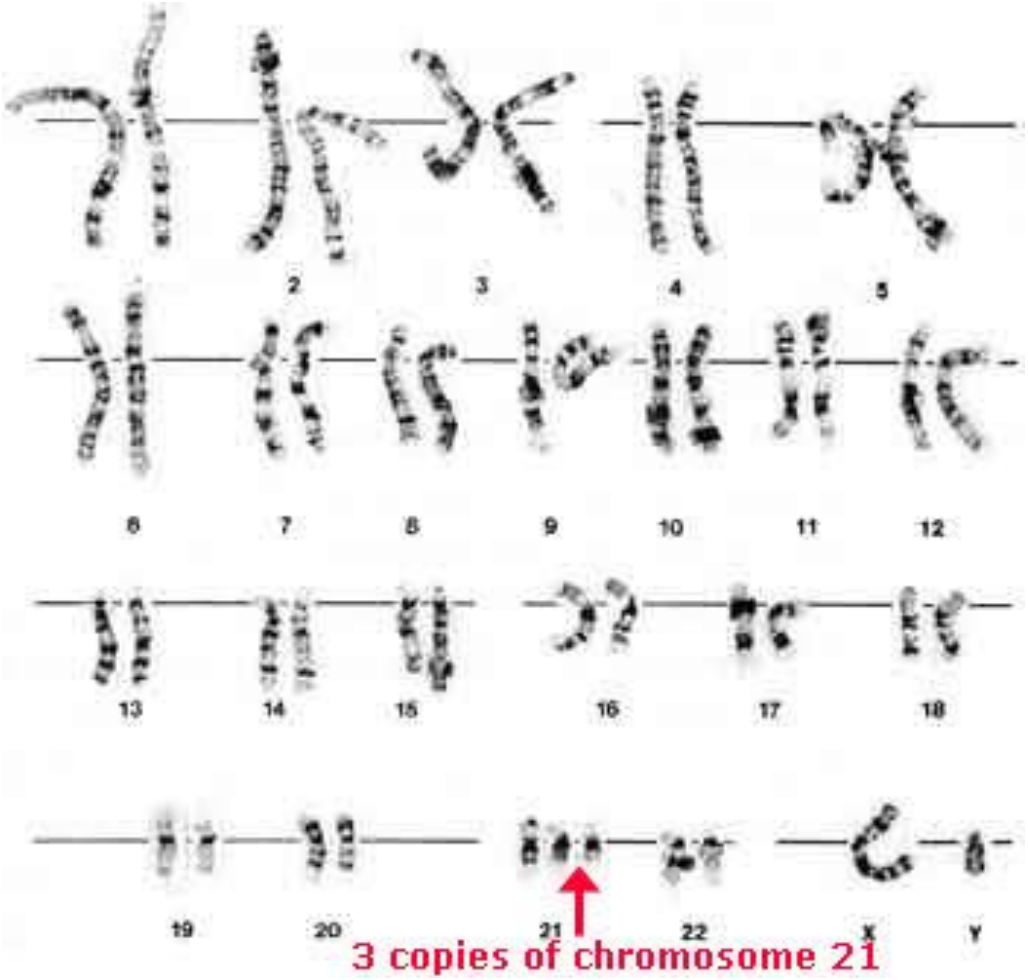
Numeric Abnormalities

2n=46

Euploid

Polyploid

Aneuploid



Numeric Abnormalities

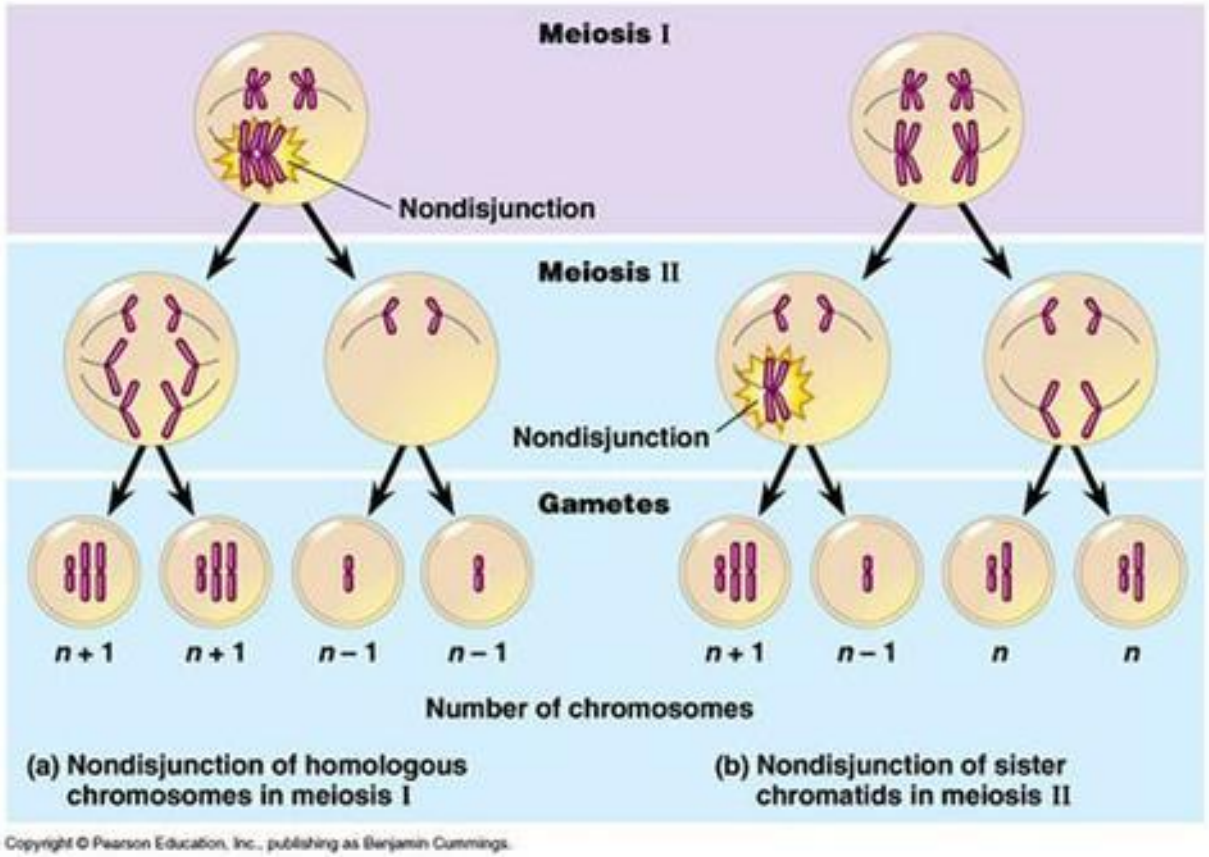
2n=46

Euploid

Polyploid

Aneuploid

Numeric Abnormalities



2n=46

Euploid

Polyploid

Aneuploid

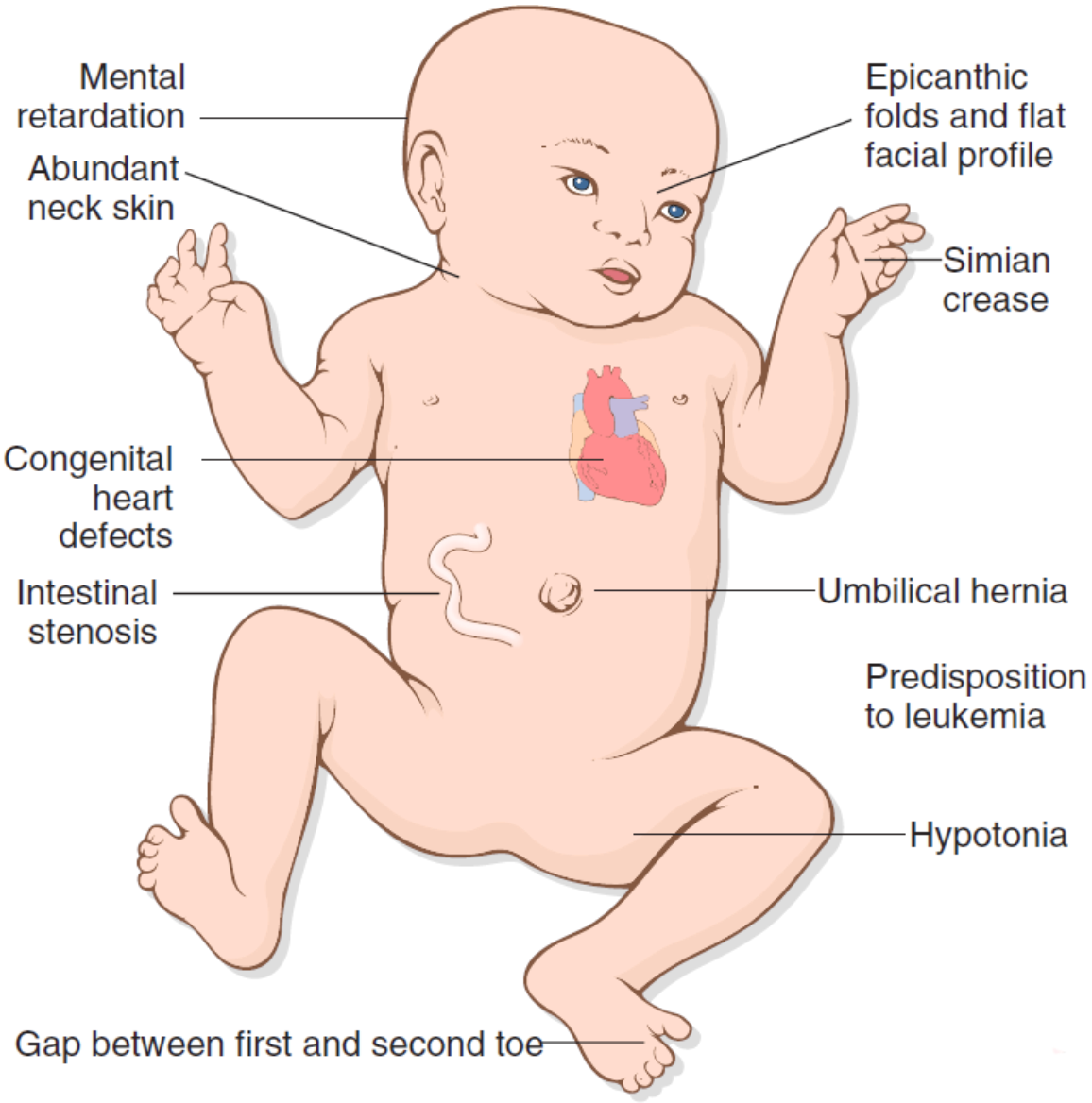
Trisomy 21: Down Syndrome

Incidence: 1 in 700 births

Karyotype
47,XY,+21 or 47,XX,+21

Can also occur due to translocations and mosaicism

47,XY,+21[10]/46,XY[10]



Trisomy 21: Down Syndrome

Normal parents

Increased incidence with maternal age reaching as high as 1:25 >45yr

Maternal meiotic nondisjunction

Majority have mental retardation associated with gentle manner

>40 gain features of Alzheimer's

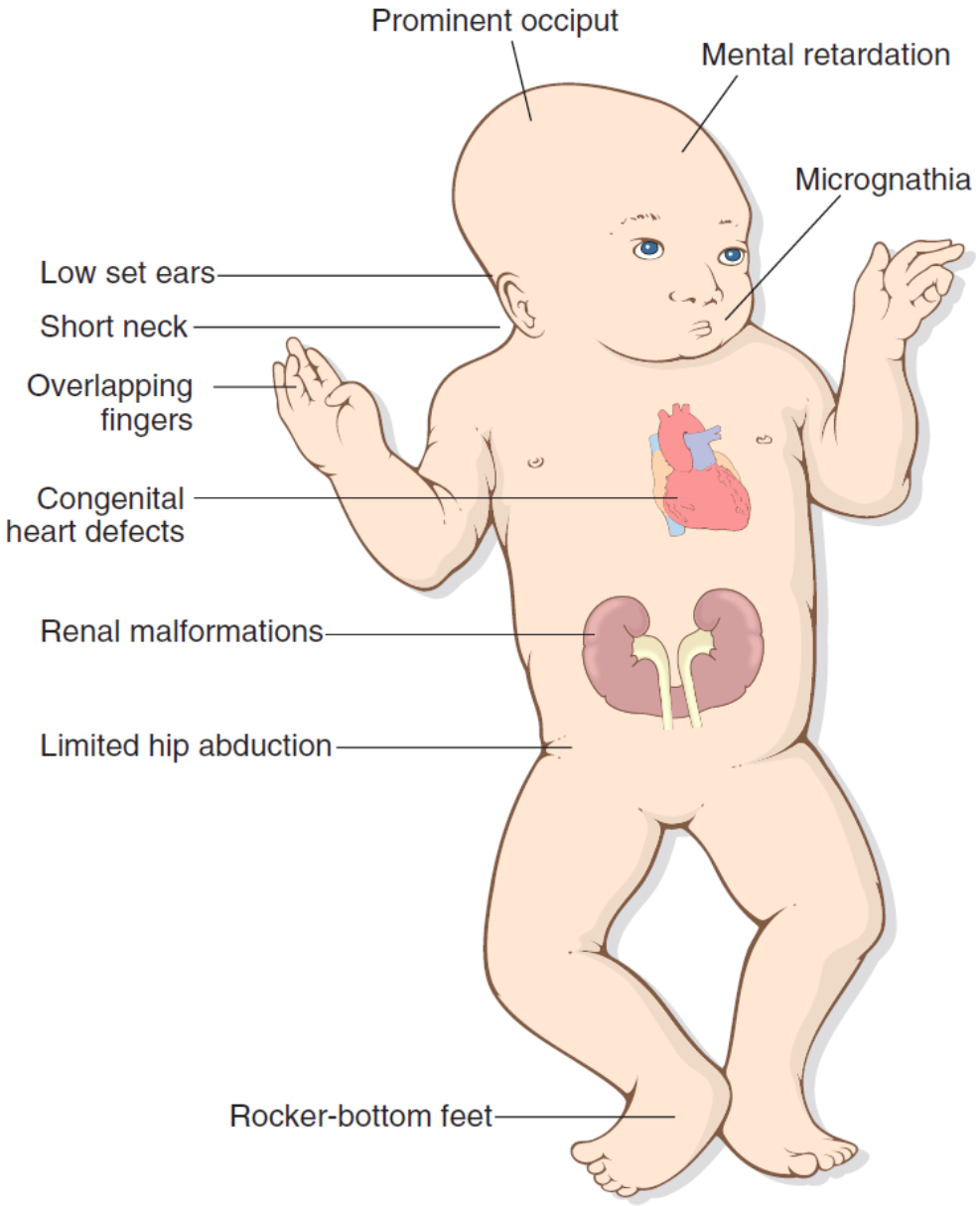
Trisomy 18: Edwards Syndrome

Second most common autosomal trisomy

Karyotypes:

Trisomy 18 type:
47,XY,+18 or 47,XX,+18

Mosaic type:
46,XX/47,XX,+18



Trisomy 18: Edwards Syndrome

As in trisomy 21, there is a significant maternal age effect, and more than 90% of trisomy 18 cases are the result of an extra chromosome transmitted by the mother.

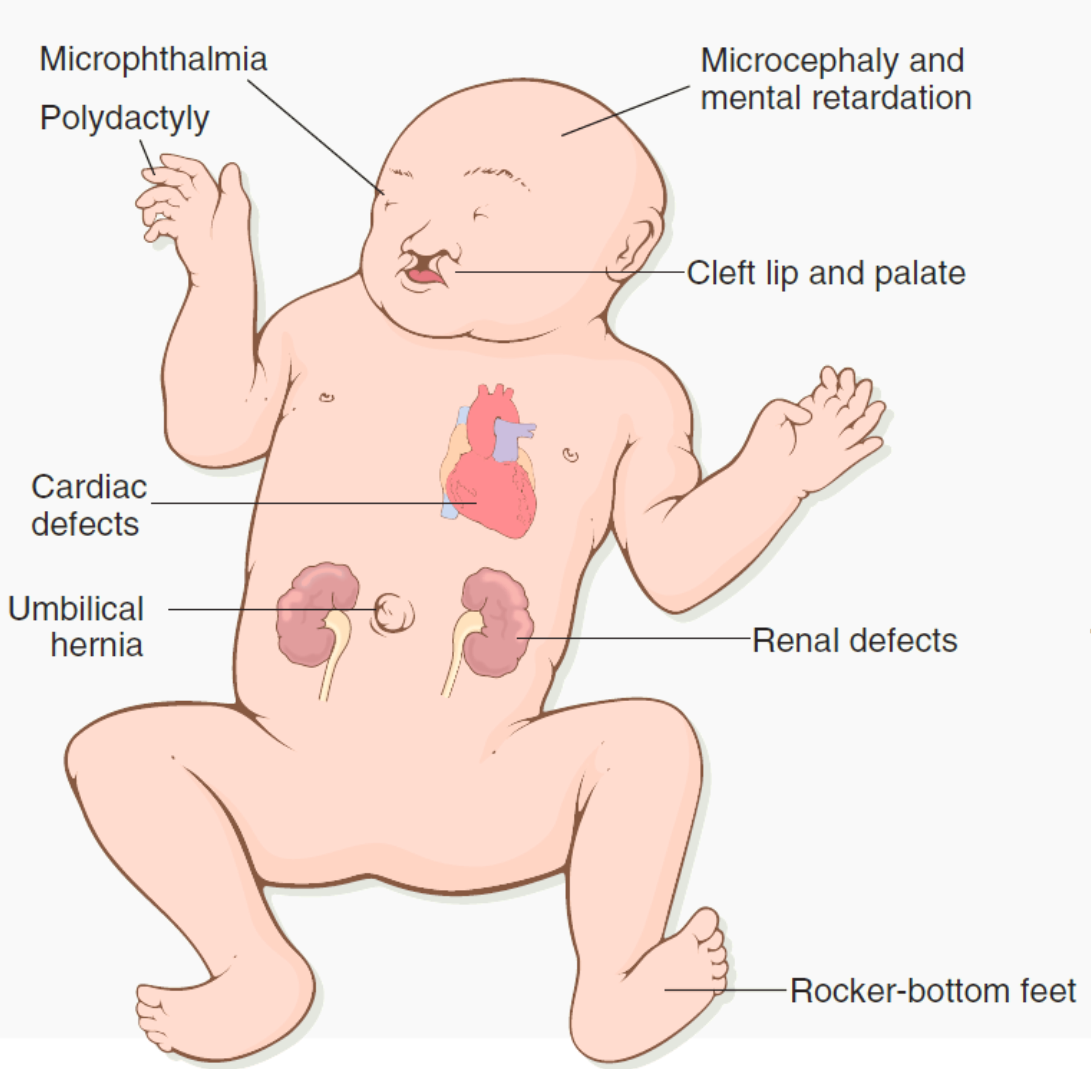
Trisomy 13: Patau Syndrome

Karyotypes:

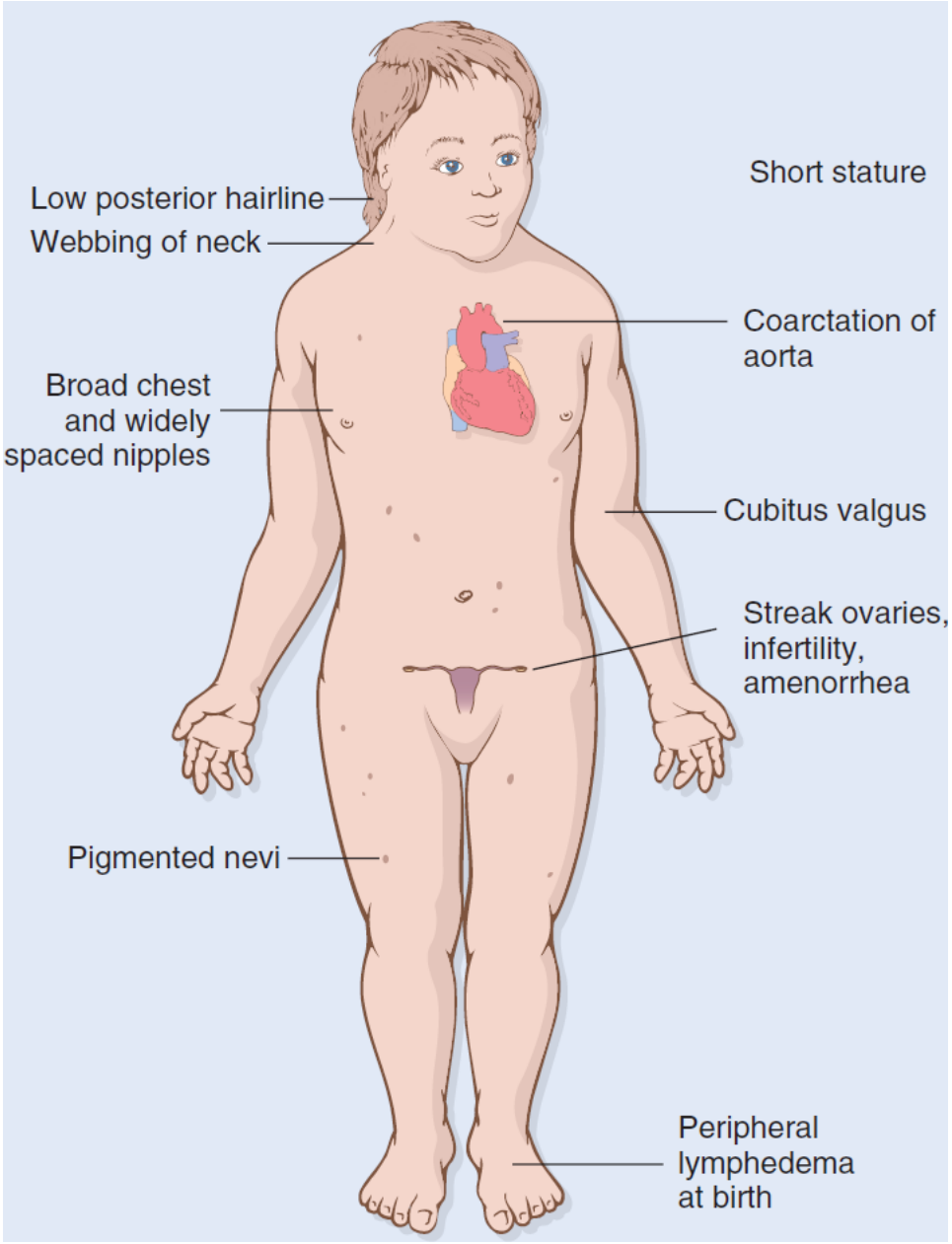
Trisomy 13 type:
47,XX,+13

Can also occur due to translocations duplicating the long arm of chromosome 13 as well as mosaicism

Trisomy 13: Patau Syndrome



Similar mortality rates to trisomy 18 with 95% not surviving through their first birthday



Turner Syndrome

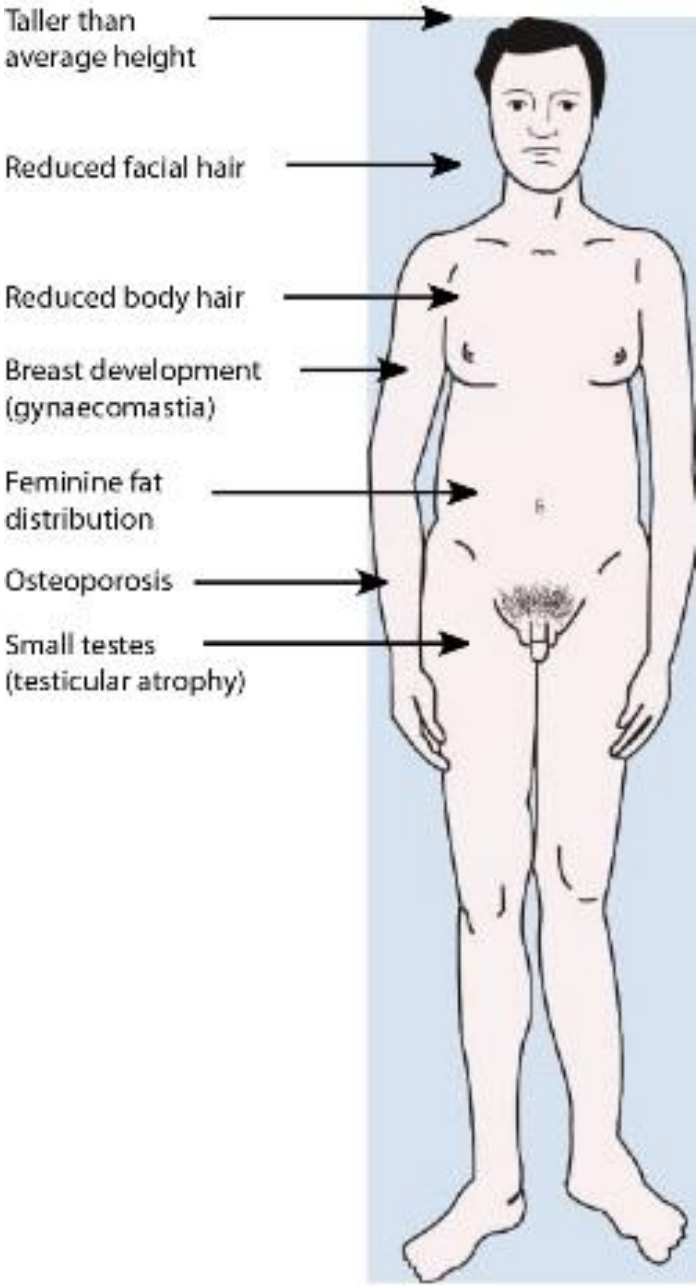
Partial or complete monosomy of the short arm of the X chromosome

Primary hypogonadism

Hypothyroid

Mosaics milder

GH & estrogen therapy



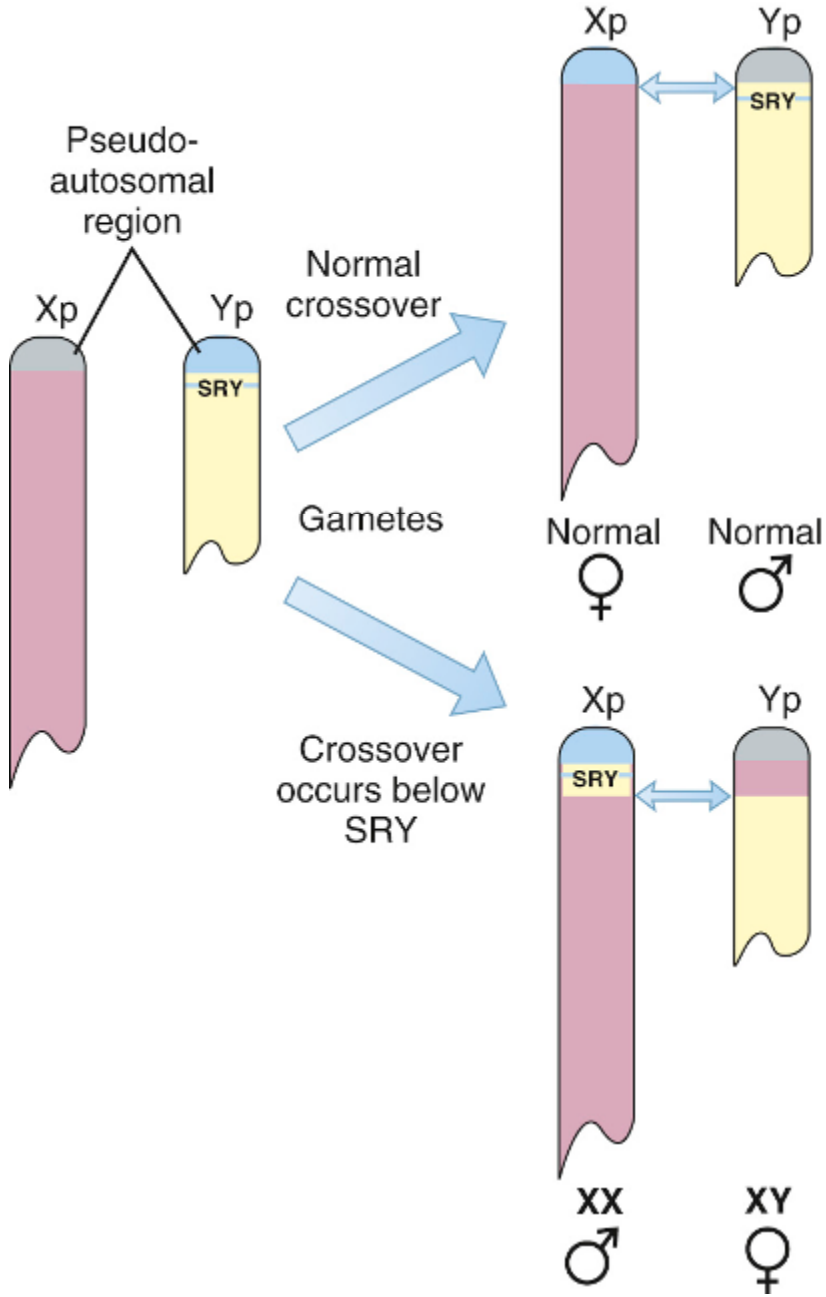
Klinefelter Syndrome

Most common cause of hypogonadism in males

Commonly 47,XXY

Mosiacs can be fertile with a milder clinical condition

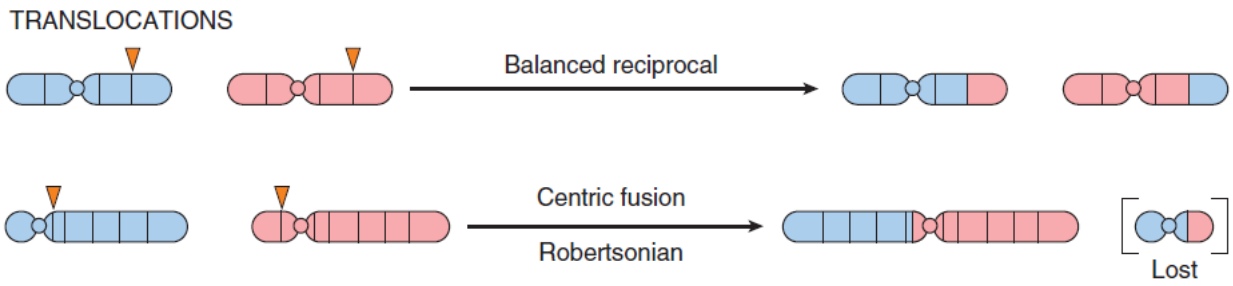
Increased risk of breast cancer



The XX and XY of it all

SRY sex-determining region on the Y

Examples?



Structural Abnormalities

unequal crossover and chromosomal breakage followed by loss or rearrangement of material

Translocation

Deletion

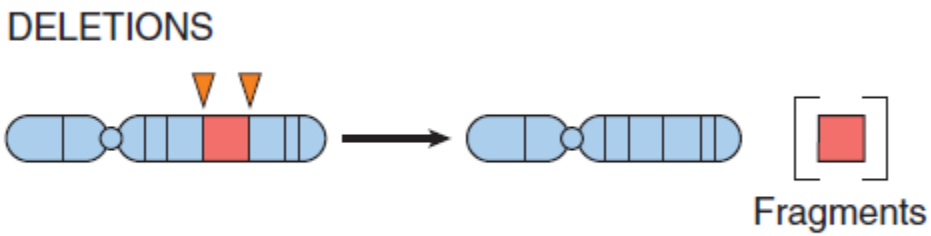
Ring chromosome

Inversion

Isochromosome

Structural Abnormalities

Examples?



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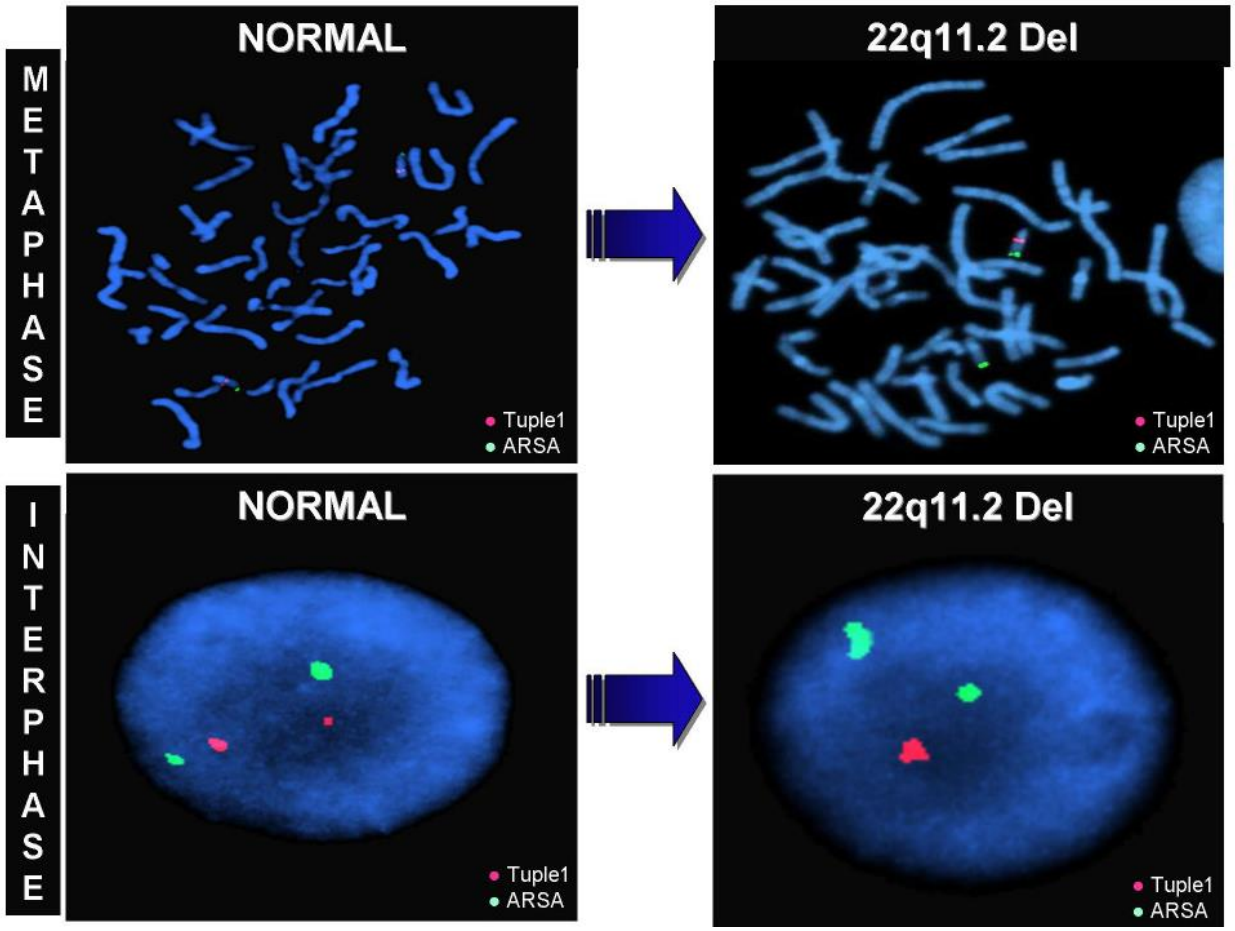

22q11.2 Deletion Syndrome

- CHD
- Palate abnormalities
- Facial dysmorphism
- Developmental delay
- Thymic hypoplasia with impaired T cell immunity
- Parathyroid hypoplasia
- Hypoclacemia

Previously, DiGeorge syndrome and velocardiofacial syndrome

Schizophrenia and Bipolar disorder?

Structural Abnormalities

unequal crossover and chromosomal breakage followed by loss or rearrangement of material

Translocation

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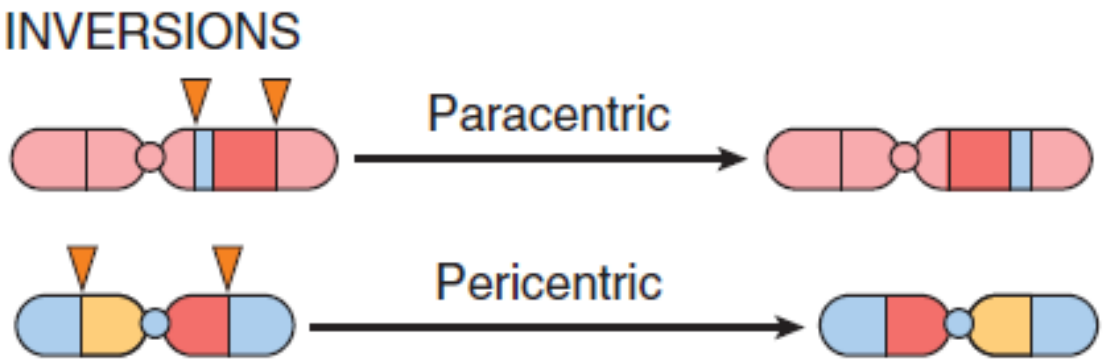
Structural Abnormalities



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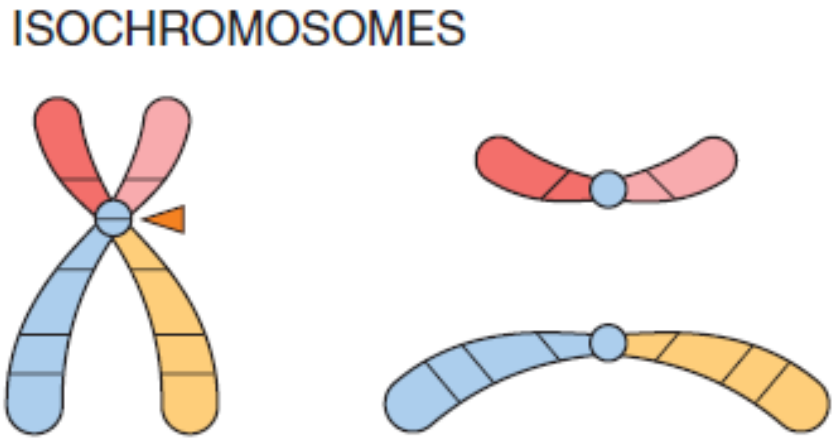
Structural Abnormalities



unequal crossover and chromosomal breakage followed by loss or rearrangement of material

Translocation

Deletion

Ring chromosome

Inversion

Isochromosome

When do we order chromosome analysis?

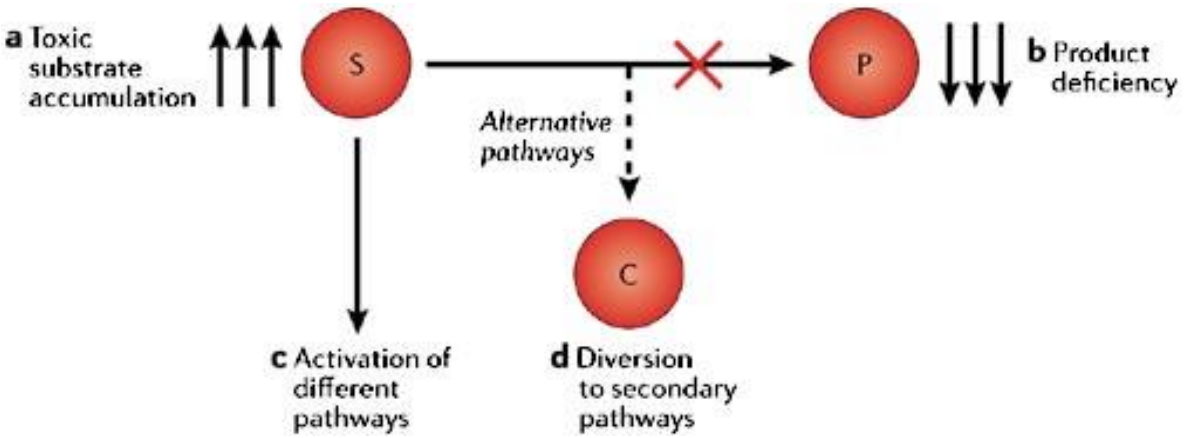
General features

- Developmental delay/intellectual disability
- Characteristic facial and limb features
- Growth delay
- Congenital malformations

Indications

- Suspected chromosomal syndrome
- ≥ 2 malformations
- Ambiguous genitalia
- Stillborn with either malformations or no recognizable reason for death
- Males with small testes and/or gynecomastia
- Short females with primary amenorrhea

Biochemical genetics
(aka inborn errors of metabolism)



Biomolecules:
nucleic acids, proteins, carbohydrates, and lipids

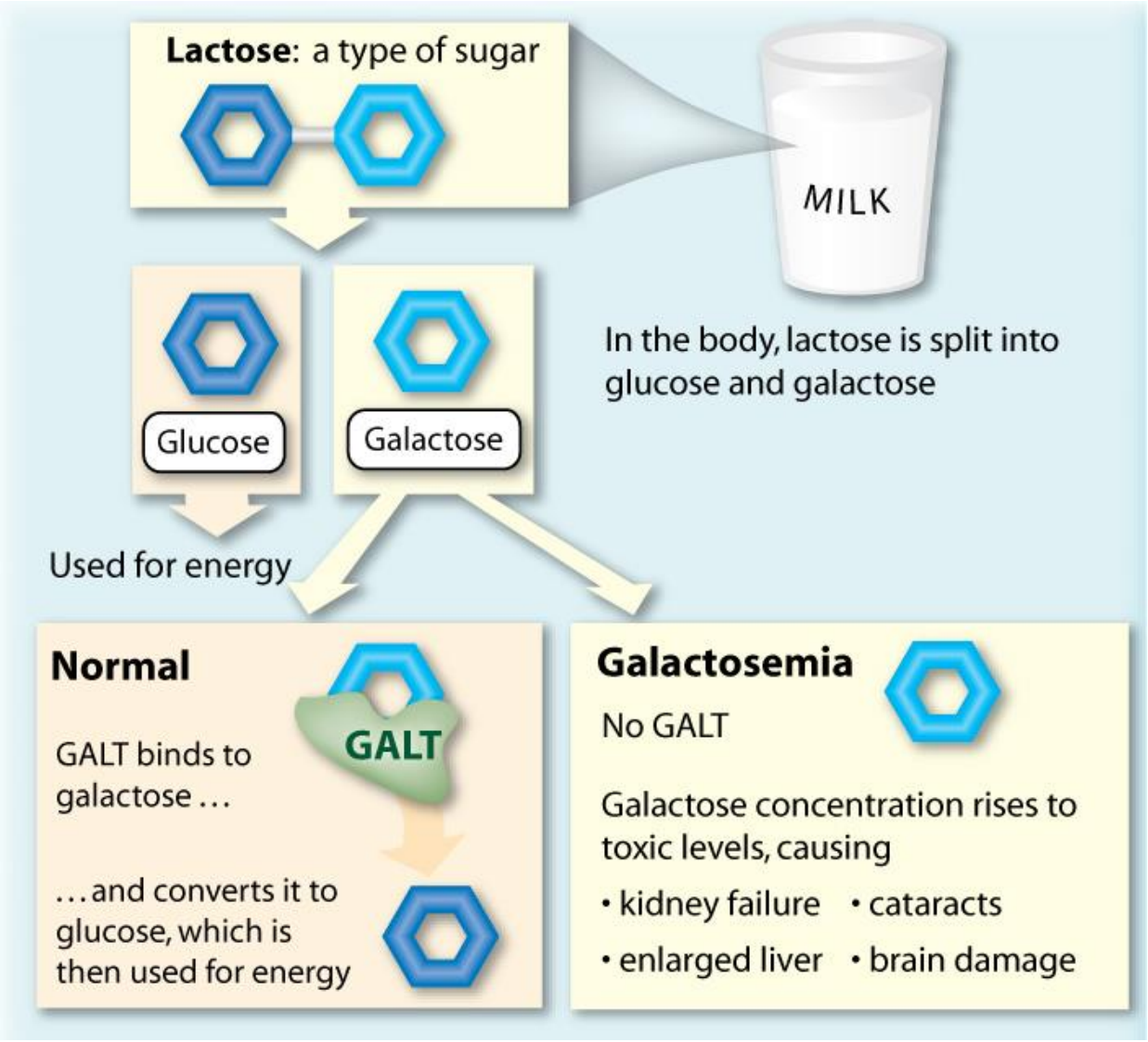
Major metabolic pathways:
glycolysis, citric acid cycle, pentose phosphate shunt, gluconeogenesis, glycogen and fatty acid synthesis and storage, degradative pathways, energy production, and transport systems

IEMs

Mostly AR

Frequently challenging to diagnose due to wide variability of presentation even within the same disease

Improved genetic testing panels make your lives easier



Carbohydrate IEMs (Galactose)

Galactosemia (classic)

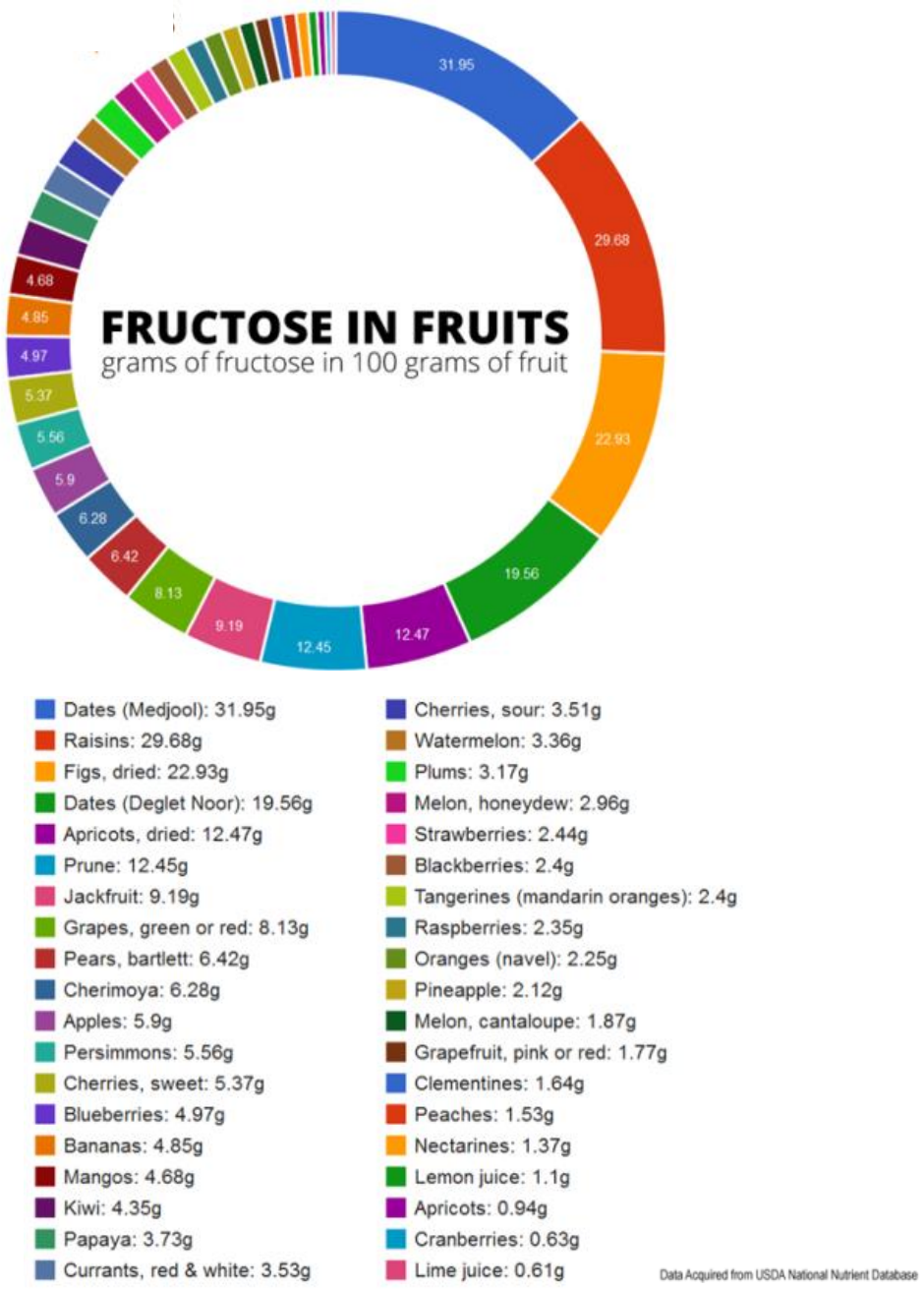
AR

galactose-1-phosphate uridyltransferase (*GALT*)

Failure to thrive from birth
- Vomiting
- Diarrhea
- Jaundice

Remove galactose from the diet at east for the first 2 years of life

Galactokinase or UDP-galactose-4-epimerase



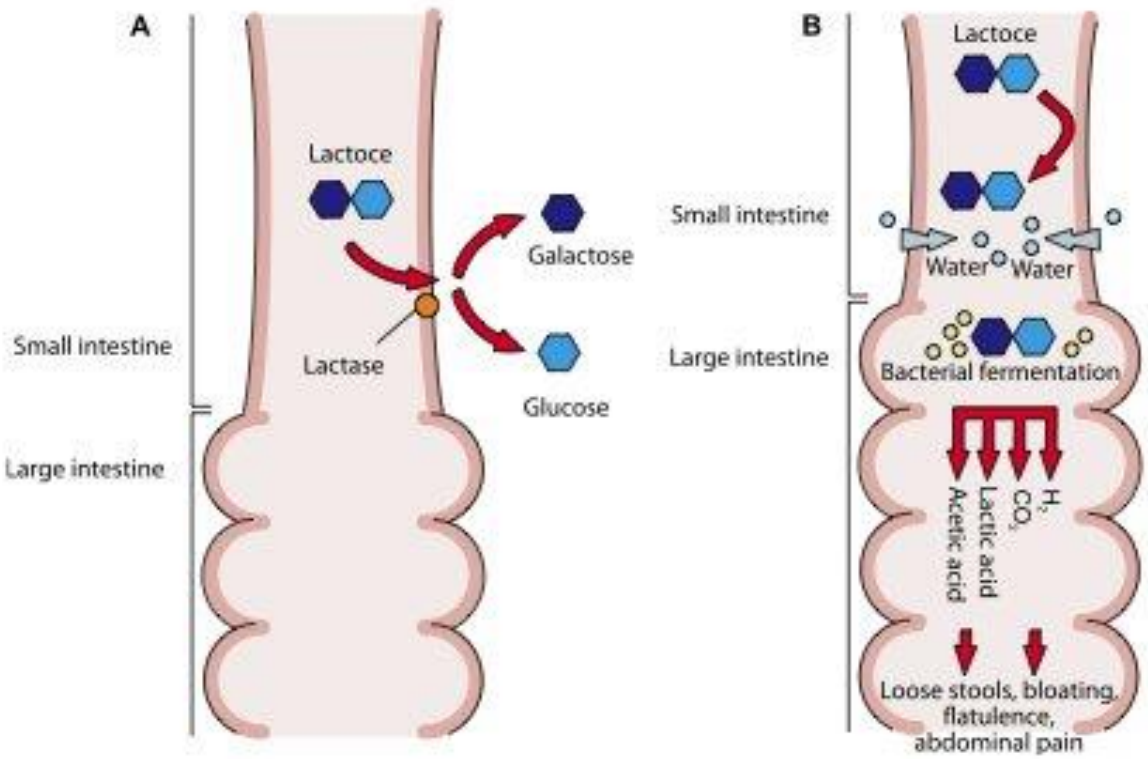
Carbohydrate IEMs (Fructose)

AR

fructokinase
- Asymptomatic
- Fructose in Urine

fructose 1,6-bisphosphate aldolase (HFI)
- poor feeding
- FTT
- Liver/renal insufficiency
- Death

fructose 1,6-bisphosphatase
- Hypoglycemia
- Metabolic acidemia

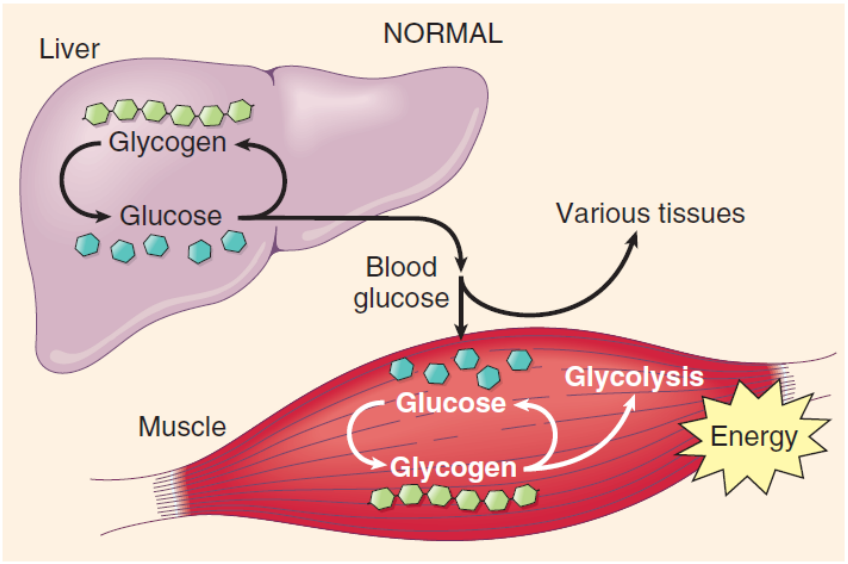


Carbohydrate IEMs (Lactose)

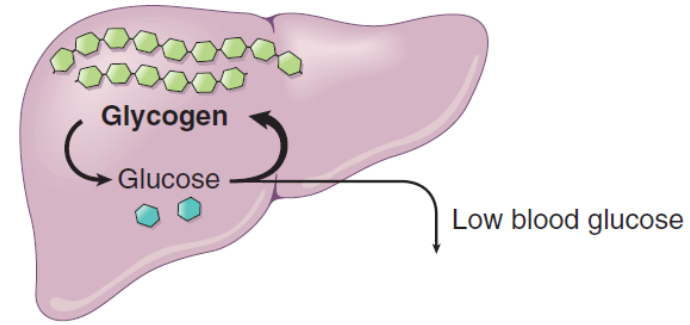
Lactase persistence - AR

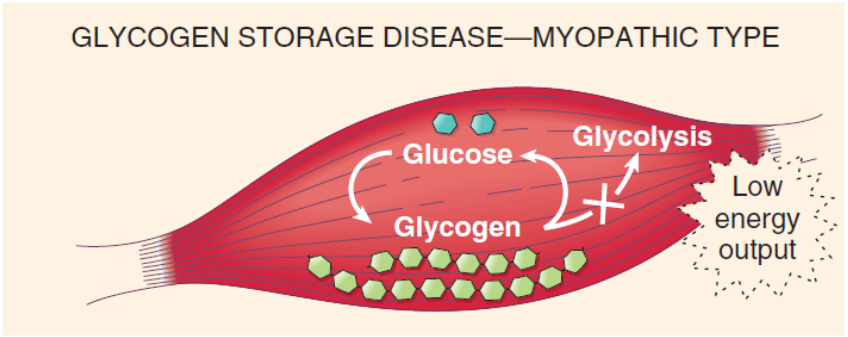
Acquired downregulation after childhood or after enteric viral/bacterial infections

Congenital lactase deficiency - AR rare



GLYCOGEN STORAGE DISEASE—HEPATIC TYPE





Carbohydrate IEMs (Glycogen)

Hepatic:
- Enlargement
- Hypoglycemia

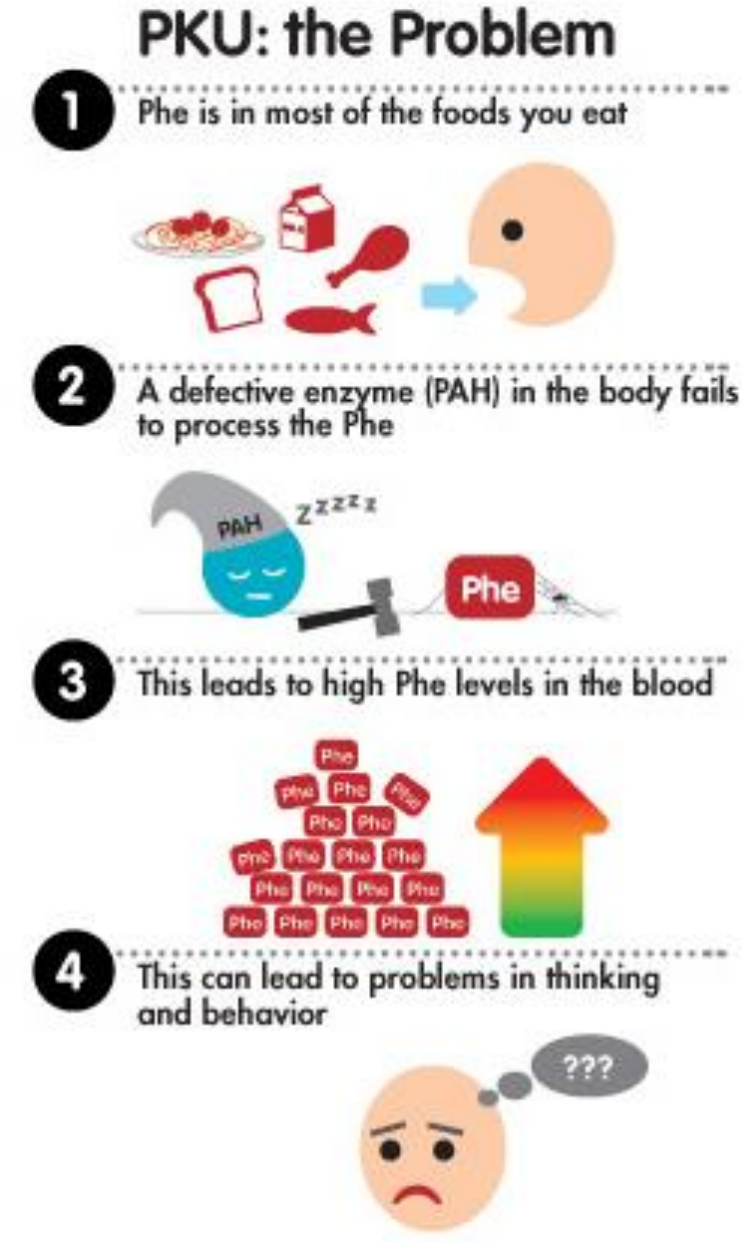
Myopathic type:
- Cramps
- Myoglobinuria
- No lactate production

TYPE	DEFECT	MAJOR AFFECTED TISSUES
Ia (Von Gierke)	Glucose-6-phosphatase	Liver, kidney, intestine
Ib	Microsomal glucose-6-phosphate transport	Liver, kidney, intestine, neutrophils
II (Pompe)	Lysosomal acid β-glucosidase	Muscle, heart
IIIa (Cori)	Glycogen debranching enzyme	Liver, muscle
IIIb	Glycogen debranching enzyme	Liver
IV (Anderson)	Branching enzyme	Liver, muscle
V (McArdle)	Muscle phosphorylase	Muscle
VI (Hers)	Liver phosphorylase	Liver
VII (Tarui)	Muscle phosphofructokinase	Muscle

Carbohydrate IEMs (Glycogen)

Hepatic:
- Enlargement
- Hypoglycemia

Myopathic type:
- Cramps
- Myoglobinuria
- No lactate production



Amino acid IEMs (PHE)

Phenylketonuria - AR

PAH (phenylalanine hydroxylase)

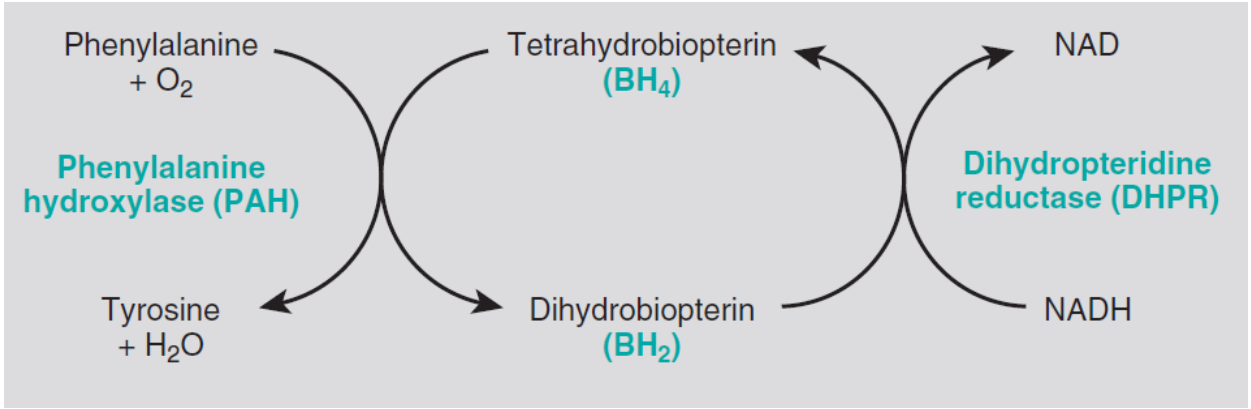
Increased PHE levels

Impaired brain development (mental retardation)

PHE restricted diet (Screening)

Maternal PKU

Sapropterin, a synthetic form of BH4 can boost PHE metabolism



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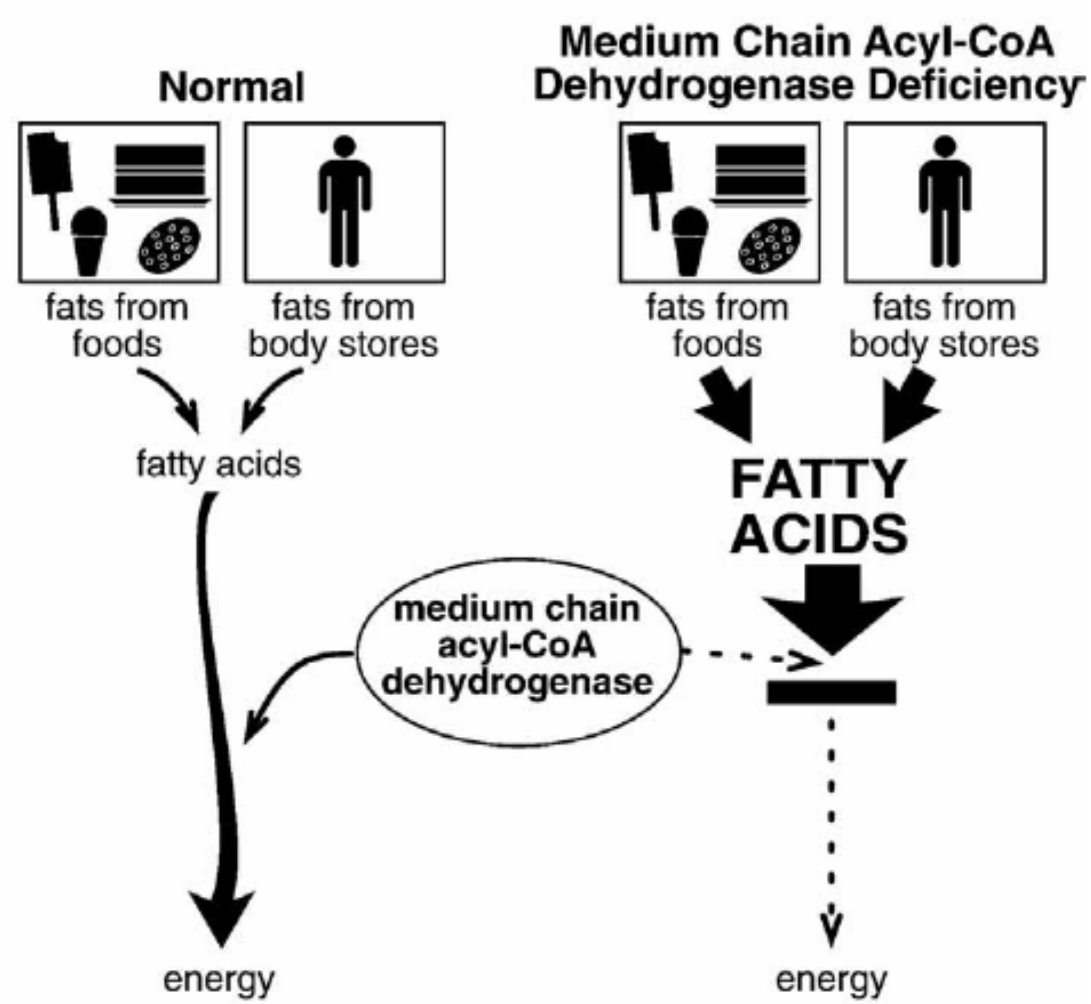


Lipid IEMs
(Fatty acids)

Medium chain

MCAD deficiency

Hypoglycemia provoked by fasting

Difficult to catch but characteristic clinical course should raise suspicion

Avoid fasting, adequate caloric intake, supportive care when required

DDx Reye's syndrome

Lipid IEMs
(Fatty acids)

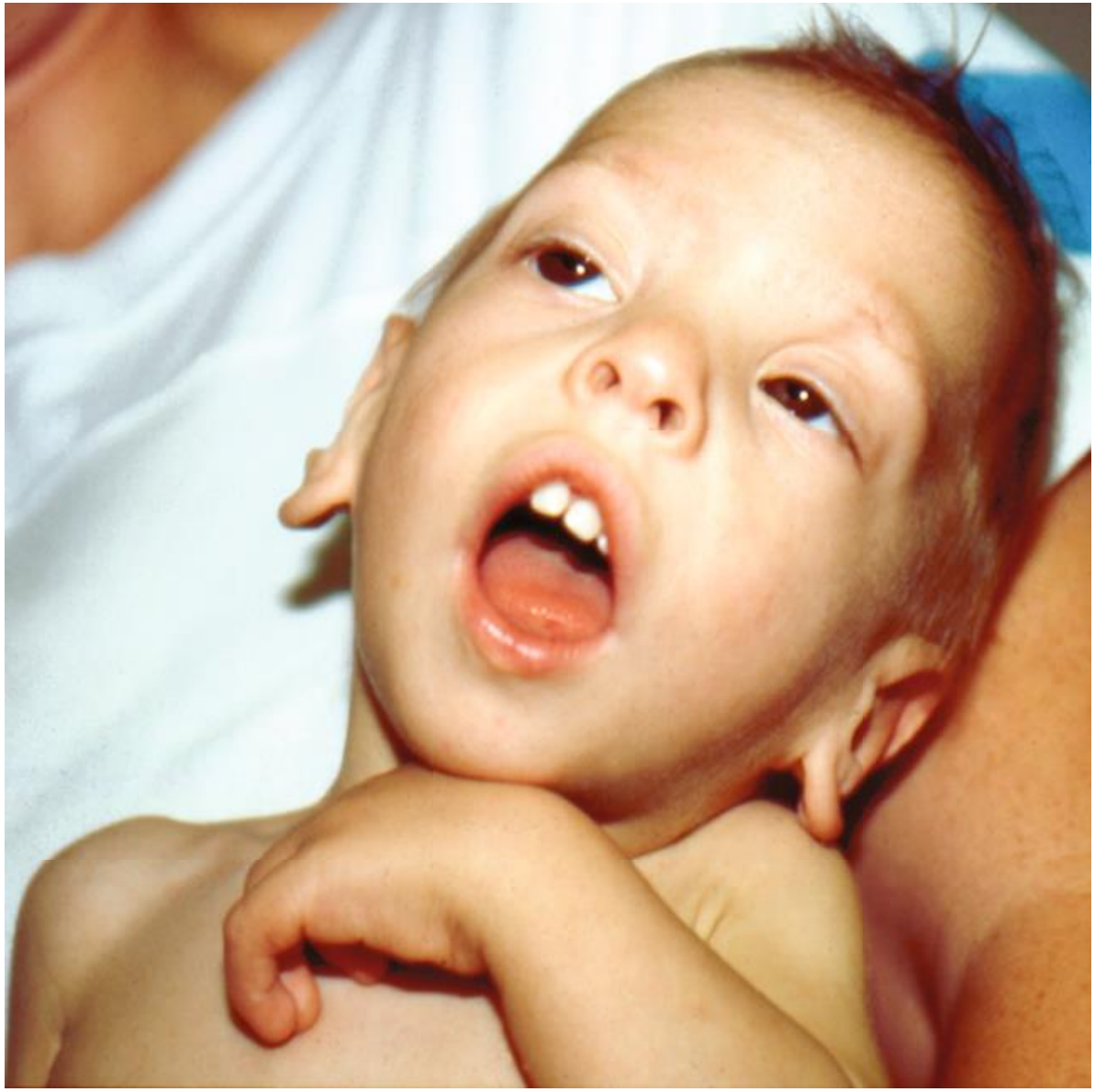
Long chain

LCHAD deficiency

Severe liver disease, cardiomyopathy, skeletal myopathy, retinal disease, peripheral neuropathy, and sudden death

Avoid fasting, low-fat diet, supplementation with medium-chain triglycerides and carnitine

Pregnancy HELLP/AFLP



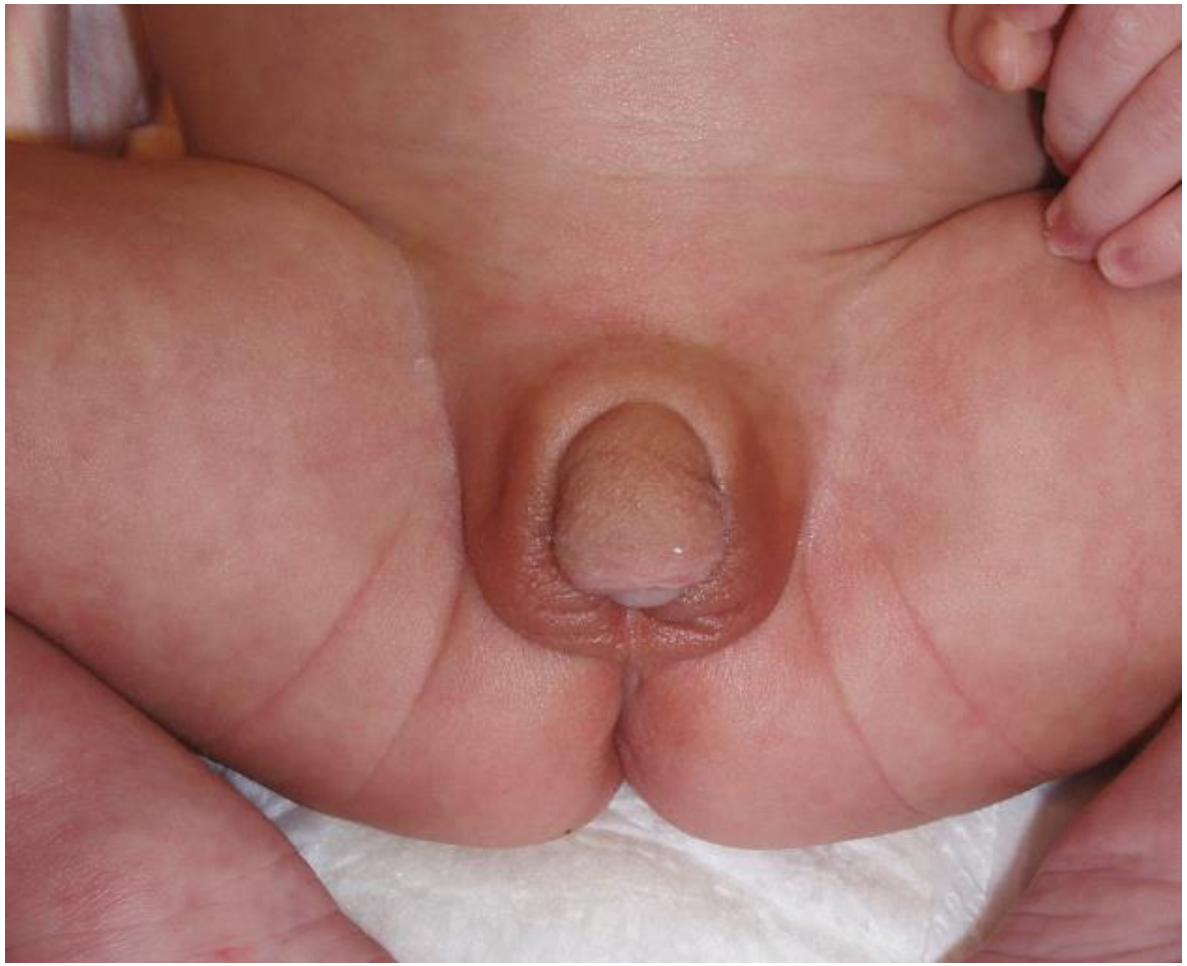
Lipid IEMs
(Cholesterol)

Smith–Lemli–Opitz syndrome

DHCR7 deficiency

Congenital anomalies of the brain, heart, genitalia, and hands

Cholesterol supplementation?



Lipid IEMs
(Steroid hormones)

Congenital adrenal hyperplasia

Heterogeneous AR disorders of cortisol biosynthesis

- cortisol deficiency
- variable aldosterone deficiency
- excess androgens

Tx: replace cortisol, supress androgens, mineralocoricoids, surgery?

the female body
by Melllorine

Steroid hormone receptor mutations

CAIS/PAIS (XLR)

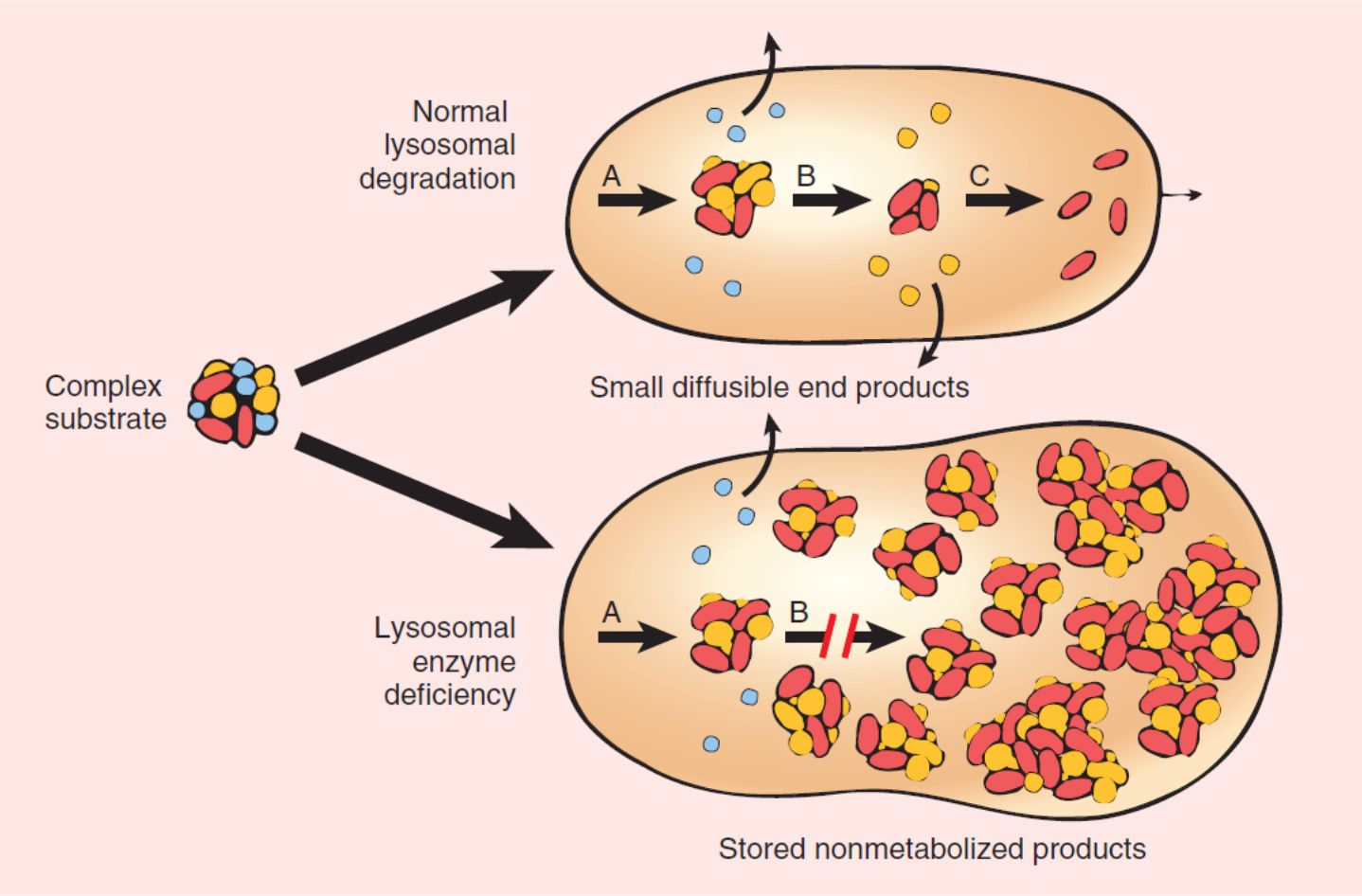
Genetically 46,XY

Mutations in the X-linked androgen receptor

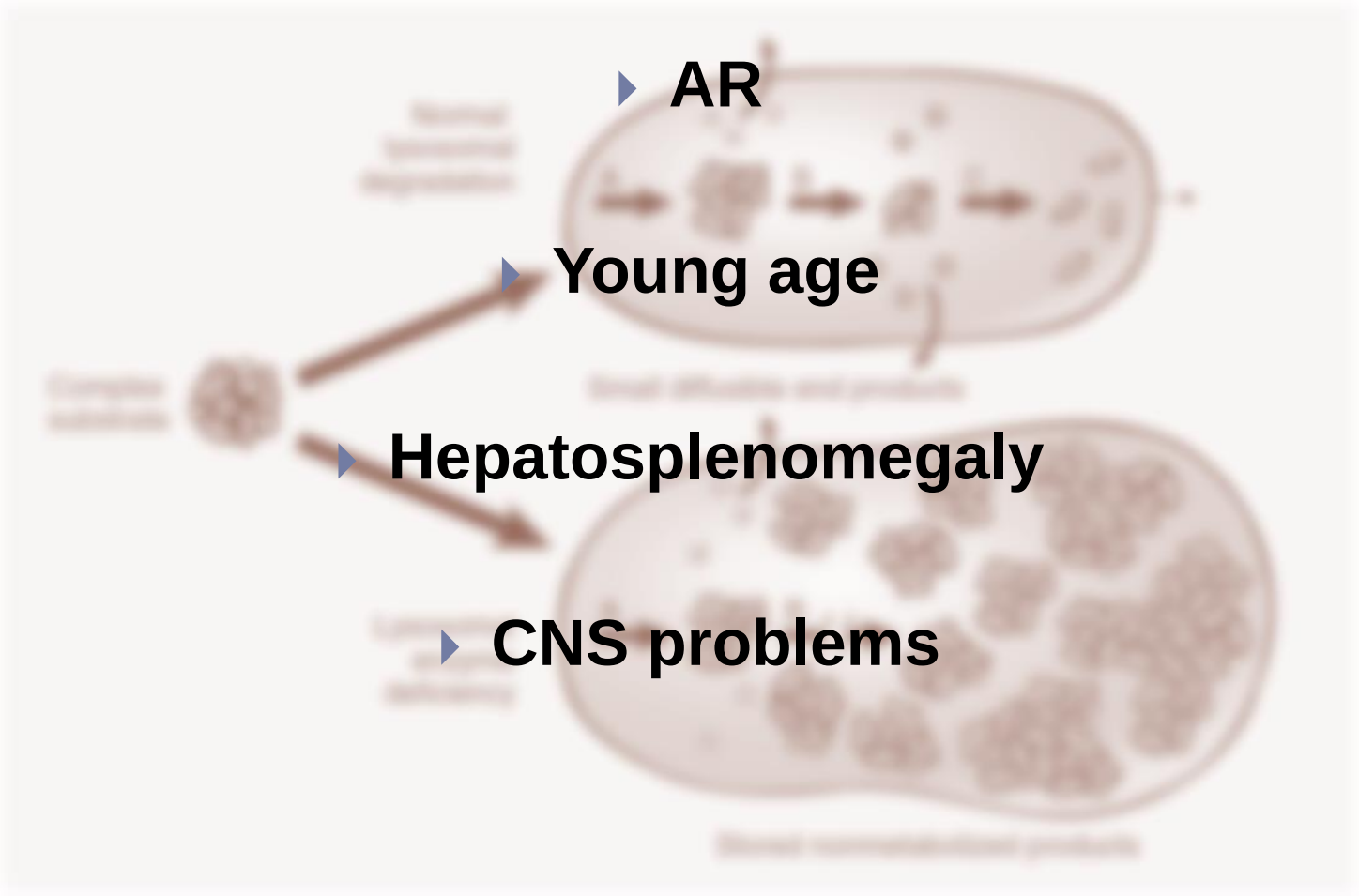
Complete: typical external female characteristics but absence of mullerian development

Partial: ambiguous genitalia

Lysosomal Storage Diseases

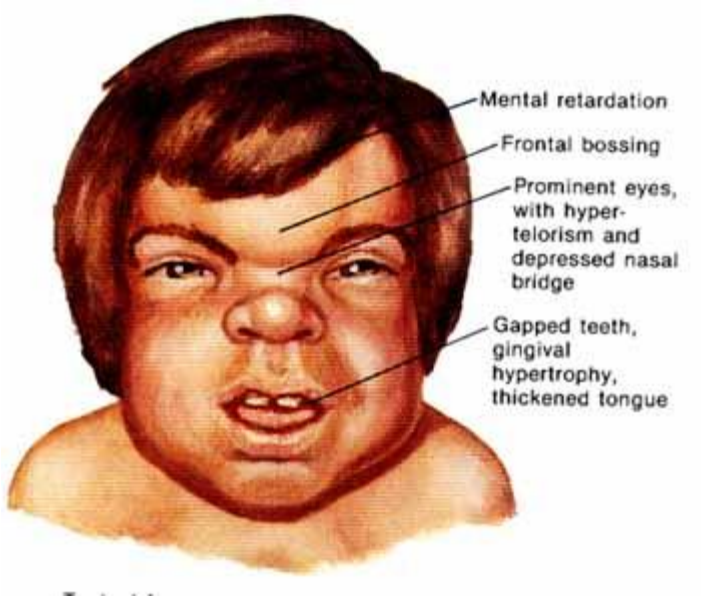


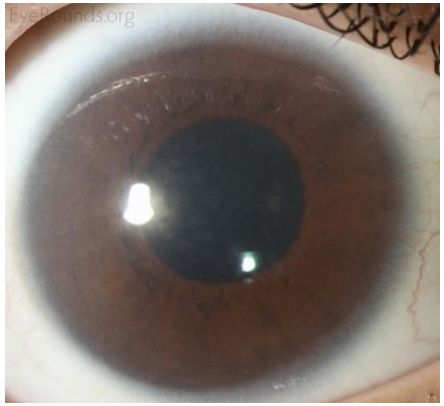
Lysosomal Storage Diseases



- AR
- Young age
- Hepatosplenomegaly
- CNS problems

Type I: Hurler Syndrome





AR
Mental Retardation
6-10 year life expectancy
Death often due to cardiac complications

Mucopolysaccharidoses

Defective degradation (and therefore excessive storage) of mucopolysaccharides

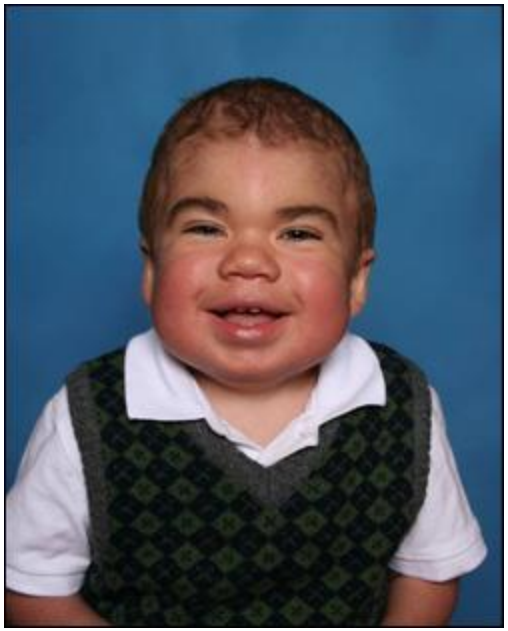
Several catabolic enzymes in the pathway

MPS types I-VII

Common findings:

- Hepatosplenomegaly
- Skeletal deformities
- Lesions of heart valves
- Subendothelial arterial deposits
- Brain lesions

Type II: Hunter Syndrome



X-Linked recessive
No corneal clouding
Milder clinical course

Mucopolysaccharidoses

Defective degradation (and therefore excessive storage) of mucopolysaccharides

Several catabolic enzymes in the pathway

MPS types I-VII

Common findings:

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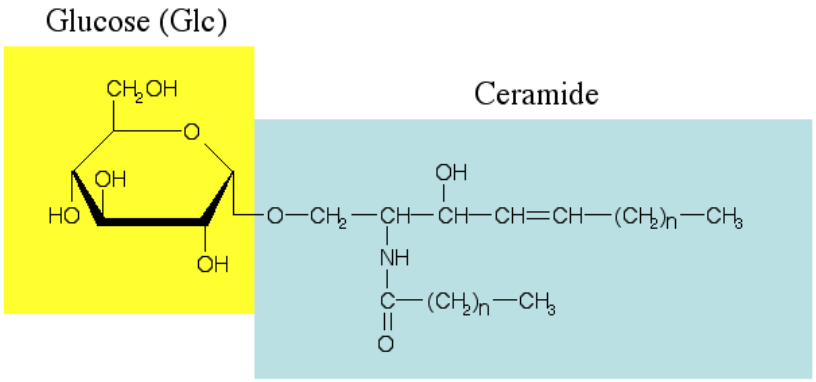
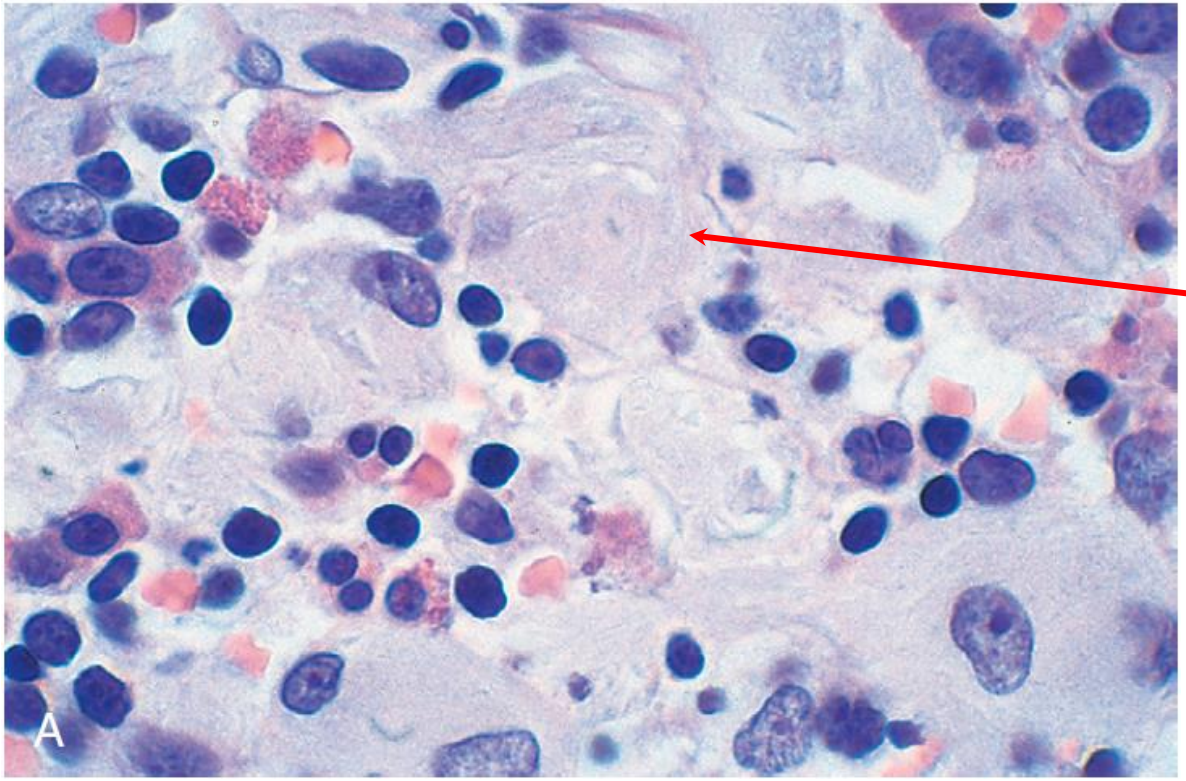


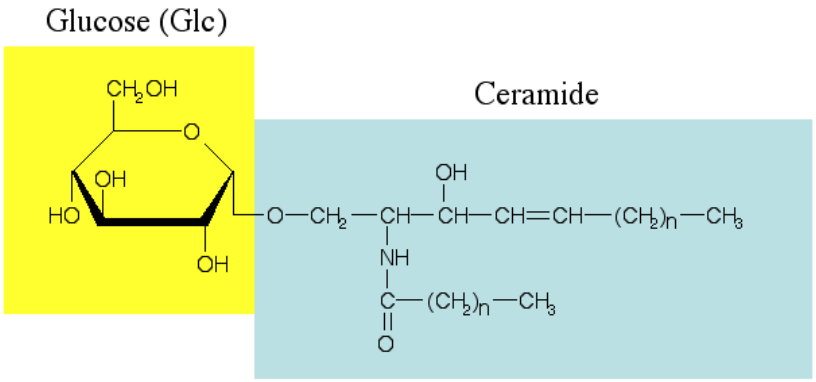


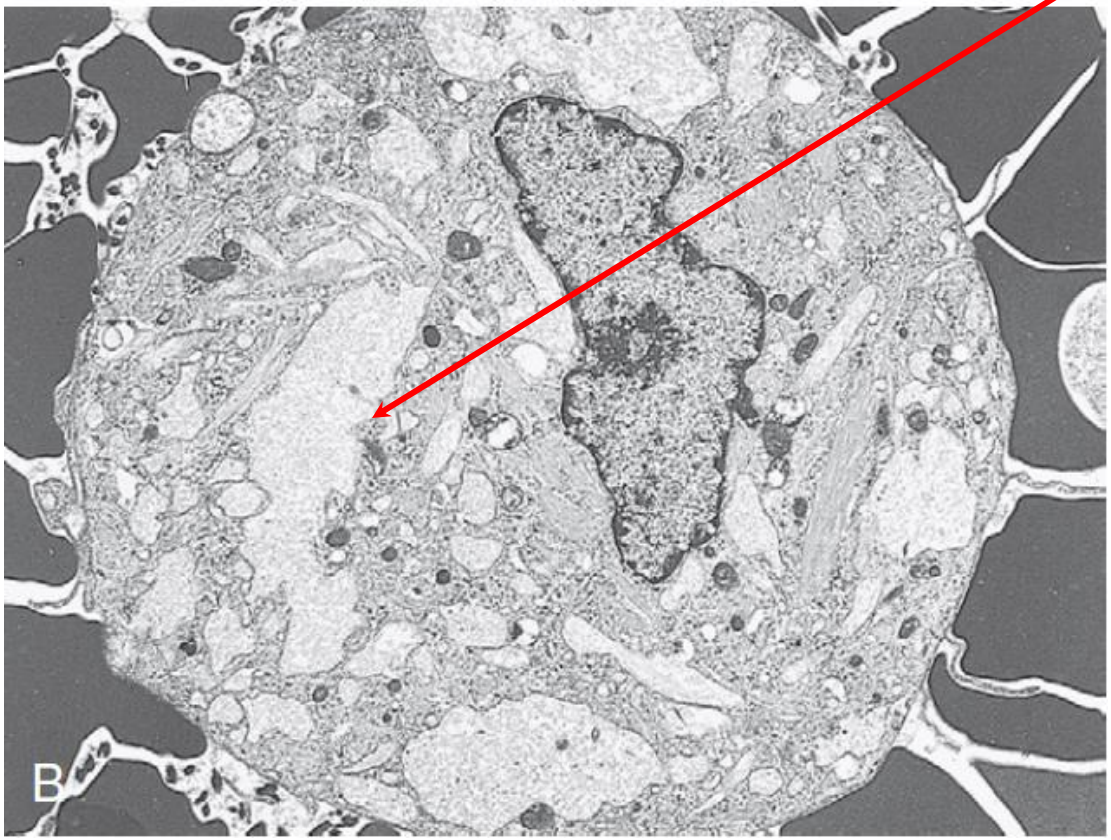
Sphingolipidoses (Gaucher Disease)

Glucocerebrosidase mutation

Accumulation of glucocerebroside in phagocytes (Gaucher cells)

“Wrinkled tissue paper” (pathognomonic)

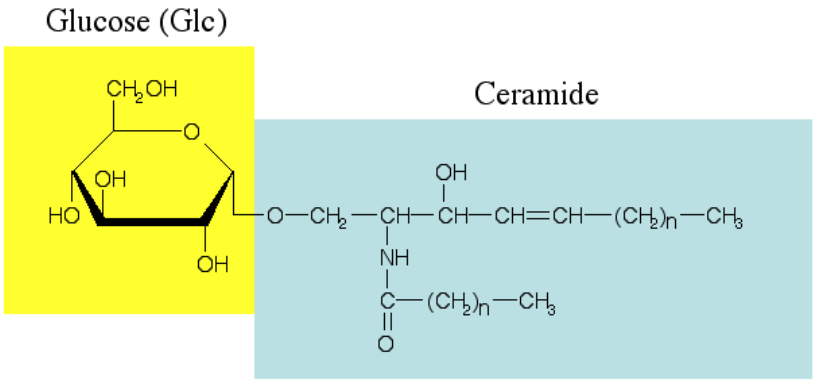


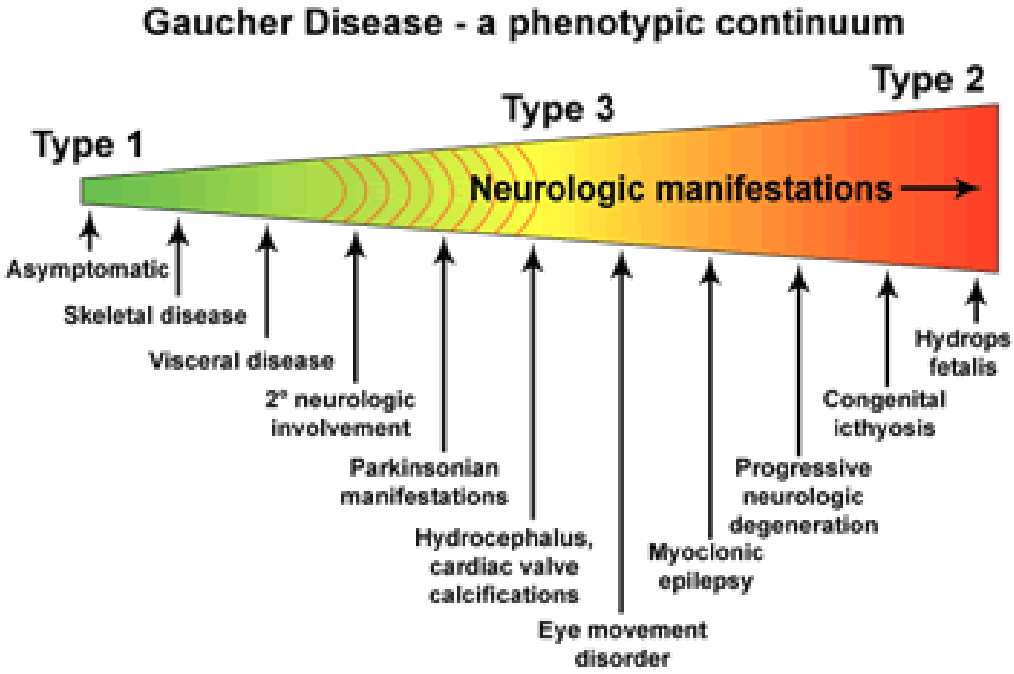


Sphingolipidoses (Gaucher Disease)

Distended elongated lysosomes

Macrophage activation (IL1, IL6, TNF), and accumulation in liver, spleen, LN, BM.





Patients with Gaucher disease can have a spectrum of symptoms, ranging from mild to severe neurological effects. The classic categories of types 1, 2 and 3 have blurry edges along this continuum.

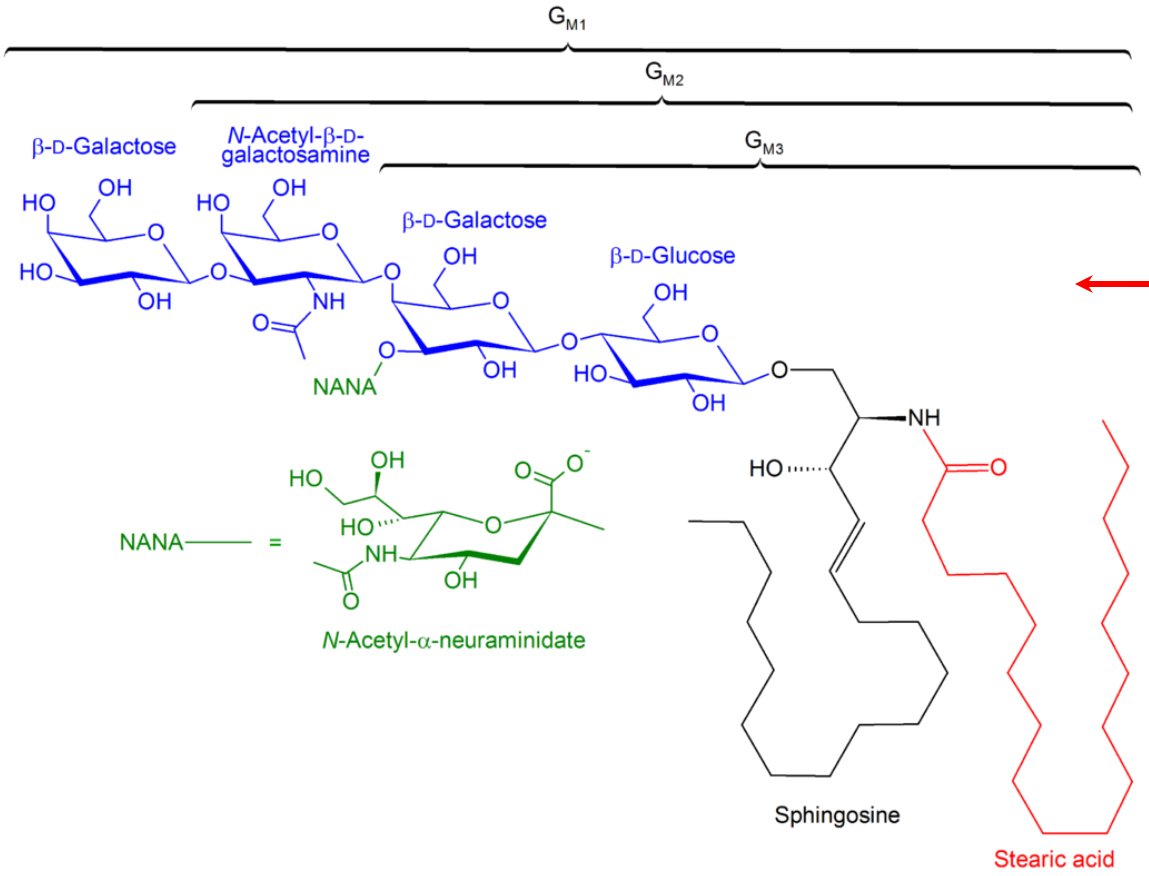
Sphingolipidoses (Gaucher Disease)

Macrophage activation (IL1, IL6, TNF), and accumulation in liver, spleen, LN, BM.

Clinical findings:
- Bone involvement
- ↓ blood elements
- Hepatosplenomegaly
- CNS involvement

Treatment:
- Enzyme replacement
- Inhibition of synthesis
- BMT

Sphingolipidoses (Tay-Sachs Disease)

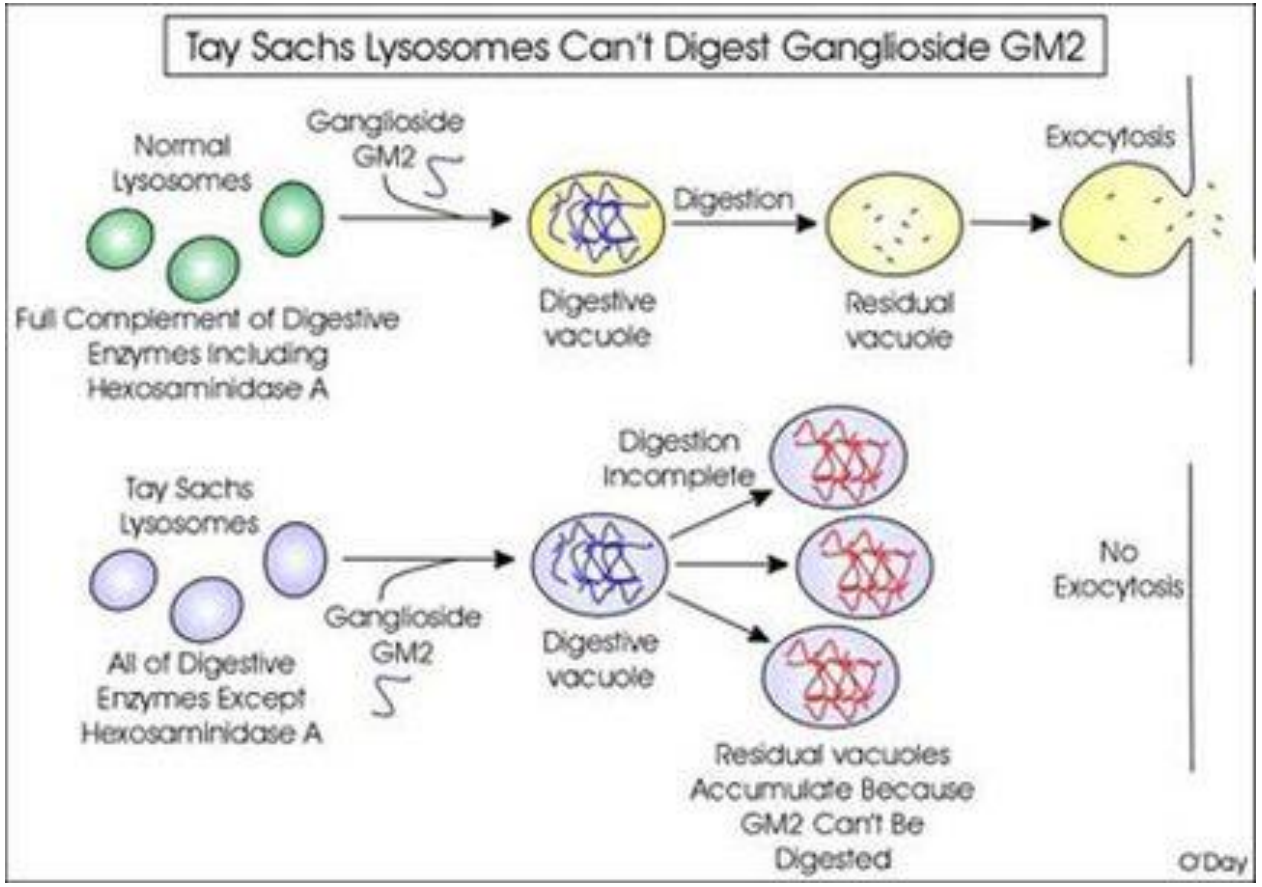


AR

Gangliosidoses

Ganglioside
- cell surface
- nervous system
- cell-cell communication
- immunity

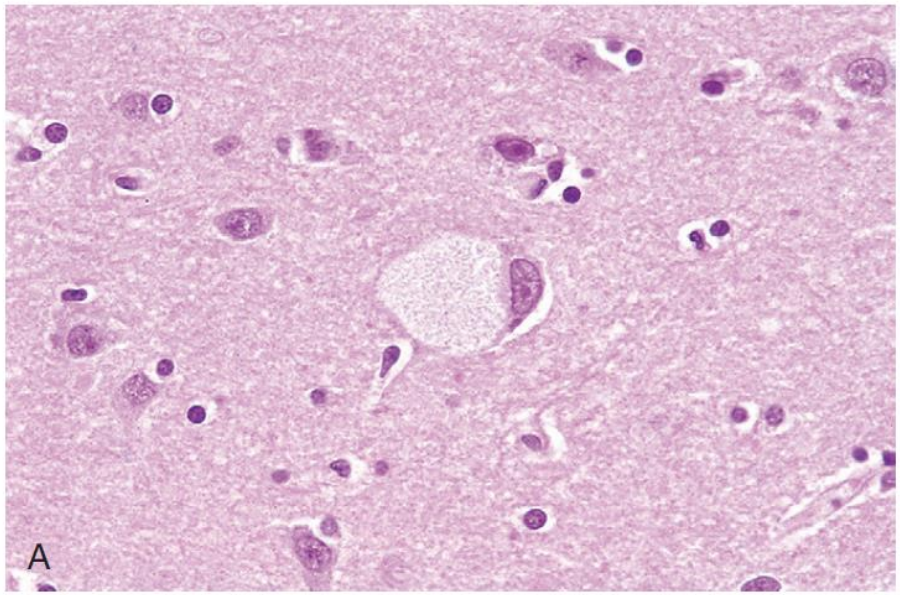
Sphingolipidoses (Tay-Sachs Disease)

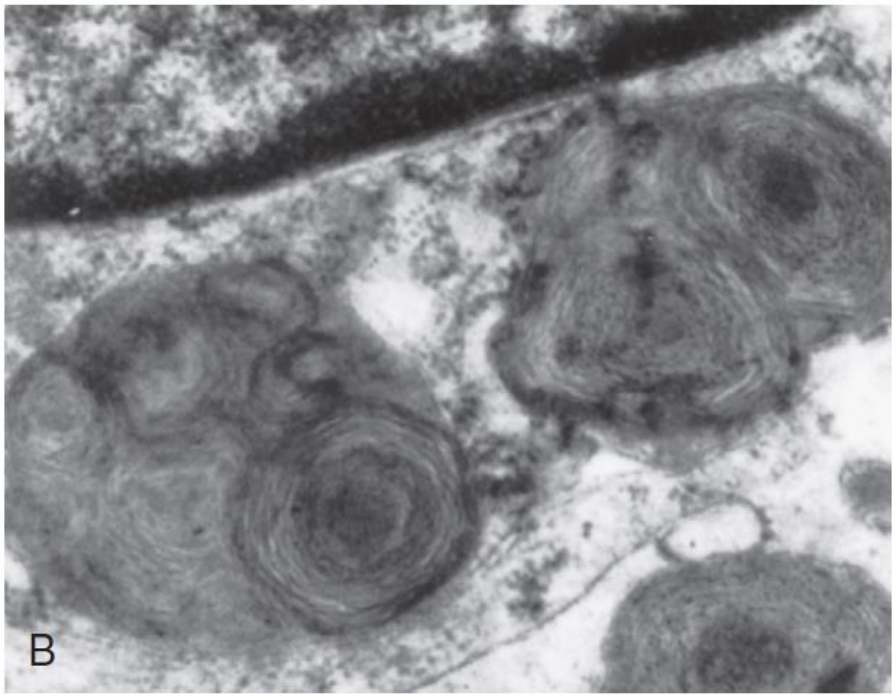


>100 mutations identified, mostly affecting protein folding

β subunit of hexosaminidase A

Brain is mostly affected





Sphingolipidoses (Tay-Sachs Disease)

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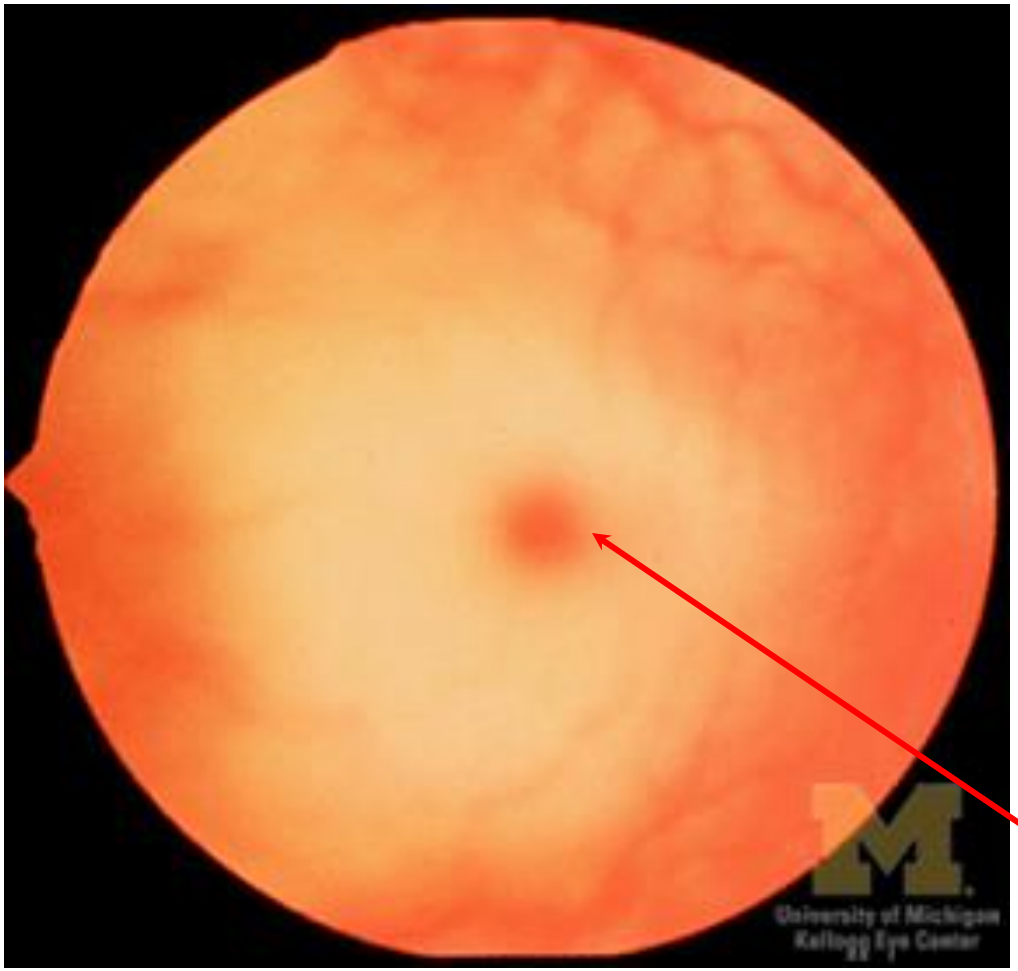
β subunit of hexosaminidase A

Brain is mostly affected

Pathological changes found throughout the CNS, peripheral nerves, and autonomic nervous system



Sphingolipidoses (Tay-Sachs Disease)

>100 mutations identified, mostly affecting protein folding

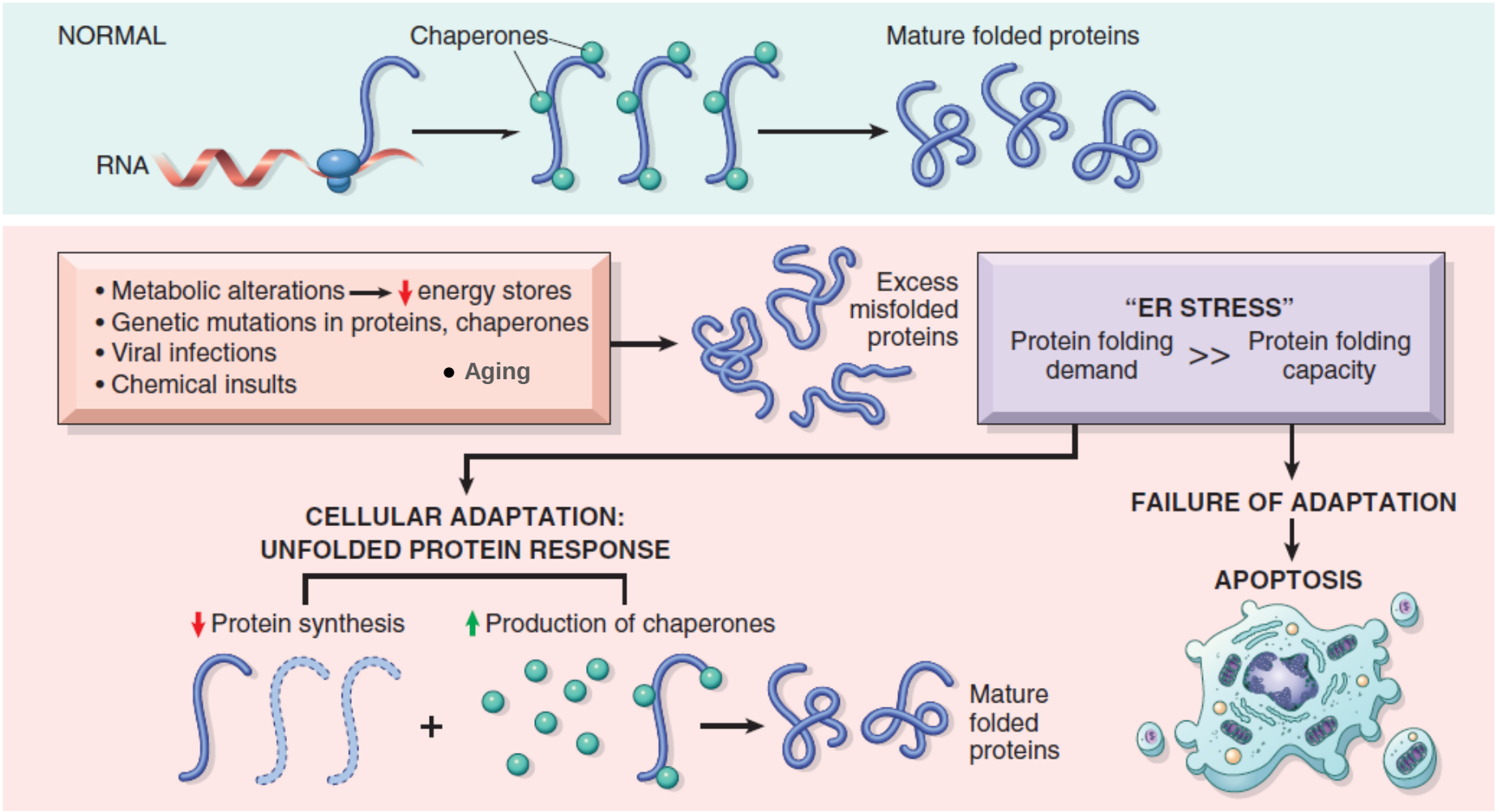
β subunit of hexosaminidase A

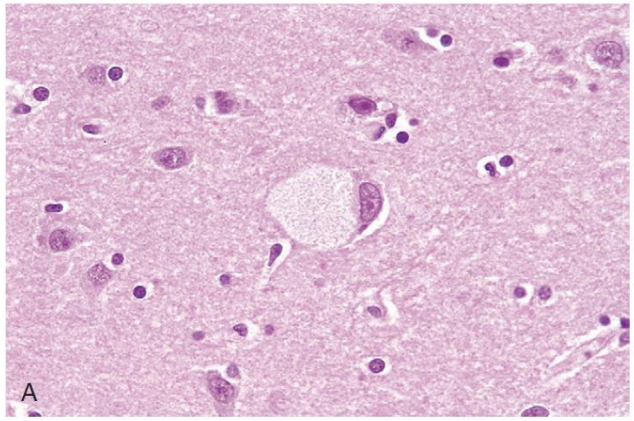
Brain is mostly affected

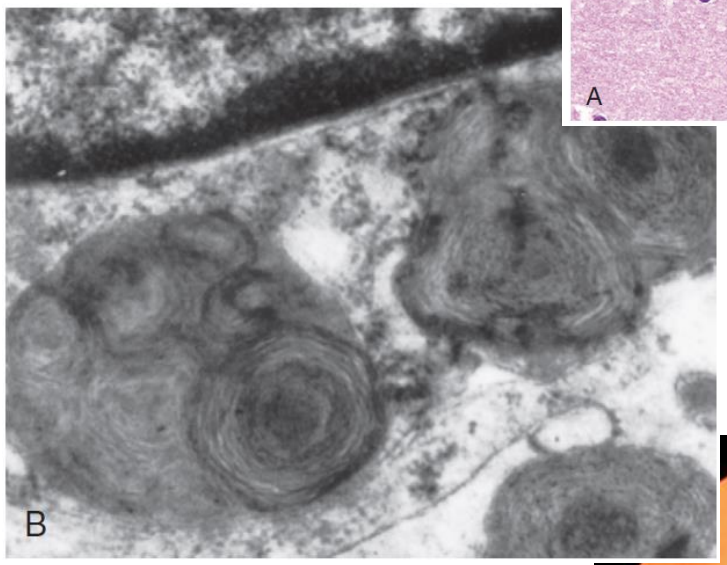
Pathological changes found throughout the CNS, peripheral nerves, and autonomic nervous system

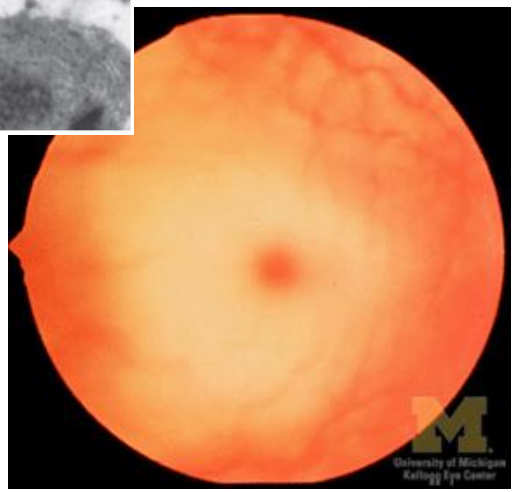
“Cherry red” spot, retina

Misfolded proteins
ER Stress









Sphingolipidoses (Tay-Sachs Disease)

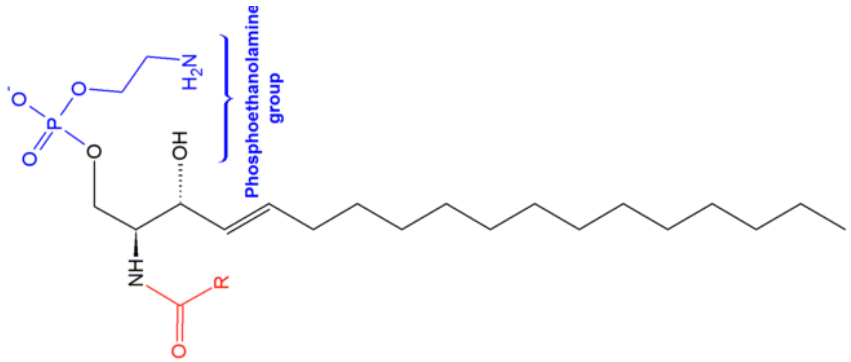
Multiple variants/presentations

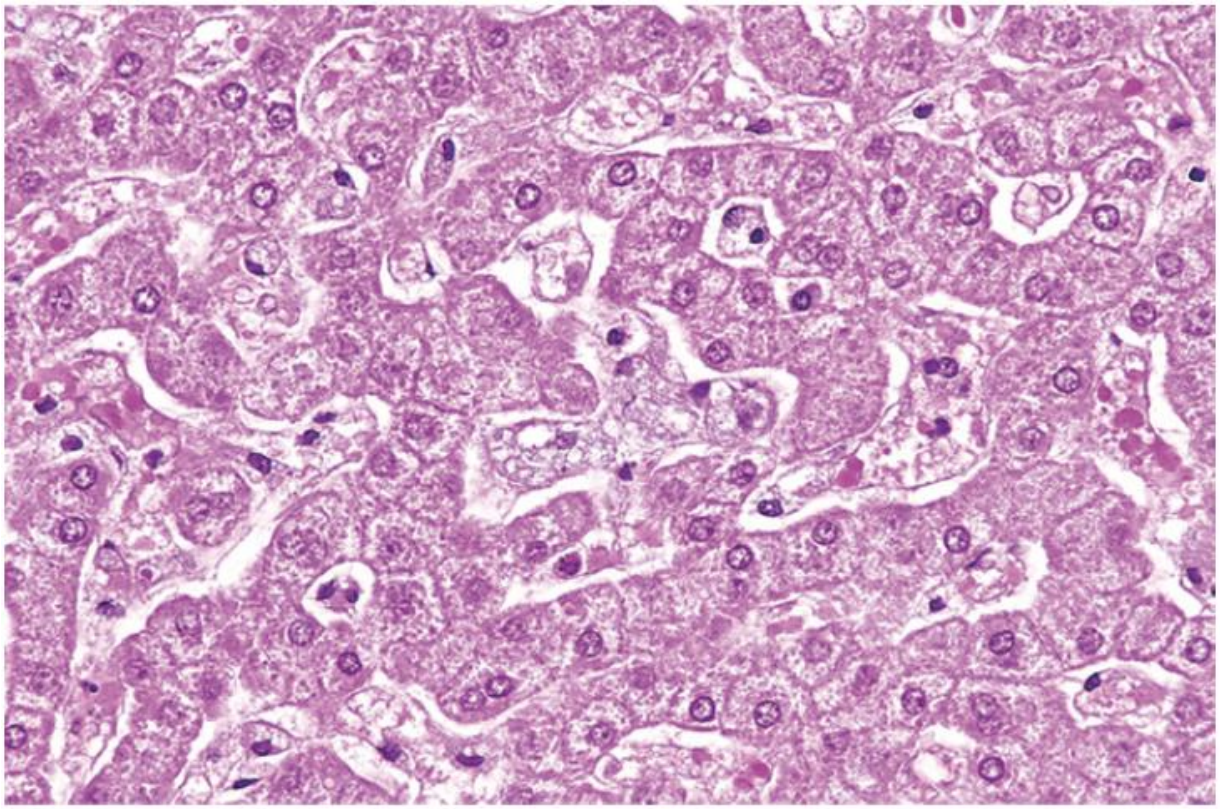
Normal at birth

Motor weakness @ 3-6 months

Blindness

Death within 2-3 years



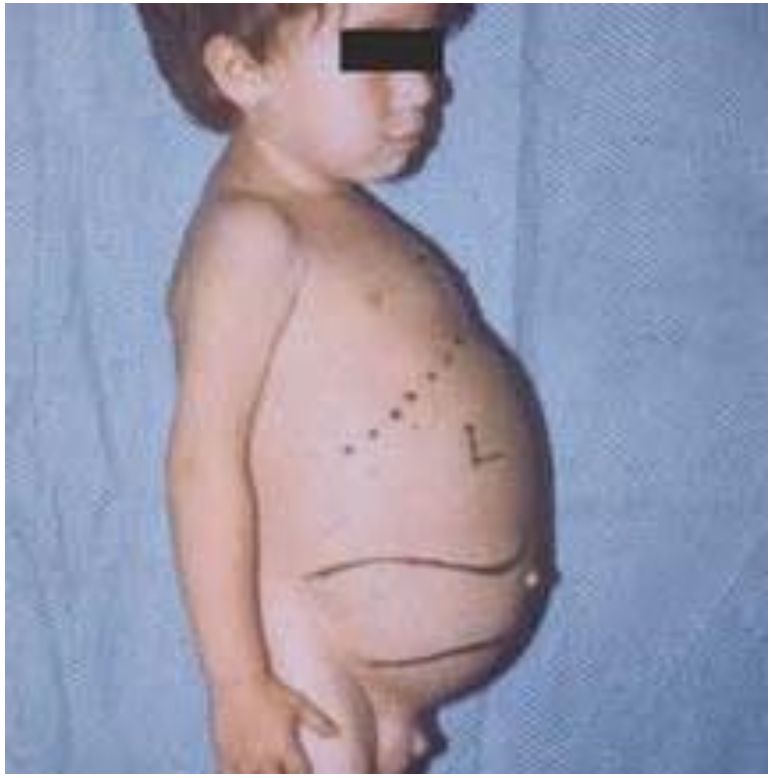


Sphingolipidoses (Niemann-Pick Disease Types A & B)

Deficiency of acid sphingomyelinase

Accumulation of sphingomyelin

- Phagocytes (spleen, liver BM, LN, lungs)
- Neurons

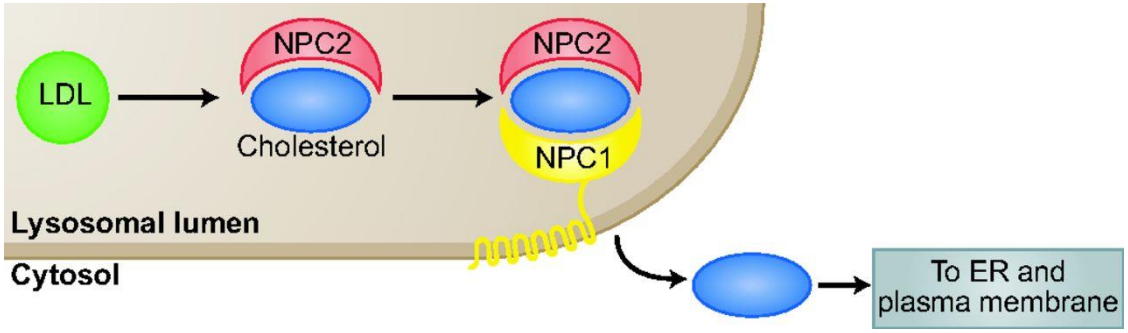


Sphingolipidoses (Niemann-Pick Disease Types A & B)

Type A

Severe deficiency:
- Massive visceromegaly
- Severe neurologic deterioration
- Death by 3yrs

Type B
- Less severe
- Organomegaly
- No neurologic manifestations



(Niemann-Pick Disease Type C)

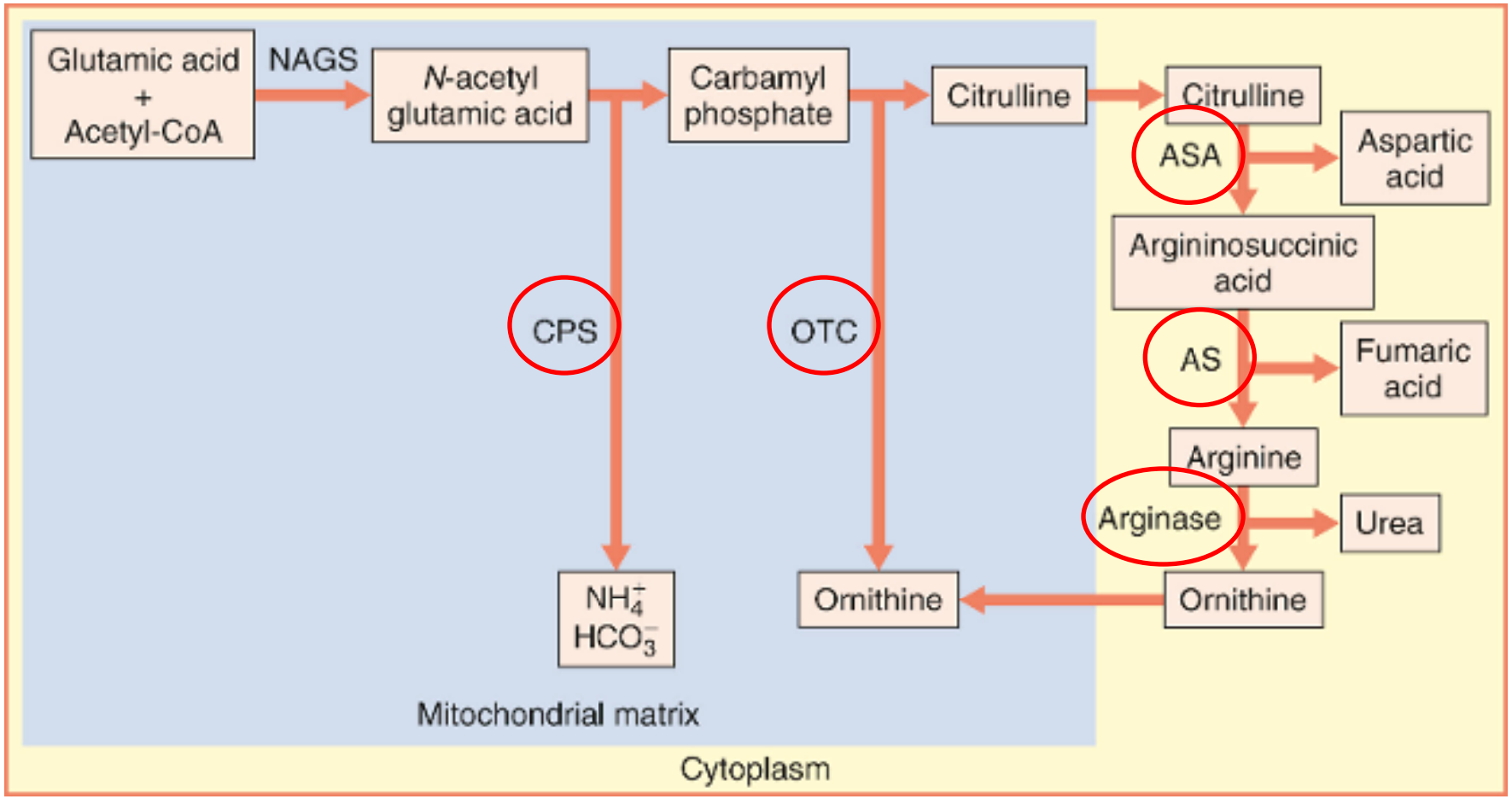
Mutations in *NPC1, NPC2*

Lipid transport problems

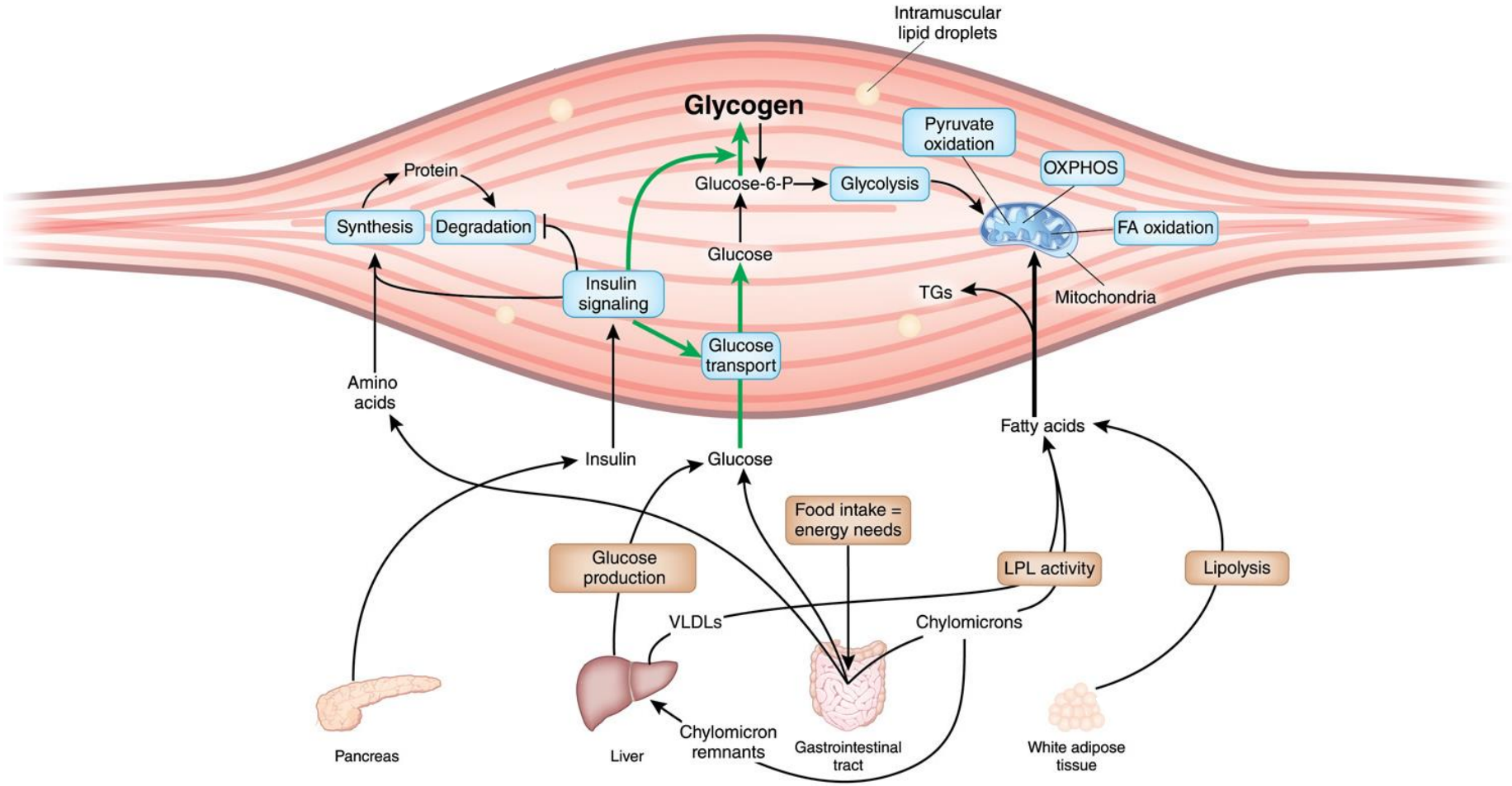
Accumulation of cholesterol as well as gangliosides

Clinically heterogeneous
- Childhood presentation
- Ataxia
- Gaze palsy
- Dystonia
- Dysarthria
- Psychomotor regression

Urea Cycle Disorders



Energy production defects



Transport system abnormalities

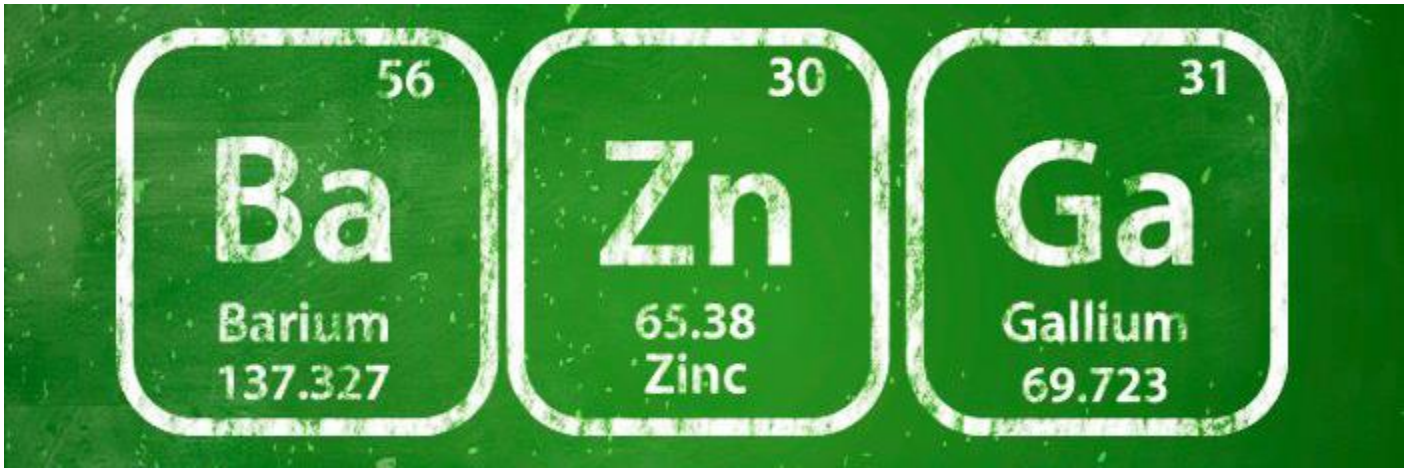
Cystinuria

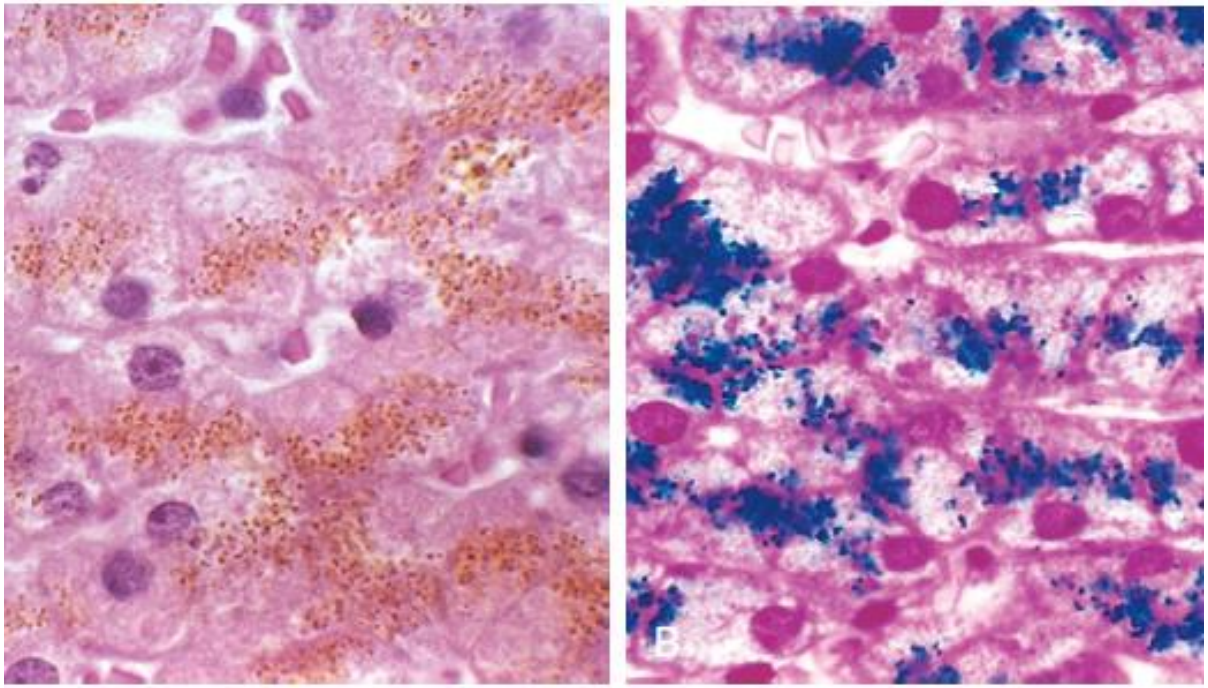
- Between cell and ECM
- Highly insoluble causing renal stones and their complications
- Tx: increase solubility (4-6L/day water), alkalinizing urine

Cystinosis

- Between lysosome and cytoplasm
- Corneal crystals, rickets, renal damage followed by later complications of DM, pancreatic insufficiency, hypogonadism, myopathy, and blindness.
- Tx: Renal transplant, cysteamine

Transport system abnormalities (Heavy metals)





Fe

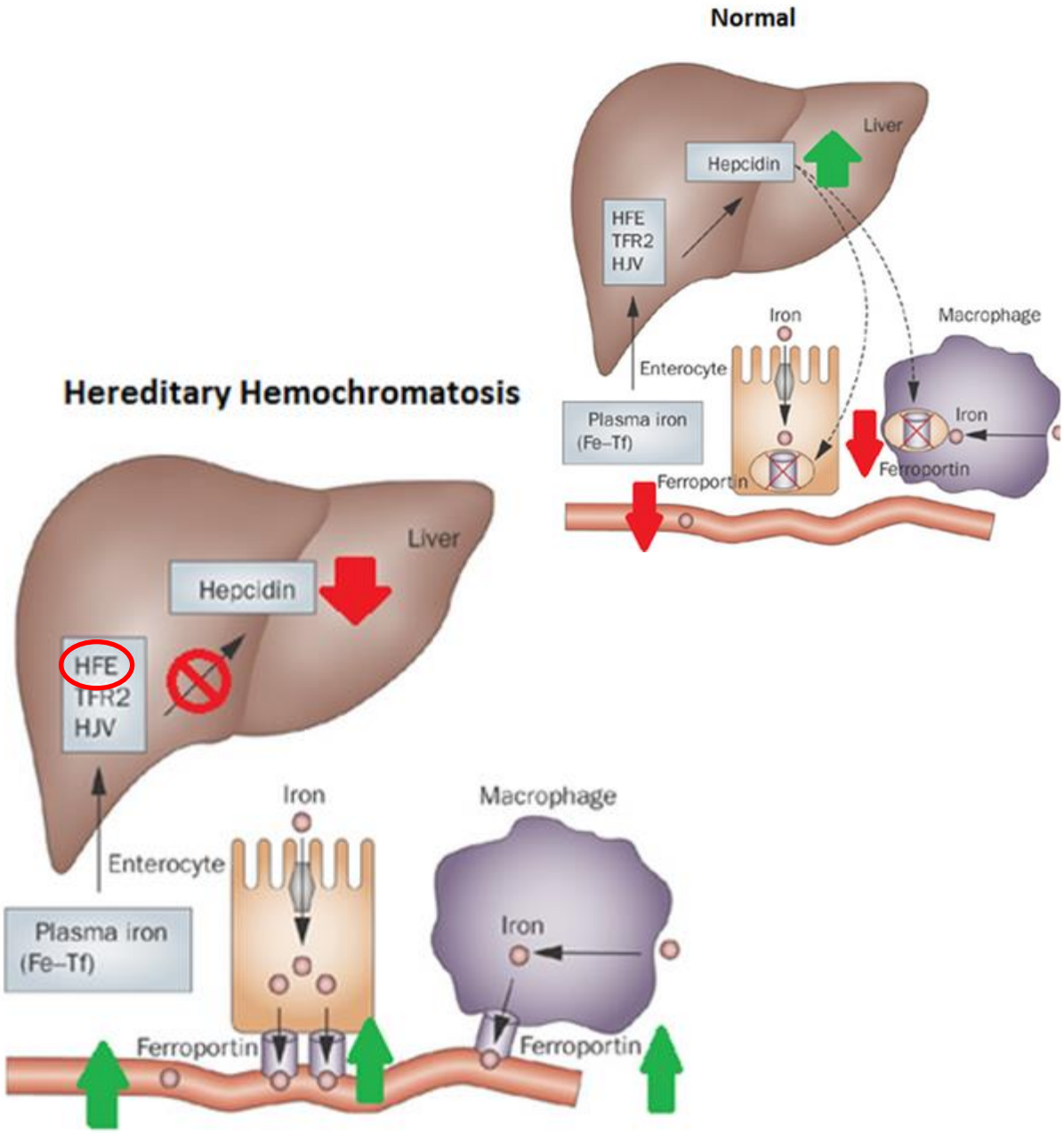
Hereditary Hemochromatosis

Most common form is AR

Incomplete penetrance

S&S: Fatigue, joint pain, diminished libido, diabetes, darkened skin, cardiomyopathy, liver enlargement, & cirrhosis

Lab: Abnormal serum iron
Histochemical staining for hemosiderin



Fe

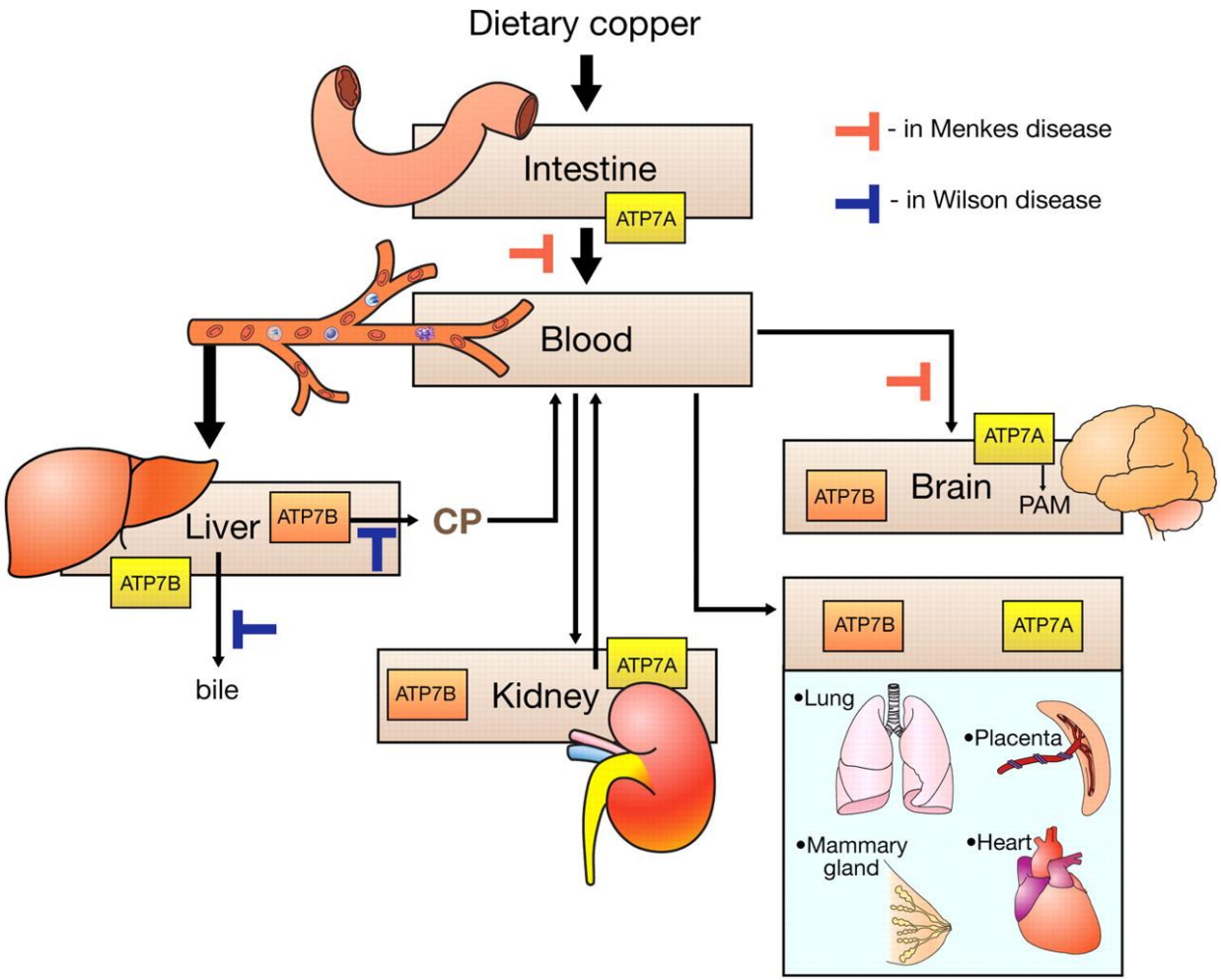
Hereditary Hemochromatosis

Most common form is AR

Incomplete penetrance

HFE mutation impairs cells ability to sense iron leading to increased uptake from intestine

Tx: Serial phlebotomy or chelation (deferoxamine)



Cu

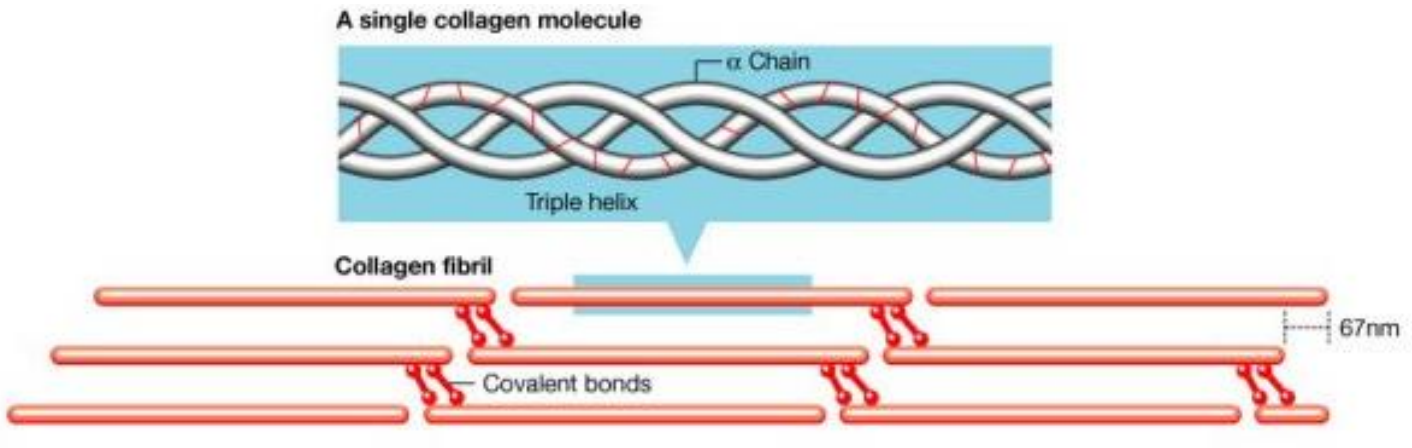
Menkes disease

X-linked recessive, impaired absorption

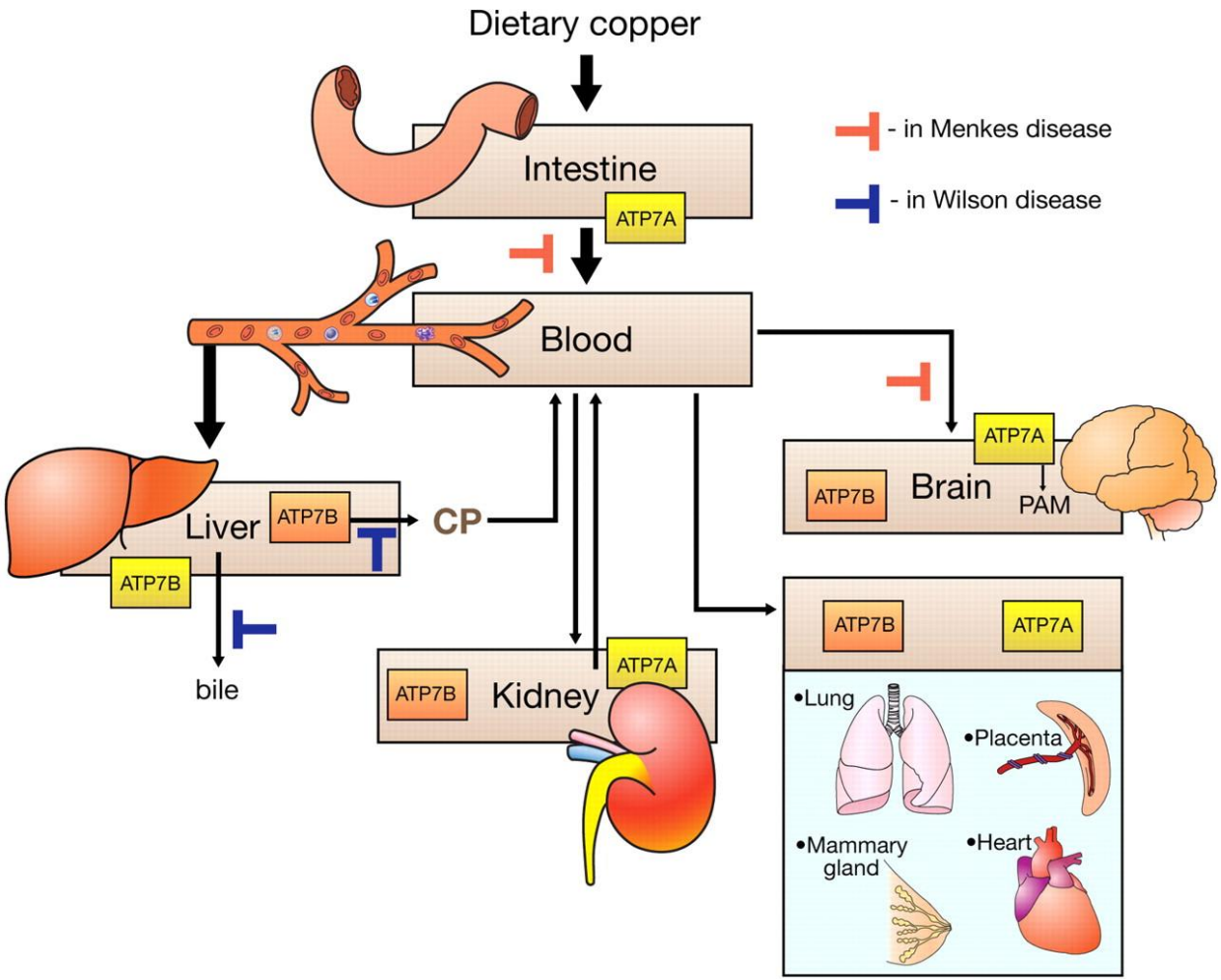
S&S: Intellectual disability, seizures, pili torti, loose skin, arterial rupture, early childhood death

Tx: Restore copper levels (subcutaneous injections)

Collagen (fibrillar)



- types I, II, III, and V
- major proportion of the connective tissue in healing/scarring
- Lateral cross-linking of the triple helices catalyzed by lysyl-oxidase (Copper dependent)/lysyl-hydroxylase (Vit C dependent)



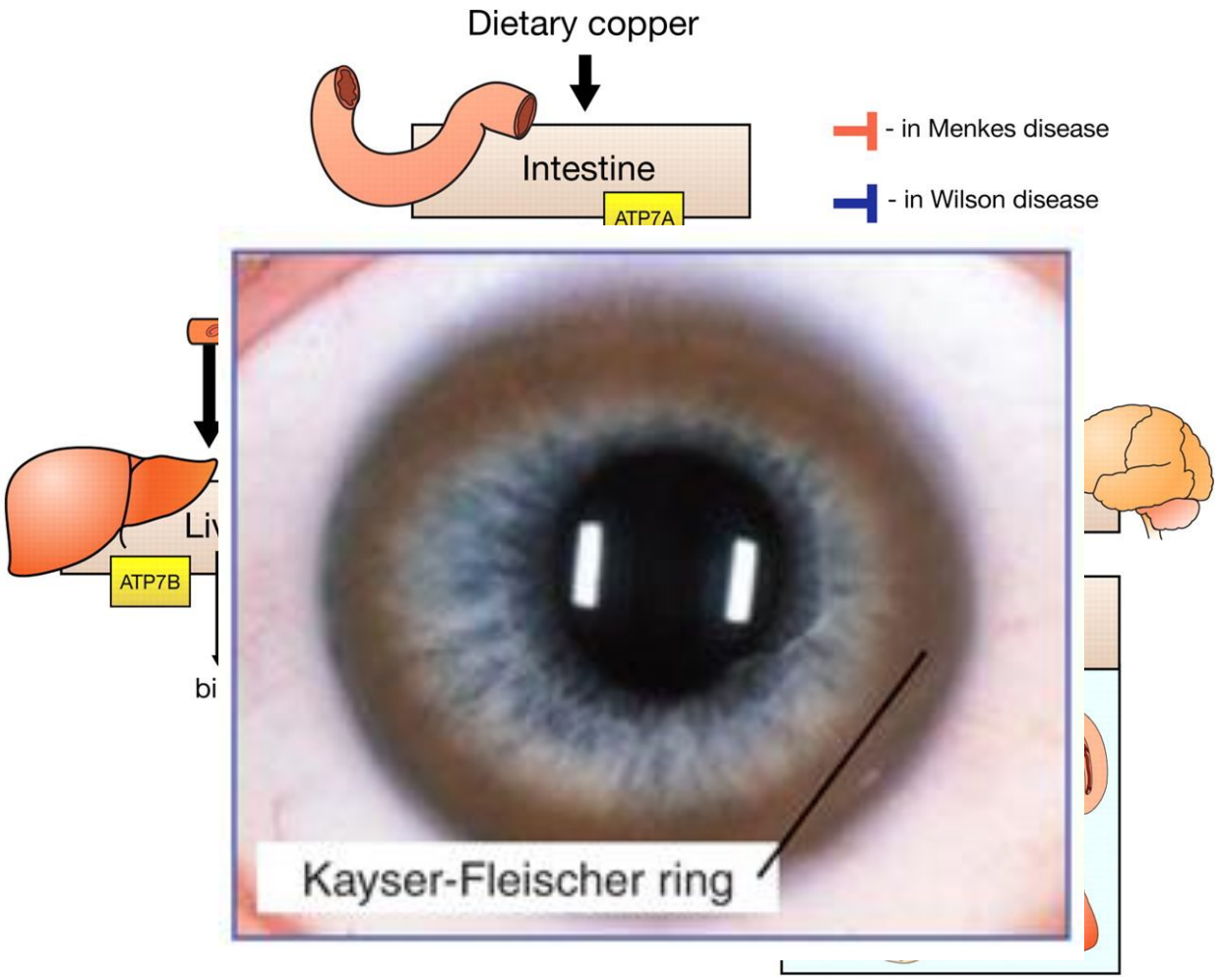
Cu

Wilson disease

AR, impaired excretion

S&S: progressive liver disease, dysarthria and diminished coordination, arthropathy, cardiomyopathy, kidney damage, and hypoparathyroidism

Tx: Reduce copper levels (chelating agents: penicillamine and trientine. Zinc salts for maintenance)



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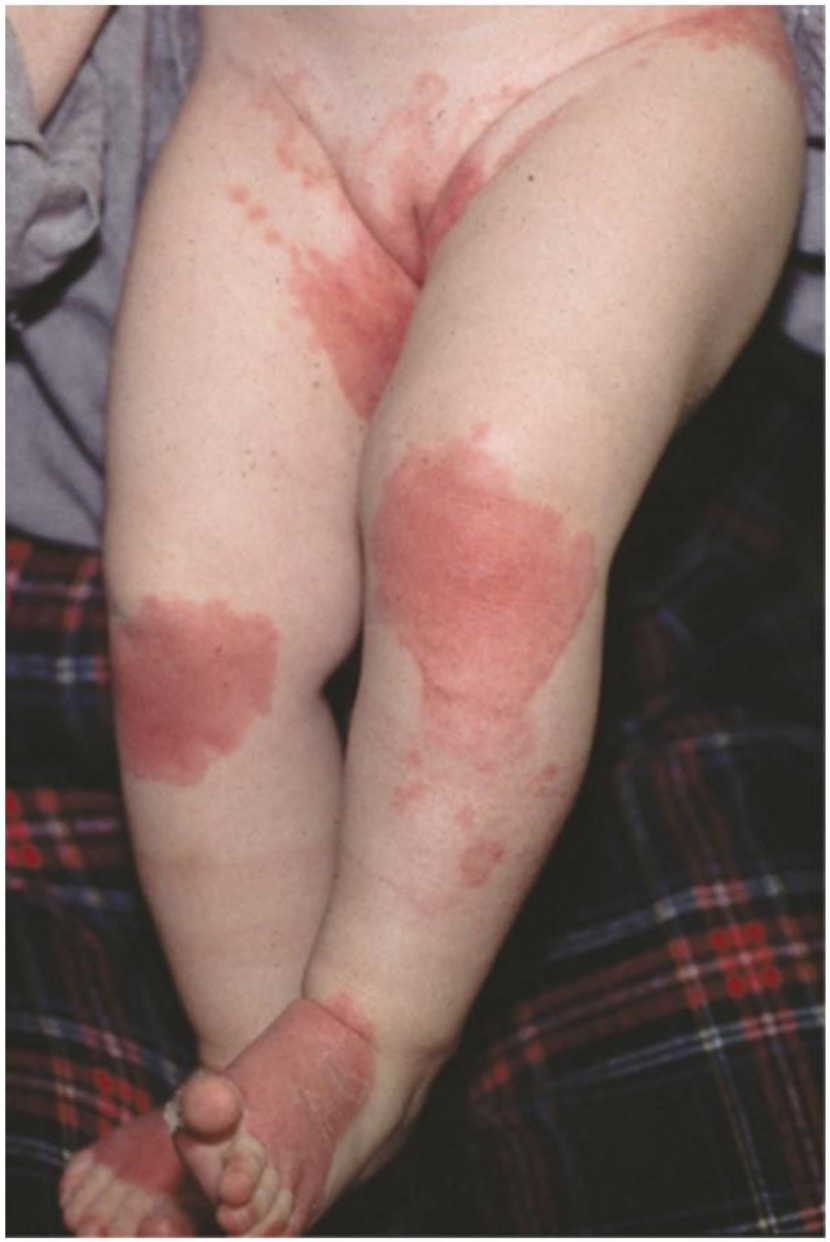

Zn

Acrodermatitis enteropathica

AR, defect in Zn intestinal absorption

S&S: growth retardation, diarrhea, immune dysfunction, and severe dermatitis

Tx: High doses of Zn