Genetic diseases

- **chromosomal disorders** (aneuploidy)

- **monogenic diseases** (mendelian transmission)

- **mitochondrial inherited diseases**
(female lineage transmission)

HOWEVER: interaction gene-environment

Some patterns of relative risk in gene–environment interactions

Gene variant	Environmental exposure	Relative risk (XP)	Relative risk (PKU)	Relative risk (emphysema)
Absent	Absent	1.0	1.0	1.0
Present	Absent	~1.0	1.0	Modest
Absent	Present	Modest	1.0	Modest
Present	Present	Very high	Very high	High

1 - Xeroderma pigmentosum (XP) ± UV:
exposure to UV light increases the risk of developing skin cancer in non-carriers of XP mutations, but the combination of these mutations and exposure to ultraviolet light vastly increases the risk of skin cancer. In theory, if individuals with XP mutations completely avoid ultraviolet light their risk of skin cancer becomes close to the background risk.

2 - Deficit of phenylalanine hydroxylase ± Phe:
only individuals with recessive mutations in the causative gene that are exposed to phenylalanine in the diet are susceptible to Phenylketonuria (PKU).

3 - α1-antitrypsin gene deficiency ± sigarette smoking:
Both non-smokers that are at genetic risk and smokers that are not at genetic risk have an increased risk of developing emphysema, and the combination (smokers that are at genetic risk) is associated with the highest risk.

There are many other patterns of gene–environment interactions, including 'protective' alleles and exposures.

Clinical relevance of genetic diseases

• about 25% of pediatric patients present with problems due to inherited genetic diseases

• some genetic disease are characterized by late onset (es. Alzheimer disease, Huntington)

• some genetic diseases are more frequent in specific populations (es: cystic fibrosis in Europeans, sickle cell disease in Mediterranean and Africa)

GENETIC, INHERITED, BIRTH DEFECT DISEASES

Not all genetic diseases are inherited (es. sporadic, new mutations, cancer)

Inherited diseases are always genetic

Birth defect diseases are present at birth, not necessarily of genetic origin (es. toxoplasmosis, talidomide exposure)

A genetic diseases occurs if mutations produce a disadvantageous allele. However, pathogenic allele may be not sufficient to lead to disease onset

TYPES OF MUTATIONS

INHERITED OR SPORADIC

Genomic due to meiotic non-disjunction (es. 21 trisomy)

Large insertions
deletions

Point transitions (purine-purine, pirimidine-pirimidine)
transversions (purine-pirimidina or viceversa)

- during DNA replication, meiotic recombination, transposition, ripair
- due to chemical, physical, biological mutagenic agents
- mutations in non-coding regions (shown by DNA/mRNA analysis)
- mutations in coding regions

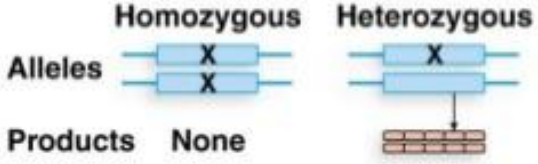
Dynamic unstable, es. triple expansion repeats
in both coding and non-coding regions

POSSIBLE CONSEQUENCES OF MUTATIONS

- **none**
- **not compatible with survival**
- **mono- or polygenic diseases**

Loss-of-Function Mutations

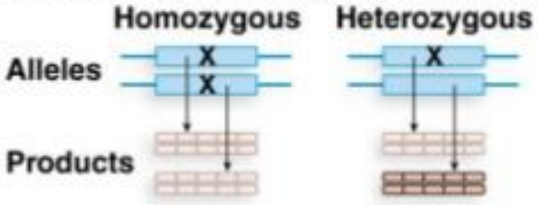
(b) Loss of function: Null/amorphic mutation



Null alleles produce no functional product. Homozygous null organisms have mutant (amorphic) phenotype due to absence of the gene product. Heterozygous organisms produce less functional gene product than homozygous wild-type organisms and may have mutant phenotype. See text for discussion of dominant versus recessive mutations.

Amorphic = no function

(c) Loss of function: Leaky/hypomorphic mutation

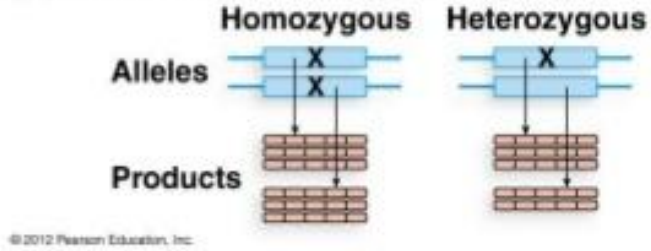


Leaky mutant alleles produce a small amount of wild-type gene product. Homozygous organisms have a mutant (hypomorphic) phenotype. Heterozygous organisms may also be mutant.

Hypomorphic = less function

Gain-of-Function Mutations

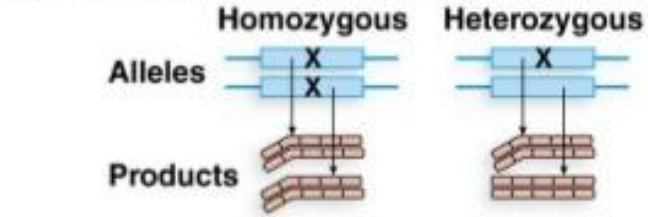
(e) Gain of function: Hypermorphic mutation



Excessive expression of the gene product leads to excessive gene action. The mutant phenotype may be more severe or lethal in the homozygous genotype than in the heterozygous genotype.

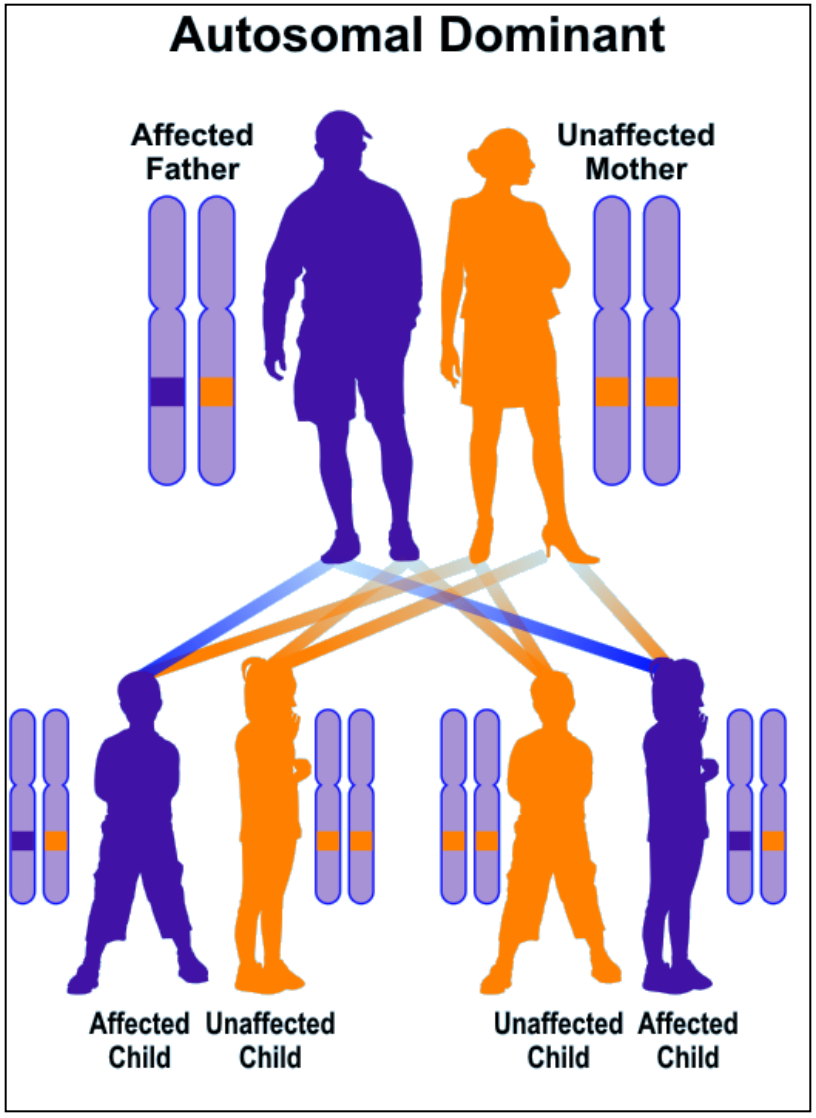
Hypermorphic = more function

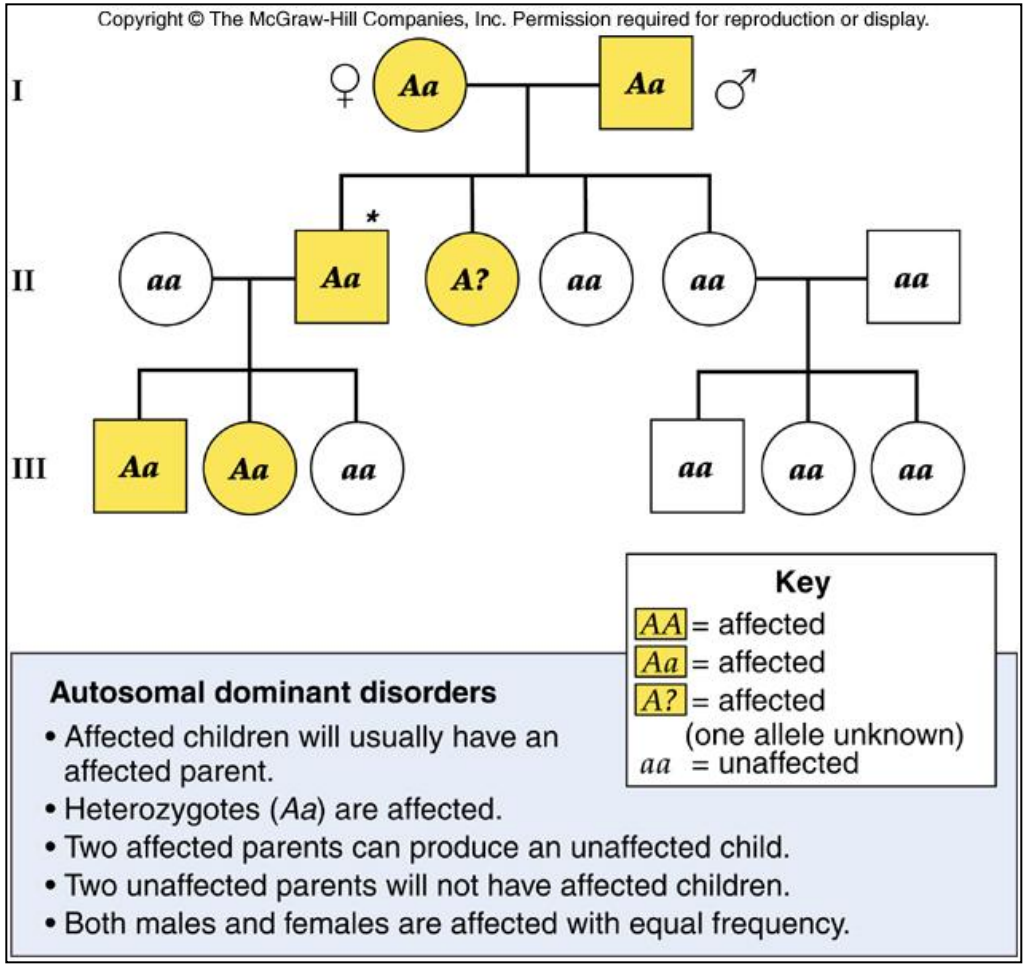
(f) Gain of function: Neomorphic mutation



The mutant allele has novel function that produces a mutant phenotype in homozygous and heterozygous organisms, and may be more severe in homozygous organisms.

Neomorphic = *new* function


Autosomal Dominant
Affected Father
Unaffected Mother
Affected Child
Unaffected Child
Unaffected Child
Affected Child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I
II
III
Aa
Aa
aa
Aa
A?
aa
aa
aa
Aa
Aa
aa
aa
aa
aa
*
Key
AA = affected
Aa = affected
A? = affected
(one allele unknown)
aa = unaffected
Autosomal dominant disorders
• Affected children will usually have an affected parent.
• Heterozygotes (Aa) are affected.
• Two affected parents can produce an unaffected child.
• Two unaffected parents will not have affected children.
• Both males and females are affected with equal frequency.

Mnemonic for **Autosomal Dominant** disorders:

Very Powerful DOMINANT Humans

- **V**on willebrand disease / **V**on hippel-lindau
- **P**seudo-hypoparathyroidism
- **D**ystrophia myotonica
- **O**steogenesis imperfecta / **O**sler-weber-rendu
- **M**arfan syndrome
- **I**ntermittent porphyria
- **N**eurofibromatosis
- **A**chondroplasia / **A**dult polycystic kidney disease
- **N**oonan syndrome
- **T**uberous sclerosis
- **H**ypercholesterolemia
- **H**untington's disease
- **H**ypertrophic obstructive cardiomyopathy
- **H**ereditary spherocytosis
- **H**ereditary non polyposis coli
- **H**ereditary hemorrhagic telangiectasia

MECHANISMS

A. Mutations that lead to excess function

es. Charcot-Marie-Tooth disease (inherited motor sensitive neuropathy), wrong DNA duplication, PMP22 (periheral myelin protien 22) over-expression (gene duplication due to disequilibrium in meiotic crossing over), leading to 3 copies of the gene

B. Haploinsufficiency

Single copy gene, es. hypercholesterolemia due to mutation in LDL receptor gene, resulting in reduced LDL receptor levels, increased circulating cholesterol and enhanced risk of cardiovascular diseases. Heterozygosis: cholesterol levels between 250-350 mg/dl. Homozygosis (very rare): cholesterol level >500 mg/dl
https://www.youtube.com/watch?v=PbfuLpXoI5g

C. Dominant negative mutations

es. *osteogenesis imperfecta*, due to mutations in the gene coding for type I collagen

D. Dynamic mutations

es. Huntington disease or X-fragile syndrome due to trinucleotide repeat expansion

FH Can Be Caused by Mutations in 4 Known Genes

FH is typically caused by mutations in LDLR, ApoB, PCSK9, LDLRAP1 or other as yet other unidentified genes[1]

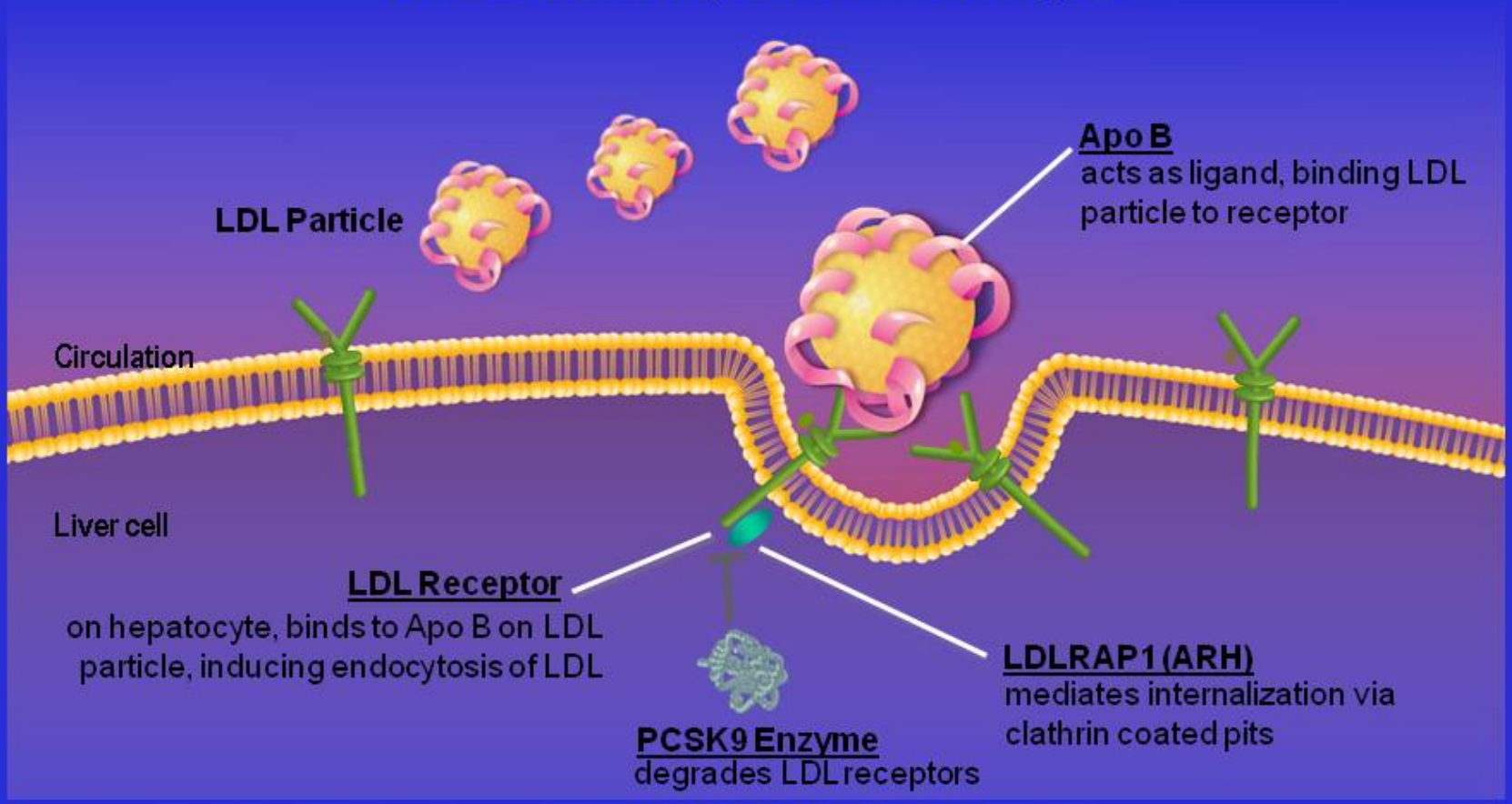
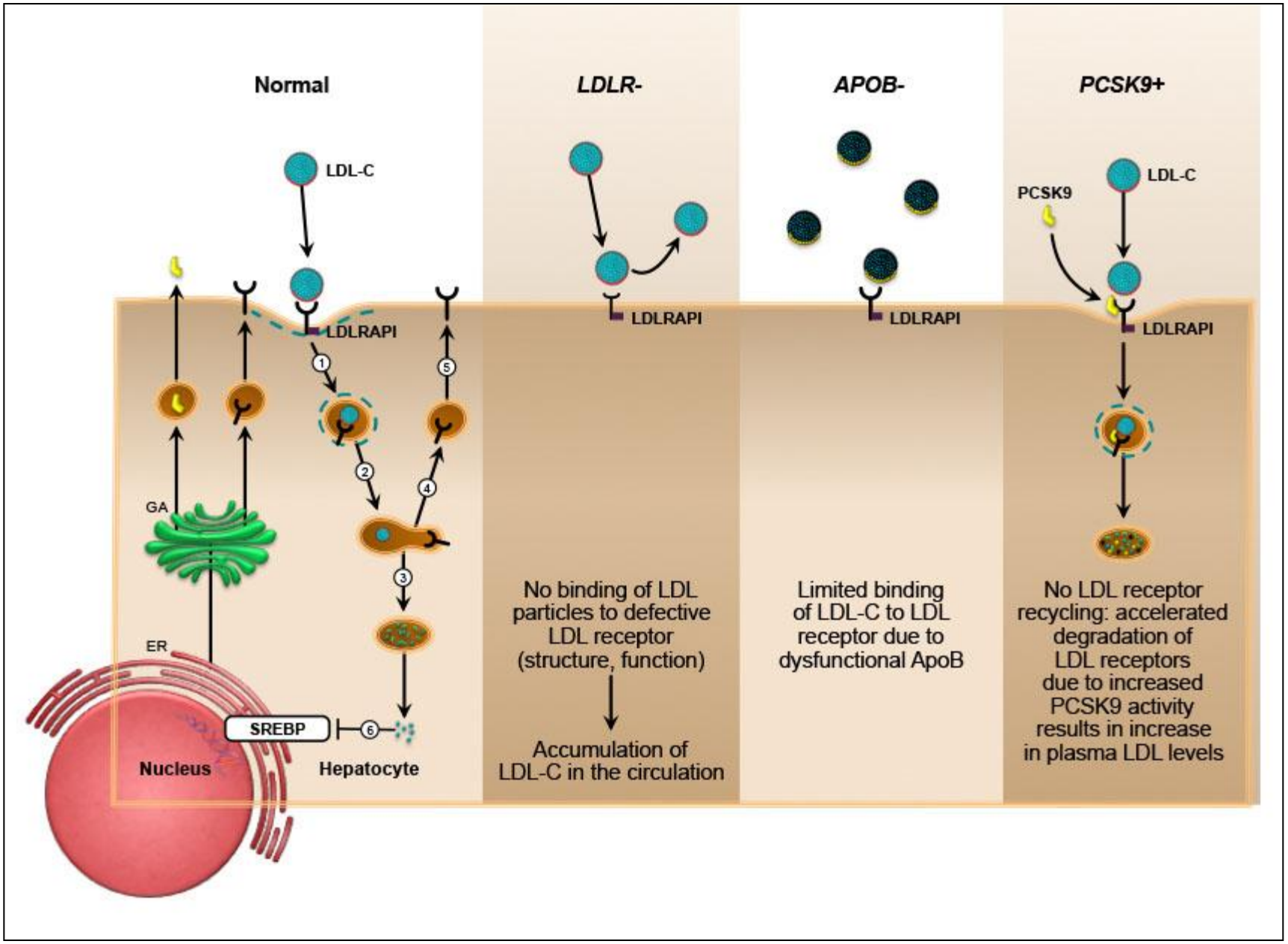


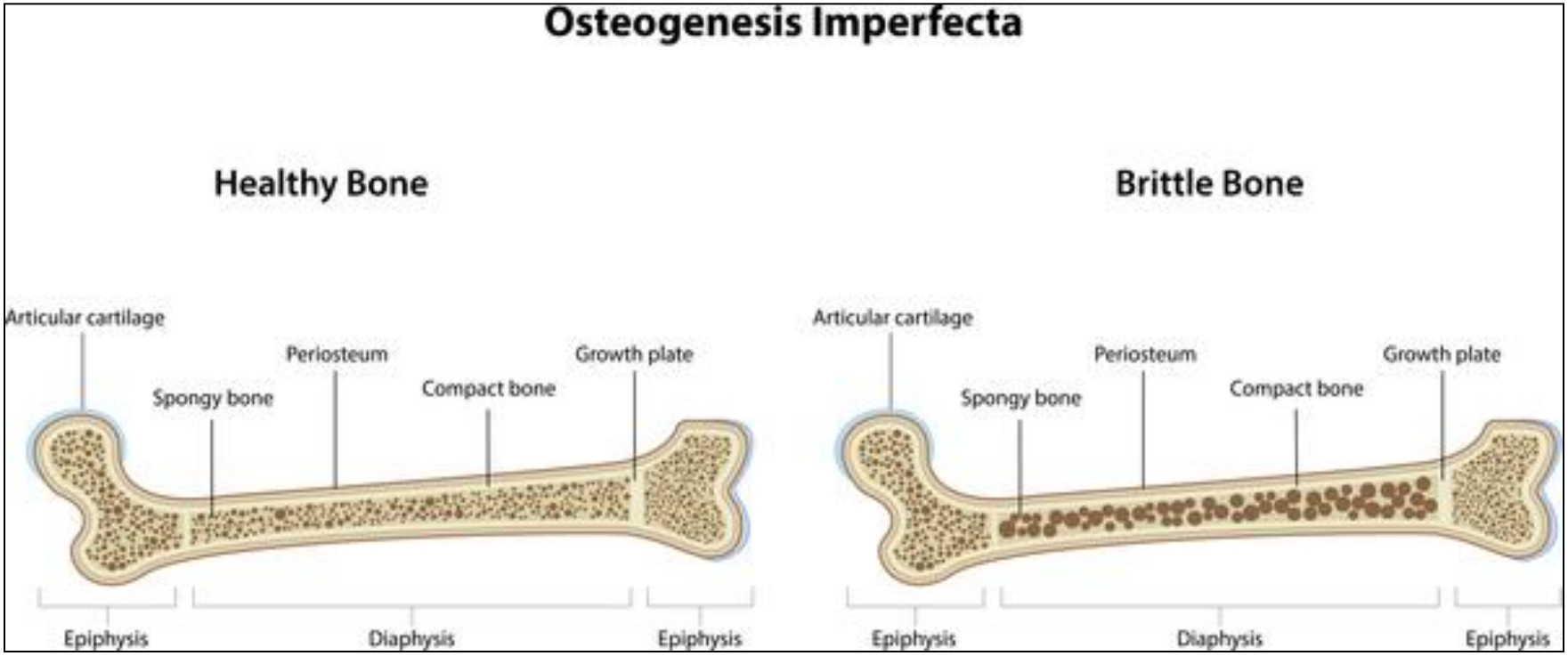
Image reproduced from http://www.dls.ym.edu.tw/ol_biology2/ultranet/Endocytosis.html.

1. De Castro-Oros I, et al. *Appl Clin Genet.* 2010;3:53-64.



http://www.mayo.edu/research/labs/cardiovascular-biomarkers/research-projects/familial-hypercholesterolemia

Osteogenesis Imperfecta



https://ghr.nlm.nih.gov/condition/osteogenesis-imperfecta

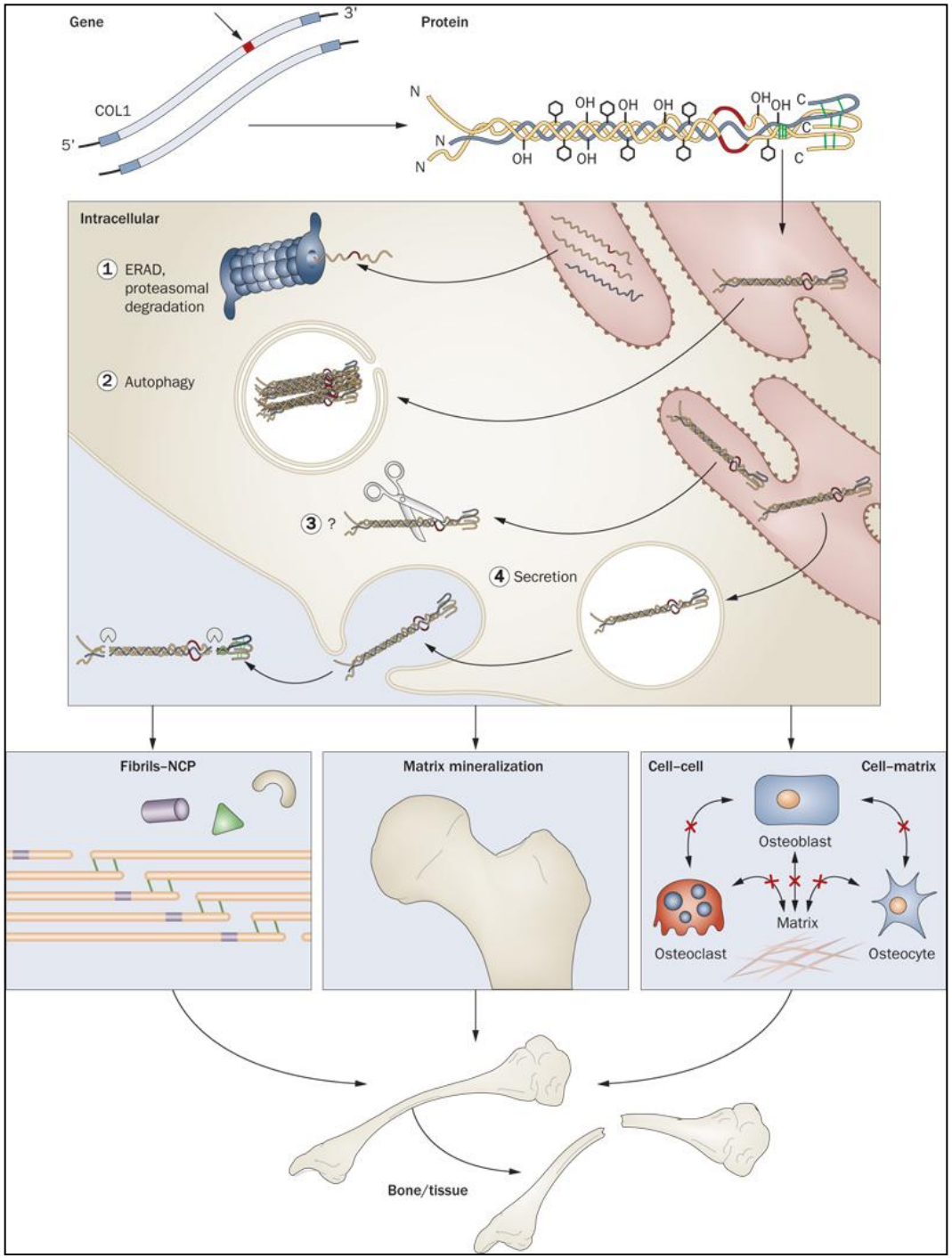


Figure 1: Mechanisms contributing to autosomal dominant osteogenesis imperfecta bone dysplasia: from mutant type I collagen gene to bone defect.Mutations in either COL1A1 or COL1A2 are translated into collagen α-chains with abnormal structure, which delay folding of the heterotrimer and result in excess post-translational modification of the collagen helical region. Mutant procollagen chains unable to incorporate into heterotrimers are retrotranslocated into the cytosol and degraded by the ERAD pathway (1); fully misfolded heterotrimers with structural defects generate supramolecular aggregates that are eliminated by autophagy (2); mutant molecules with triple helical mutations are degraded through an unidentified pathway (3). Finally, abnormal procollagen can be secreted, processed and incorporated in the extracellular matrix (4). The secreted mutant collagen affects fibril structure and interactions of noncollagenous proteins with matrix, as well as matrix mineralization and osteoblast development and cell–cell and cell–matrix crosstalk. The overall result is bone deformity and fragility, although the relative importance of various contributions is under investigation. Abbreviations: ERAD, endoplasmic reticulum-associated proteasomal degradation; NCP, noncollagenous proteins (Forlino et al., 2011).

AUTOSOMIC RECESSIVE DISEASES

most of inherited diseases

frequently in blood relatives (healthy carriers)

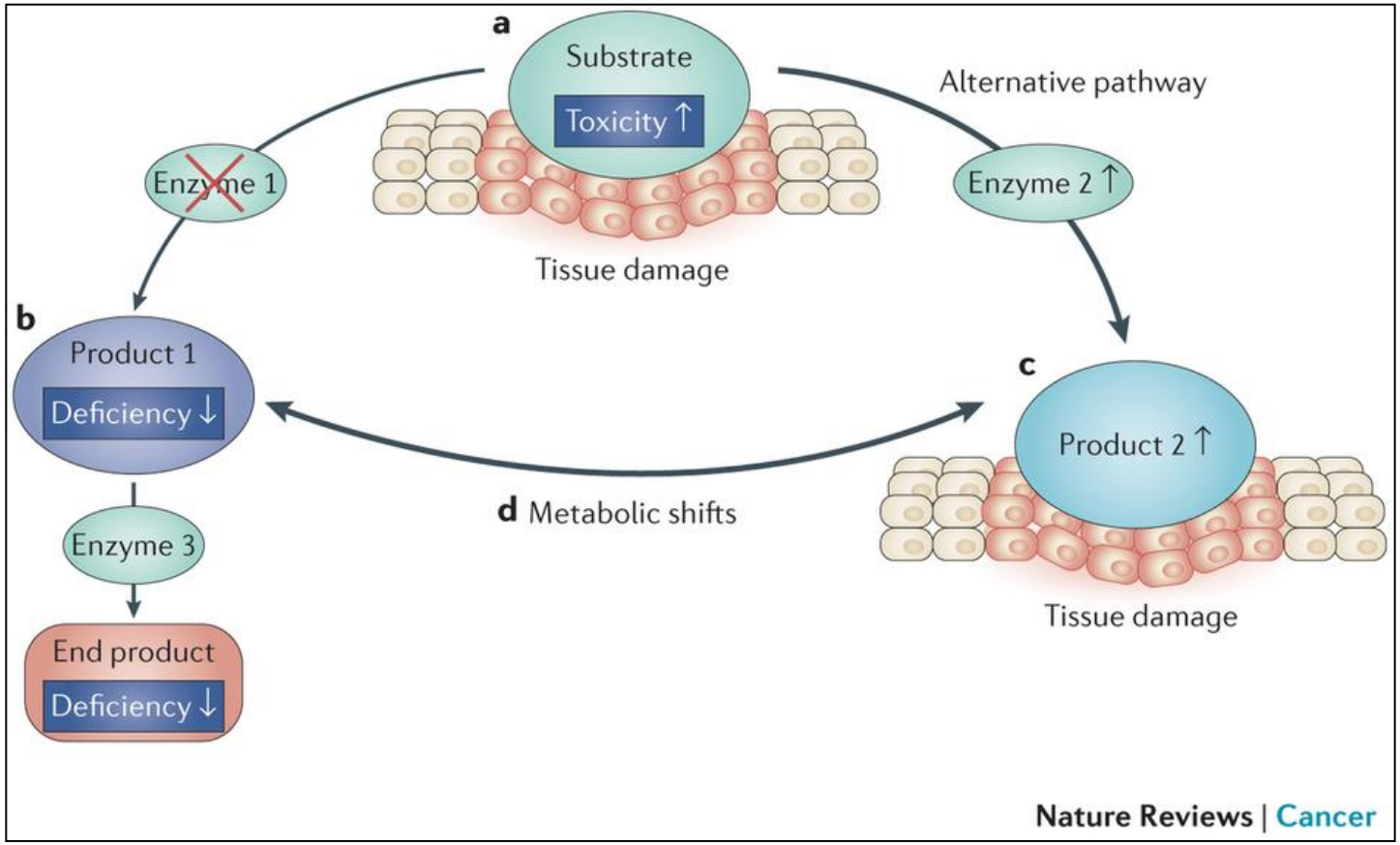
mutated gene usually codes for a regulatory protein (½ of gene product sufficient for normal phenotype)

	A	a
A	AA healthy	Aa carrier
a	Aa carrier	aa ill

Autosomal Recessive Disorders – Inborn errors of metabolism

- Lysosomal storage diseases
  - Inherited single gene abnormality
  - Group of disorders characterized by deficiency of a specific single lysosomal enzyme resulting in an accumulation of abnormal metabolic products - - - > cellular and, ultimately, organ damage
    1) Lipid storage diseases
       - Tay-Sachs disease, Gaucher disease, Niemann-Pick disease
    2) Mucopolysaccharidoses
       - Ex. - Hurler syndrome
    3) Glycogen storage disease
       - von Gierke disease, Pompe disease, Cori disease, McArdle syndrome
- Disorders of carbohydrate metabolism
  - Classic galactosemia, galactokinase-deficiency galactosemia
- Disorders of amino acid metabolism
  - Phenylketonuria, alkaptonuria, maple syrup urine disease
- Cystic fibrosis

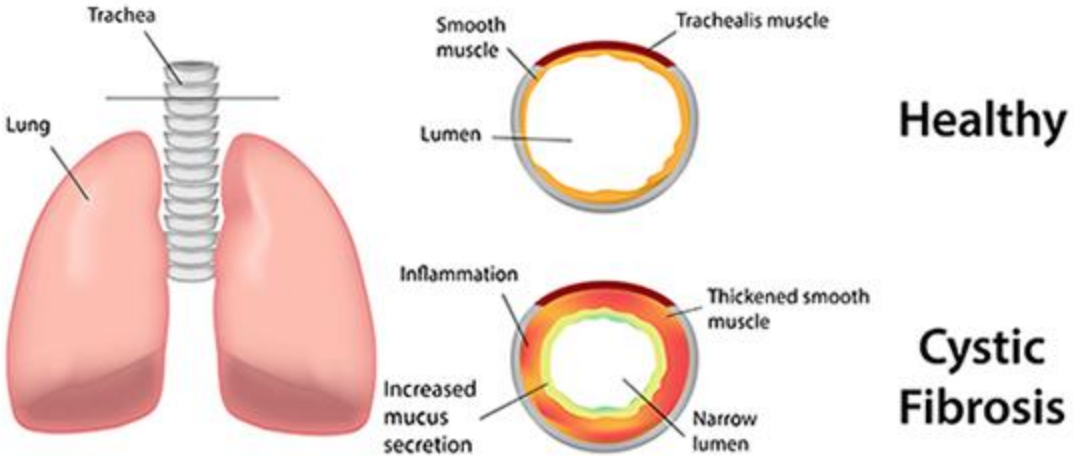
INBORN ERRORS OF METABOLISM



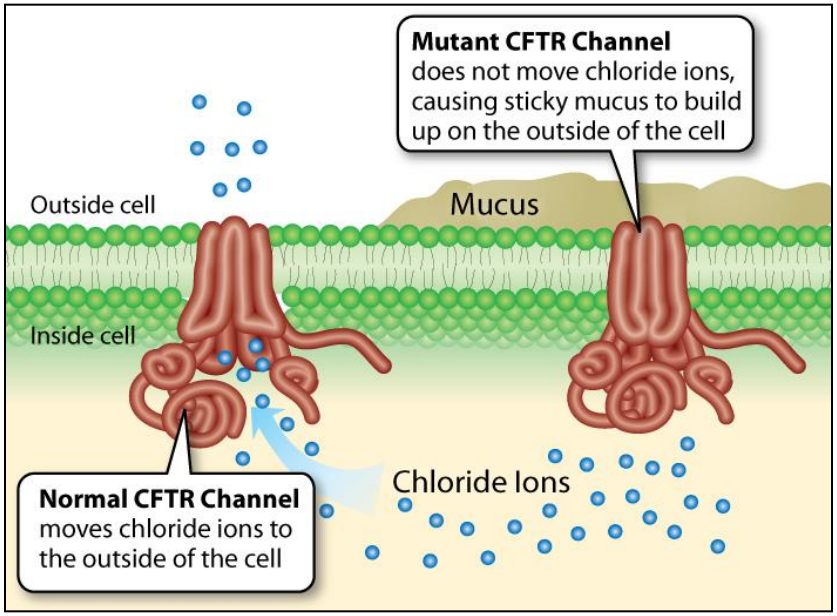
Loss of function of a metabolic enzyme (enzyme 1) may result in one or more of the following: toxicity caused by the accumulating upstream substrate, which may lead to tissue damage (**a**); deficiency of the product of enzyme 1, reducing activity of downstream enzymes in the pathway and ultimately depleting the pathway's end product (**b**); or activation of alternative pathways (for example, enzyme 2) using the same substrate as enzyme 1 (**c**). Because enzyme 1 is inactive, there will be a shift in the intensity of the fluxes between the two pathways (**d**) and an accumulation of product 2, which may also be toxic. The arrows inside the product shapes represent their change in abundance (increase or decrease) following enzyme 1 inactivation.

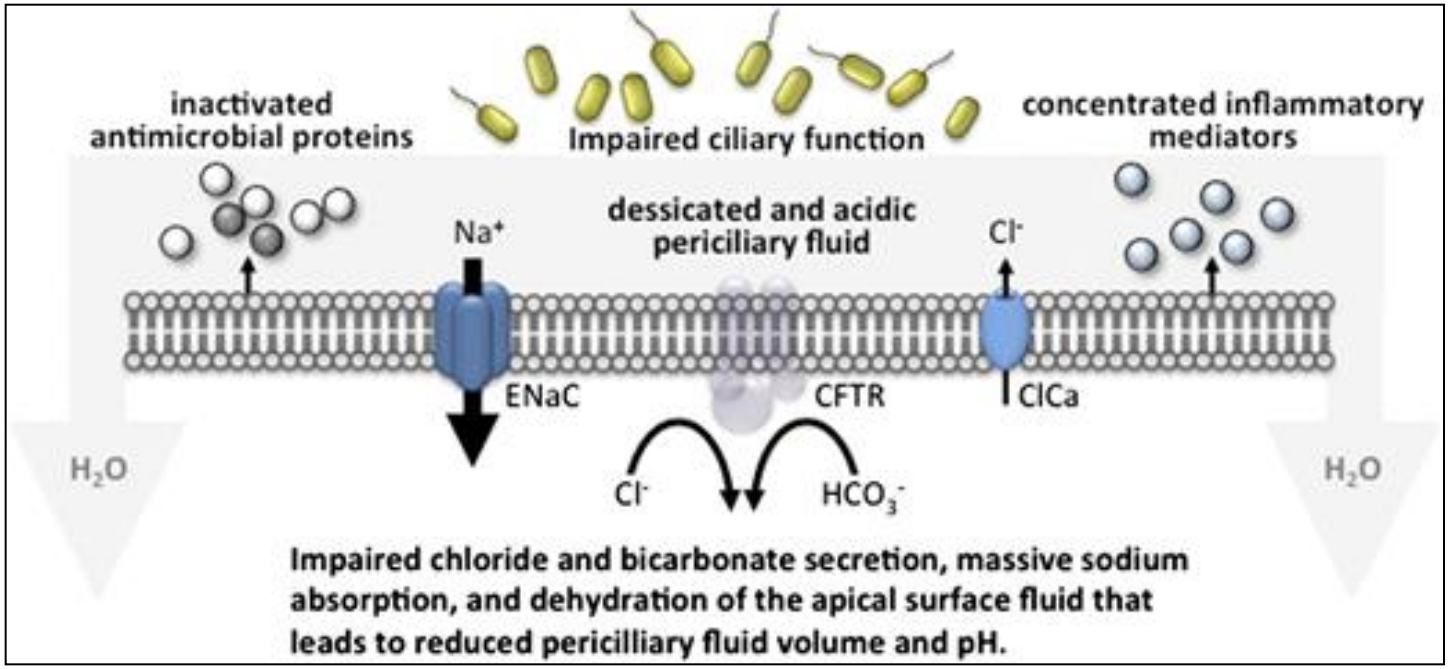
Erez and Deberardinis, 2015

Cystic Fibrosis

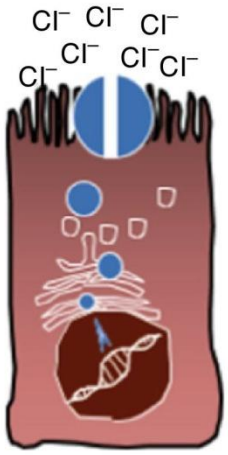
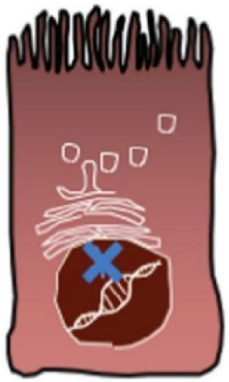
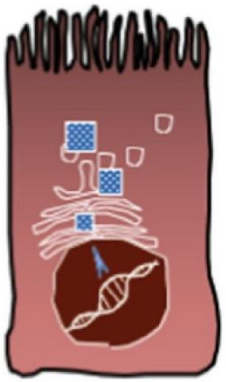
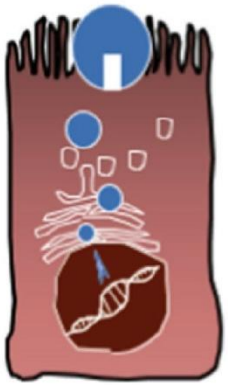
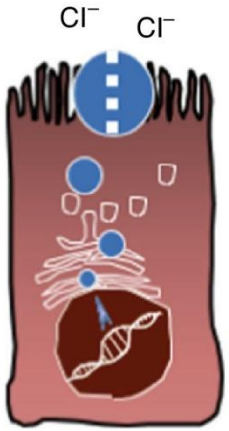
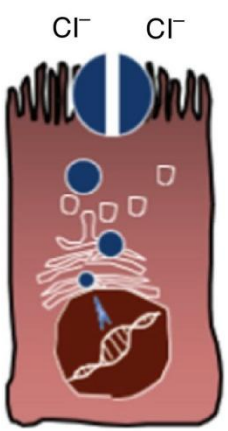
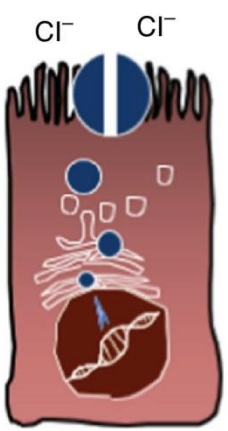


- most frequent lethal AR disease
- abnormally viscous mucous secretion result in lung obstruction. The mucus is easily colonized by bacteria. Also pancreatic fibrosis (secondary diabetes)
- due to mutations of CFTR (cystic fibrosis transmembrane conductance regulator) gene on chromosome 7, encoding a Cl^- channel in secreting epithelial cells





Pittman and Ferkol, 2015

	Class of mutation					
Normal	I	II	III	IV	V	VI
						
Molecular defect	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Functional abnormality	Protein is not synthesized	Folding defect	Channel opening defect	Ion transport defect	Decreased protein synthesis	Decreased half-life of the protein
Main mutations	Gly542X Trp128X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

Inherited enzymatic defects due to point mutations

A. reduced enzymatic activity

B. reduced enzyme levels

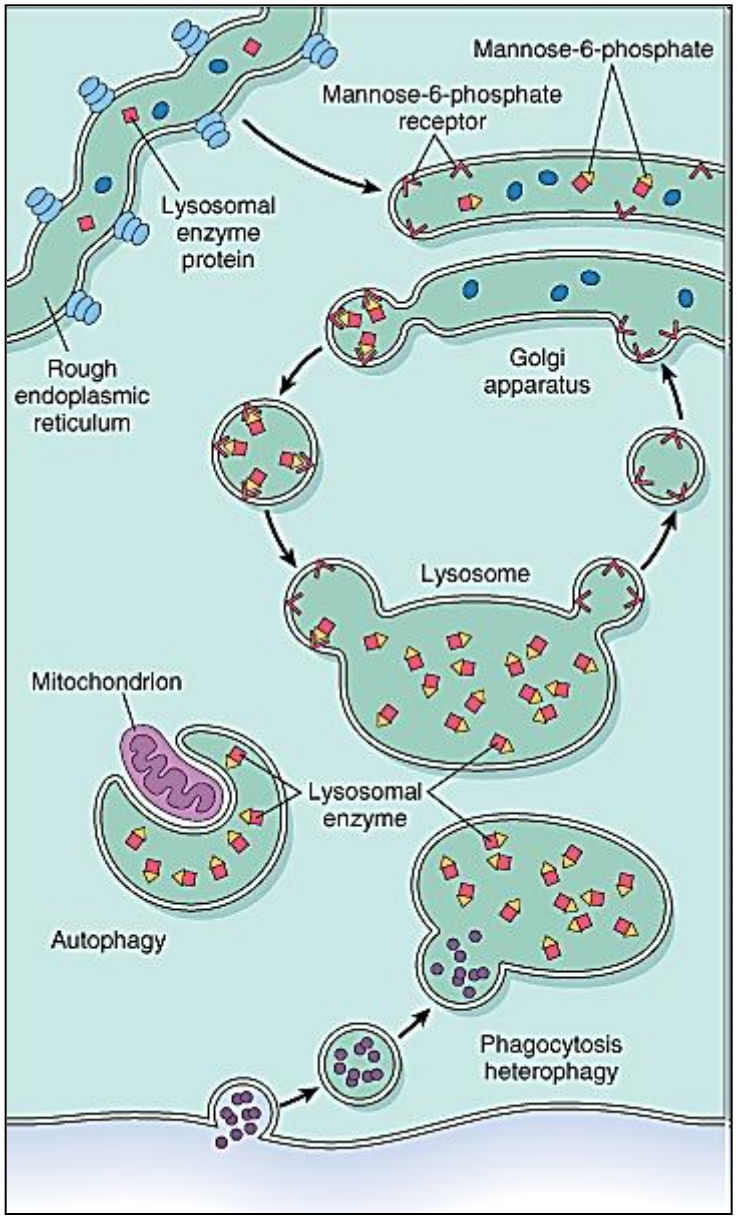
→ **metabolic block**

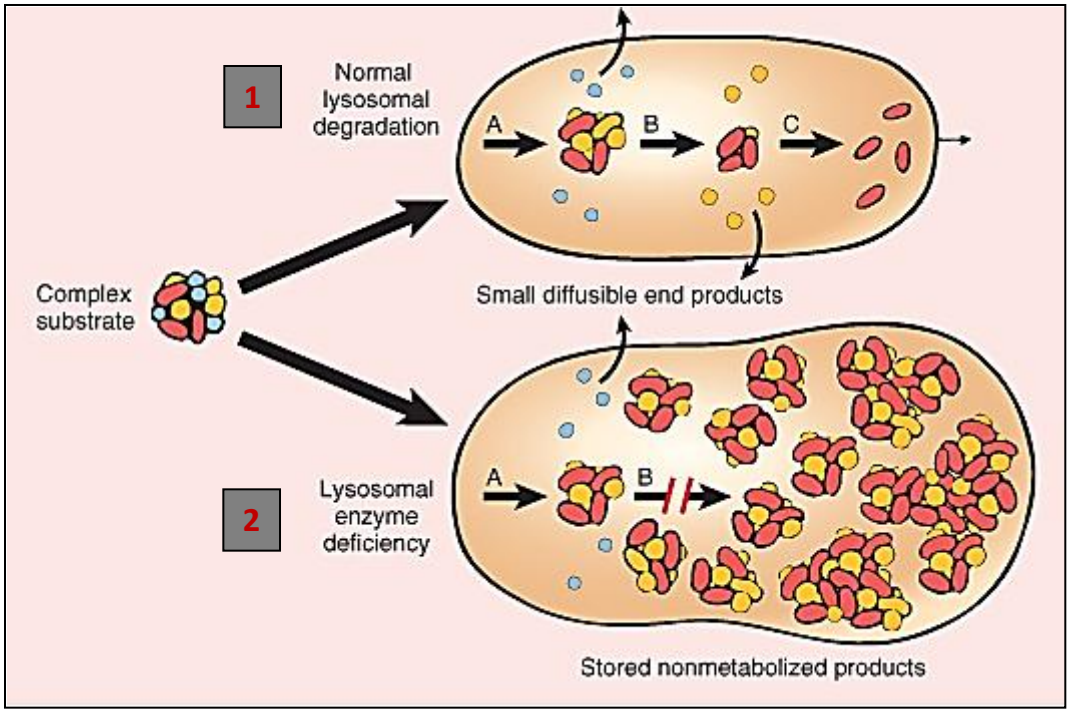
a. substrate or intermediate products accumulation → tissue toxicity (es. PKU; deficit Phe-hydroxylase)

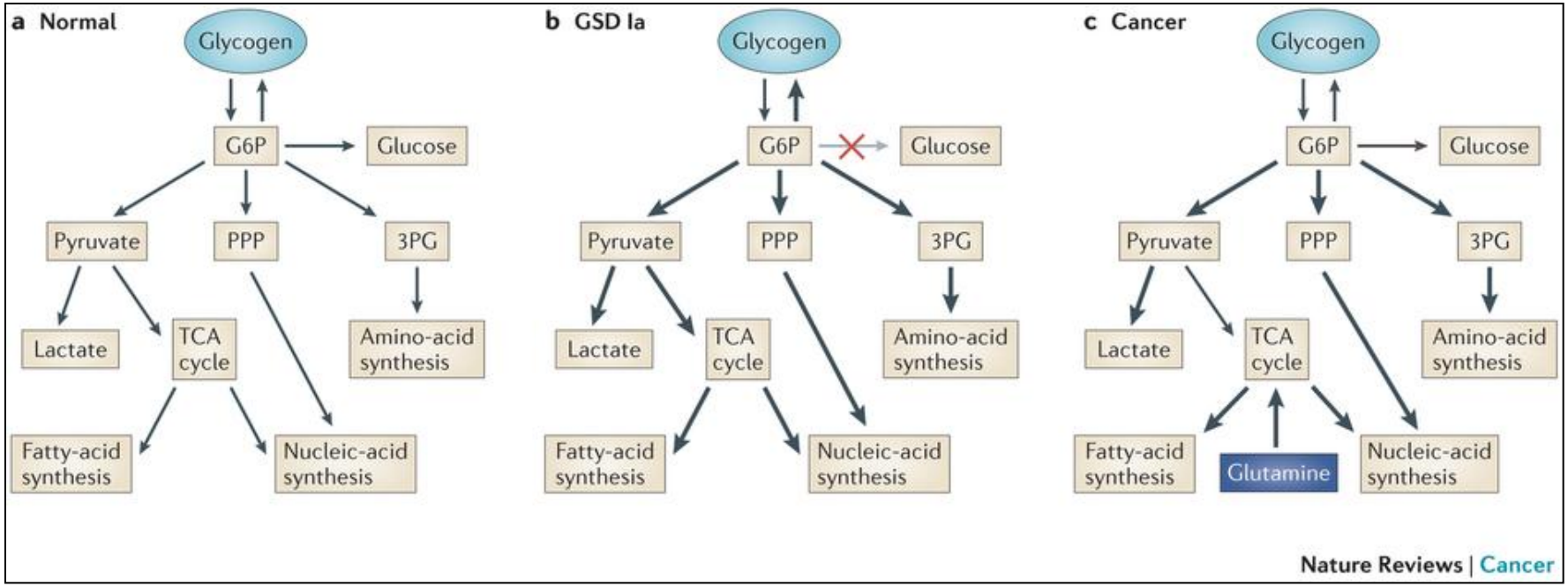
b. reduced final products (es. tirosinase deficit: melanine lack)

c. lack of elimination of toxic substrates (es. α1-antitrypsine deficit → no elastase inactivation in lung → lung elastine degradation → emphysema)

LYSOSOMAL STORAGE DISEASES

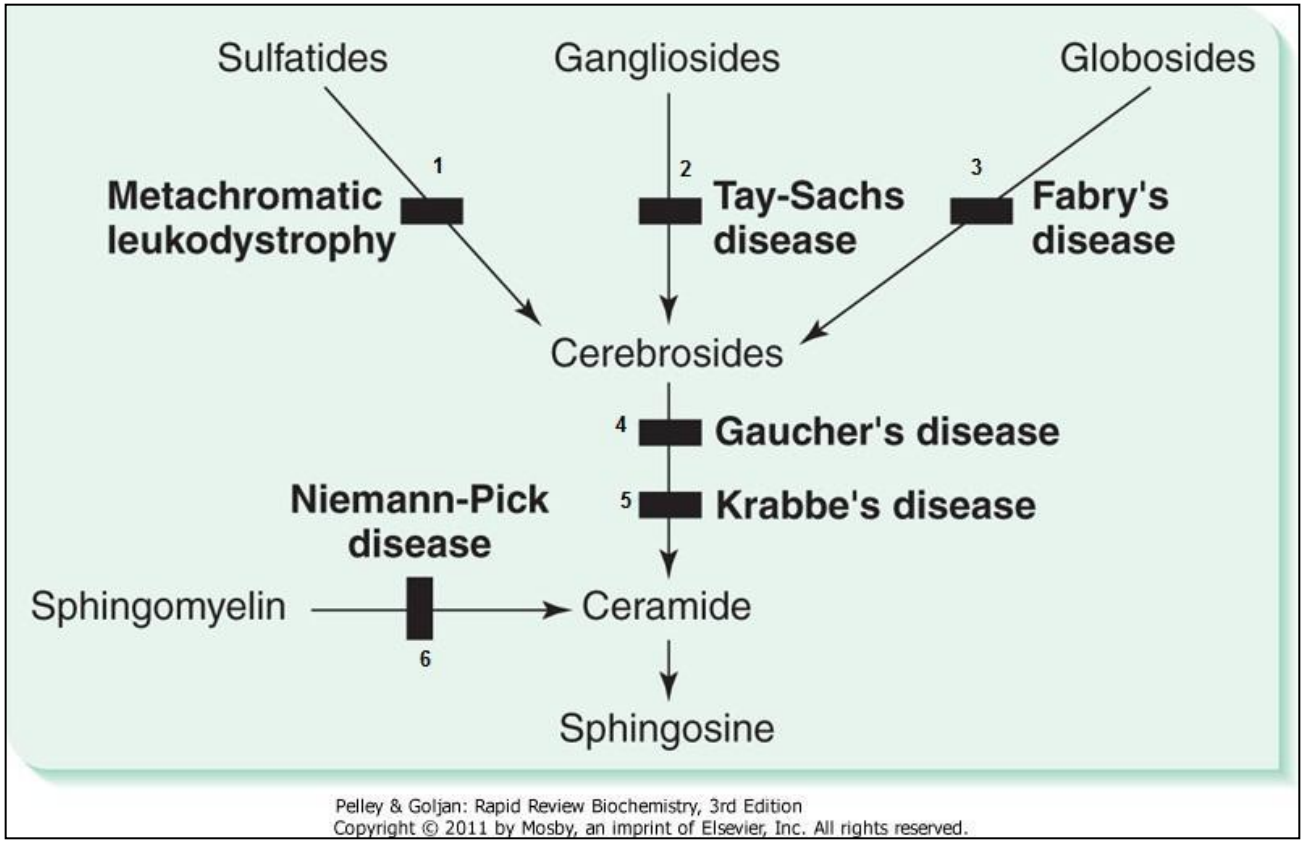




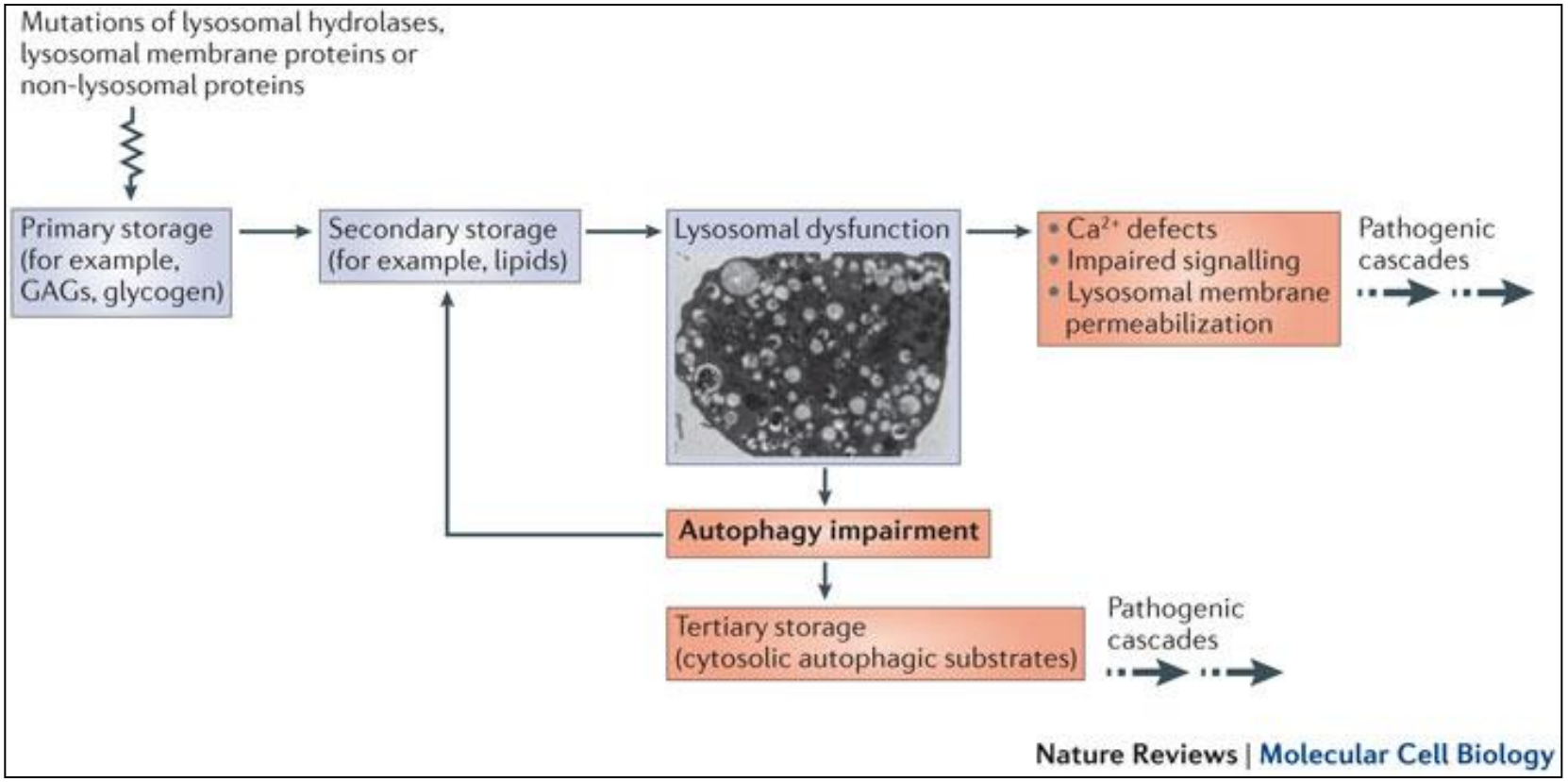


a | During normal glycogenolysis, glucose-6-phosphate (G6P) is converted to glucose. **b** | In glycogen storage disease Ia (GSD Ia), there is deficiency in the glucose-6-phosphatase complex, resulting in an inability to convert G6P to glucose and subsequent hypoglycaemia, lactic acidosis and hyperlipidaemia. Biochemically, there is an increased shunting of G6P to the pentose phosphate pathway (PPP) (represented by thick arrows). **c** | Canonical metabolic changes observed in cancer favour the shunting of G6P towards anabolism of amino acids, nucleic acids and fatty acids that support enhanced proliferation. 3PG, 3-phosphoglyceric acid; TCA, tricarboxylic acid.

Erez and Deberardinis, 2015



Disease	Enzyme deficiency & accumulated product	Age at Onset	Clinical Signs	Pathology
Tay-Sachs disease	hexosaminidase A; GM2 gangliosides	3-8 mos	psychomotor arrest, exaggerated startle reflex, seizures, retinal cherry-red spot	storage in central & peripheral neurons
Niemann-Pick disease type A	Sphingomyelinase; sphingomyelin	1-6 mos	psychomotor arrest, spleen enlargement, retinal cherry red spot sometimes,	storage in neurons, spleen
Metachromatic leukodystrophy	cerebroside sulfatase; sulfatides	early childhood	progressive mental & motor deterioration, sometimes peripheral neuropathy signs	myelin deficit in CNS & often PNS; storage in glia
Krabbe disease	galactocerebrosideß-galactosidase; galactocerebroside	3-6 mos	irritibility, crying, mental & motor deterioration, seizures	Myelin deficit; globoid cells (large multi-nucleated macrophages)



LSDs are a group of rare and recessively inherited metabolic dysfunctions with an overall incidence of 1 in 5000. LSDs are caused by mutations of genes encoding proteins that localize to the lysosomal lumen, lysosomal membrane or other cellular compartments that contribute to lysosomal function. These disorders are characterized by the progressive accumulation of material that has not been degraded in the lysosomes of most cells and tissues. Approximately 60 different types of LSDs have been recognized. Historically, LSDs have been classified on the basis of the type of material that accumulates in the lysosomes, such as mucopolysaccharides, sphingolipids, glycoproteins, glycogen and lipofuscins. LSDs often show a multisystemic phenotype that is associated with severe neurodegeneration, mental decline, cognitive problems and behavioural abnormalities. Other tissues that are commonly affected are bone and muscle. Cell and tissue pathology are the result of a complex series of pathogenic cascades that occur downstream of lysosomal dysfunction. The figure illustrates the main steps underlying LSD pathogenesis. Mutations in genes that are important for lysosomal function result in the accumulation of specific substrates that have not been degraded in the lysosome (primary storage). This leads to the accumulation of additional lysosomal substrates (secondary storage) due to a blockage in lysosomal trafficking. Excessive lysosomal storage has a broad impact on lysosomal function by causing defects in Ca^{2+} homeostasis, signalling abnormalities and lysosomal membrane permeabilization. In addition, lysosomal dysfunction is associated with autophagy impairment, due to defective fusion between lysosomes and autophagosomes. This causes the accumulation of autophagic substrates such as aggregate-prone proteins and dysfunctional mitochondria (tertiary storage), which contributes to neurodegeneration. GAGs, glycosaminoglycans (Settembre et al., 2013).