14th Annual Congress of Iranian Pediatric Hematology & Oncology Society

White Blood Cell Disorders in Children

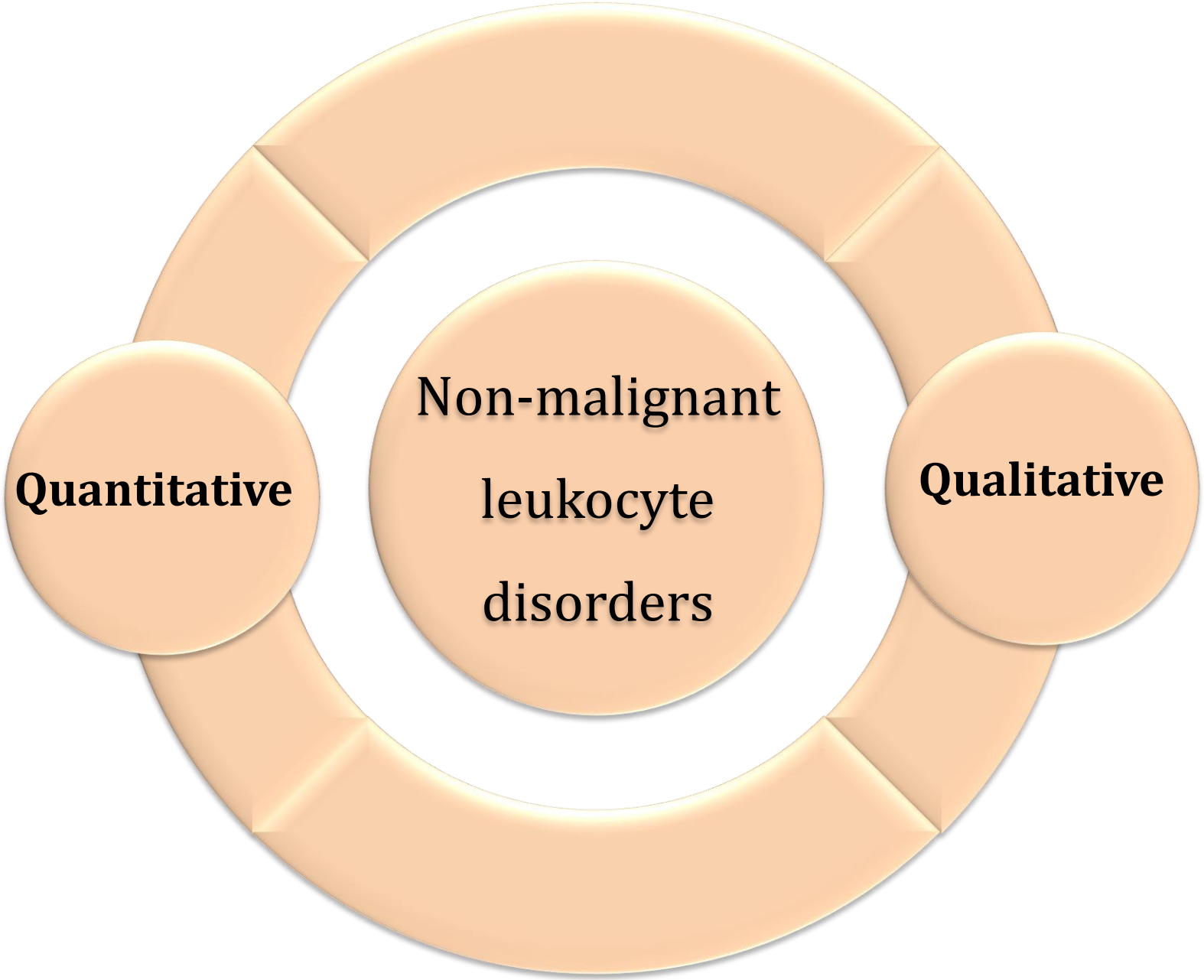
16-17 Feb 2023; Hotel Eram, Tehran

انجمن خون و سرطان کودکان ایران

Iranian Pediatric Hematology & Oncology Society

Genetic Basis of Leukocyte Disorders

Non-malignant leukocyte disorders



Non-malignant leukocyte disorders

Quantitative

A. Severe Congenital neutropenia (SCN)

B. Cyclic neutropenia

C. Syndromic Congenital Neutropenia (WHIM syndrome)

D. Autoimmune neutropenia (AIN)

Non-malignant leukocyte disorders

1. Functional disorders

Degranulation abnormalities

a. Hermansky- Pudlak Syndrome type 2
b. Chédiak-Higashi syndrome
c. Griscelli syndrome, type 2
d. Familial hemophagocytic lymphohistiocytosis

Leukocyte Adhesion Deficiency

LAD I-IV

Inherited Defects in microbicidal activity

a. Chronic Granulomatous Disease (CGD)
b. Myeloperoxidase deficiency
c. Papillon–Lefevre syndrome

Qualitative

2. Morphological disorders

Cytoplasmic abnormalities

a. Alder–Reilly anomaly
b. MYH9-related disorders

Nuclear abnormality

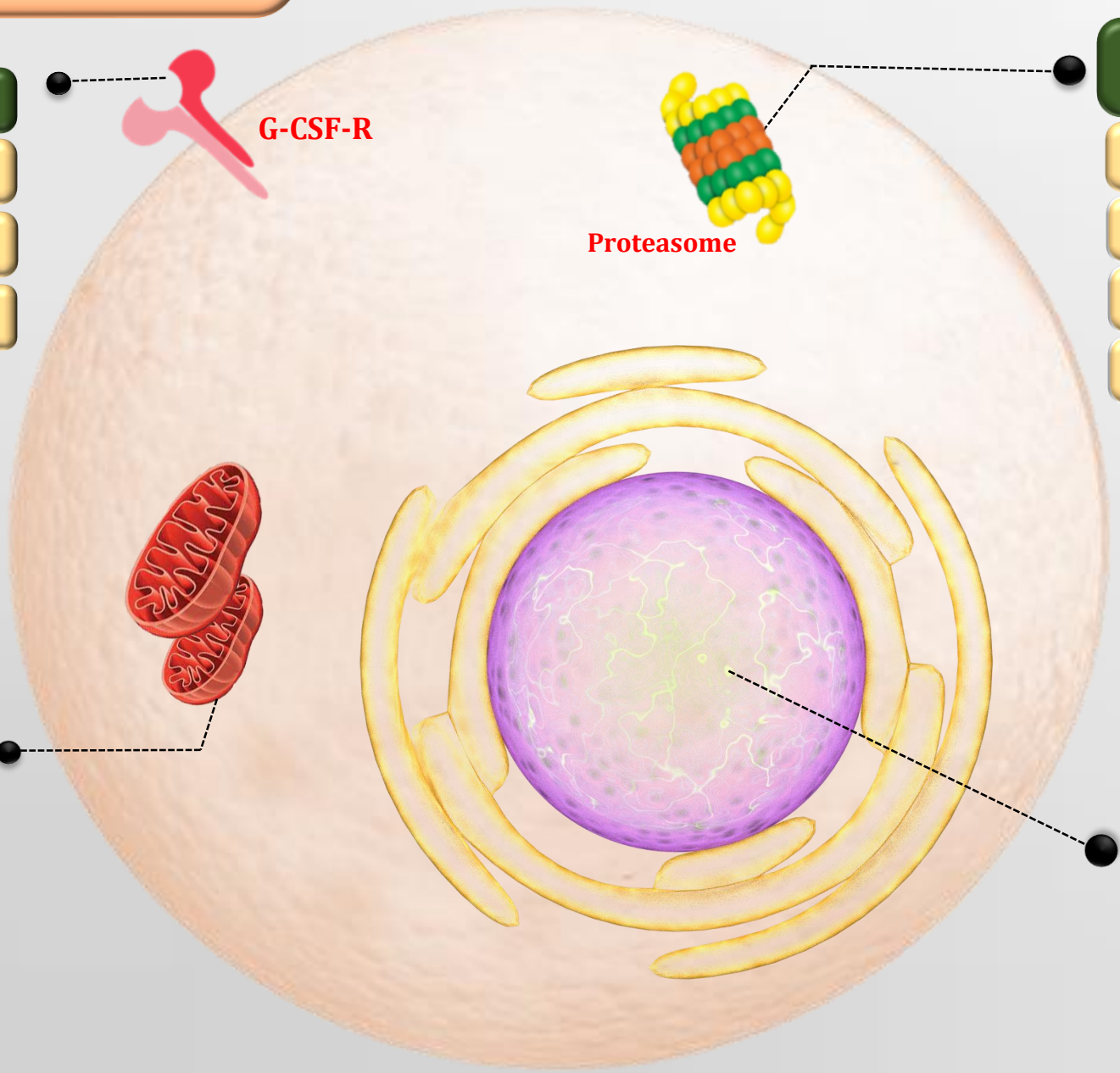
a. Pelger–Huët anomaly
b. Pelger-Huët Anomaly with mild Skeletal anomalies
c. Greenberg skeletal dysplasia
d. Nuclear projections of neutrophils

Qualitative

Severe Congenital Neutropenia (SCN)

Decreased G-CSF-R Signaling

- HAX1 (SCN3)
- VPS45 (SCN5)
- G-CSFR (SCN7)



Activation of UPAR Genes

- ELANE (SCN1)
- G6PC3 (SCN4)
- JAGN1 (SCN6)
- SRP54 (SCN8)

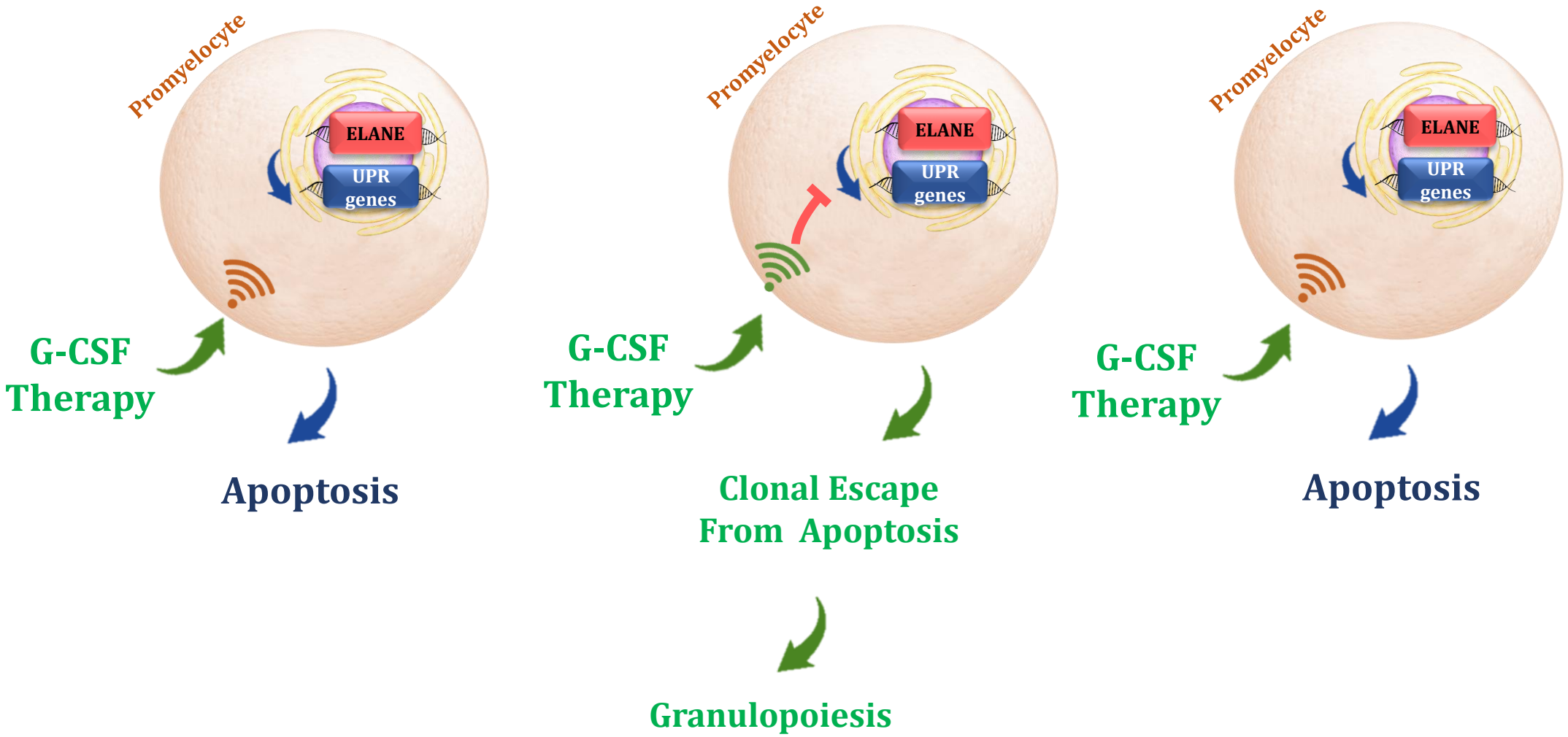
Increased Apoptosis

- CLBP (SCN9)

Inappropriate Granulocyte Differentiation

- GFI1 (SCN2)

Proposed Pathogenesis:



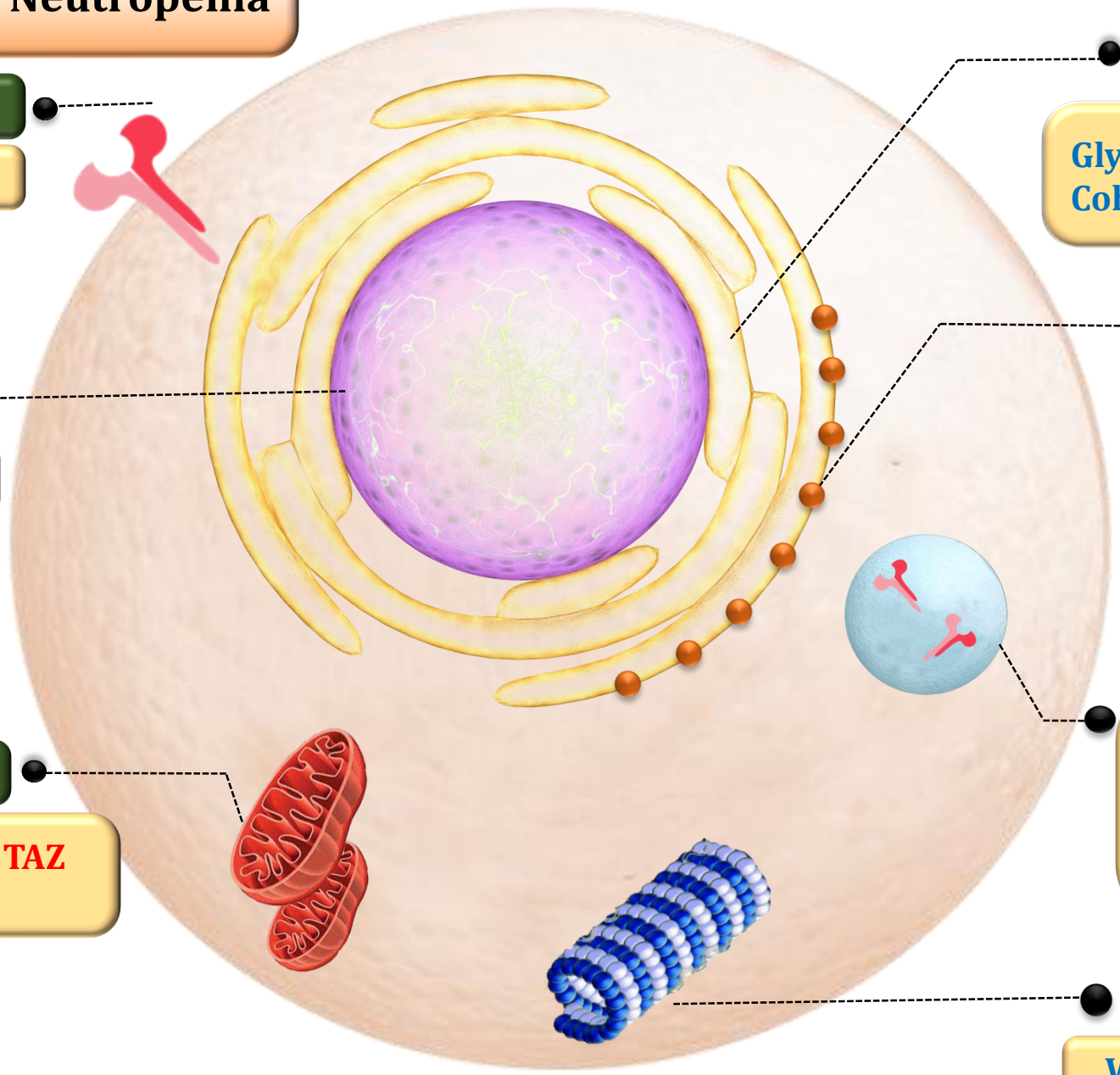
Cyclic Neutropenia in Summary

Taken together,

ELANE Mutation → UPR Response → Apoptosis → Neutropenia

G-CSF therapy → UPR Suppression → Clone escape → Granulopoiesis

Syndromic Congenital Neutropenia



CXCR2,CXCR2

WHIM Syndrome

Nucleus

GATA2 Syndrome: GATA2

Mitochondria

Barth syndrome (BTHS): TAZ
SCID: AK2

Endoplasmic reticulum

Glycogen storage disease: G6PT1
Cohen syndrome: VPS13B

Ribosomes

Shwachman-Diamond: SBDS

Endosomes & lysosomes

HPS: AP3BP1
CHS: LYST
Griscelli syndrome: RAB27A
FAMMM syndrome: p14

Cytoskeleton

Wiscott Aldrich: WAS

Autoimmune neutropenia (AIN)

The patients with AIN

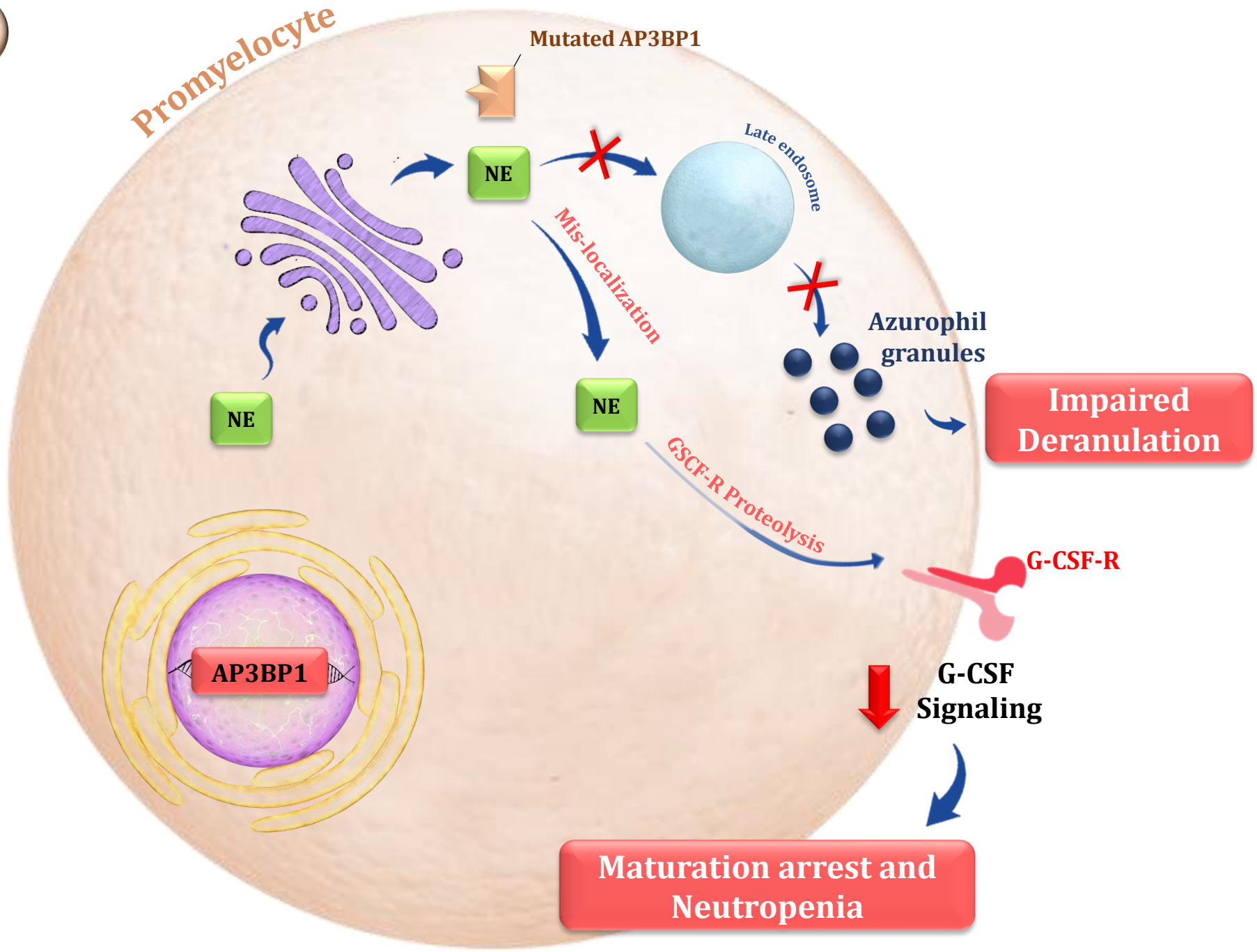
Next-generation sequencing (NGS) analysis

TACI variants
A gene associated with
common variable immunodeficiency (CVID)

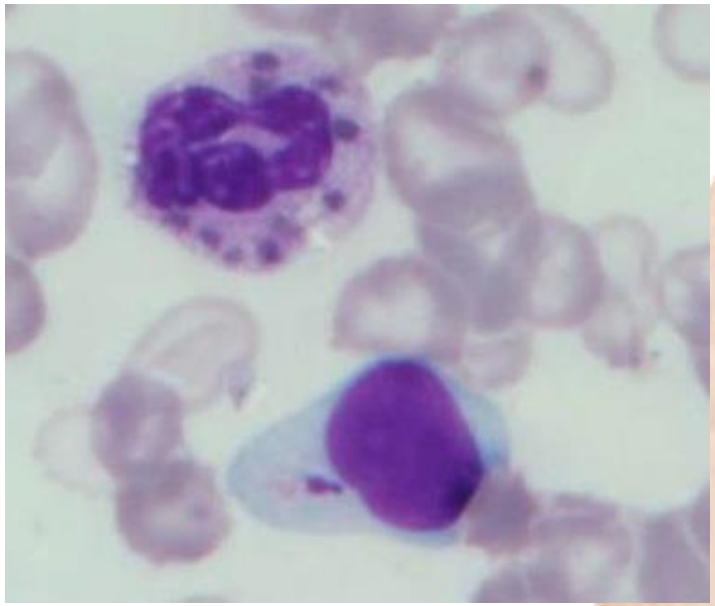
TINF2 Variants
A gene associated with
Dyskeratosis congenita (DC)

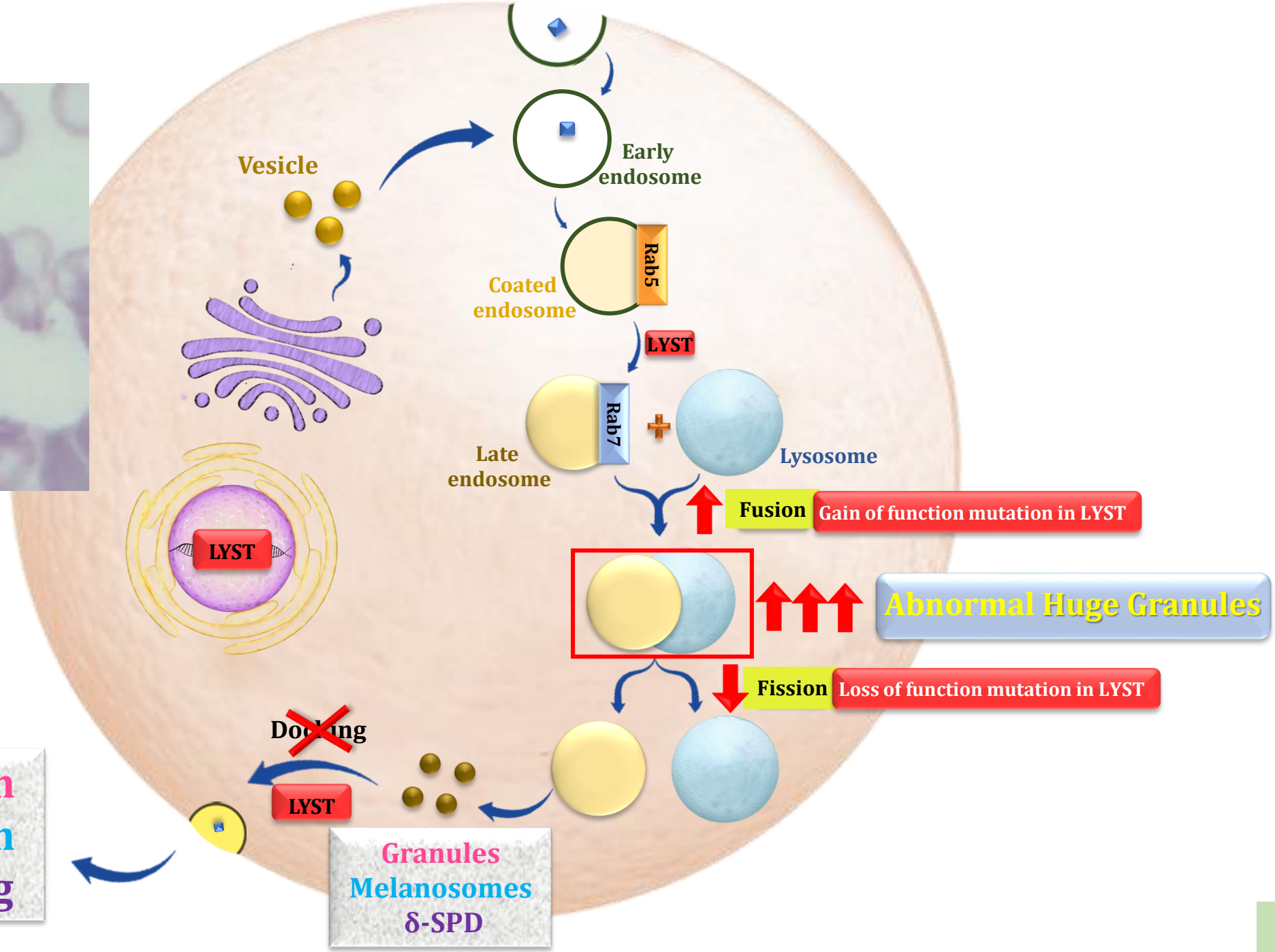
TACI variants and TINF2 variants may serve as underlying condition in AIN

HPS2: AP3BP1 Mutation

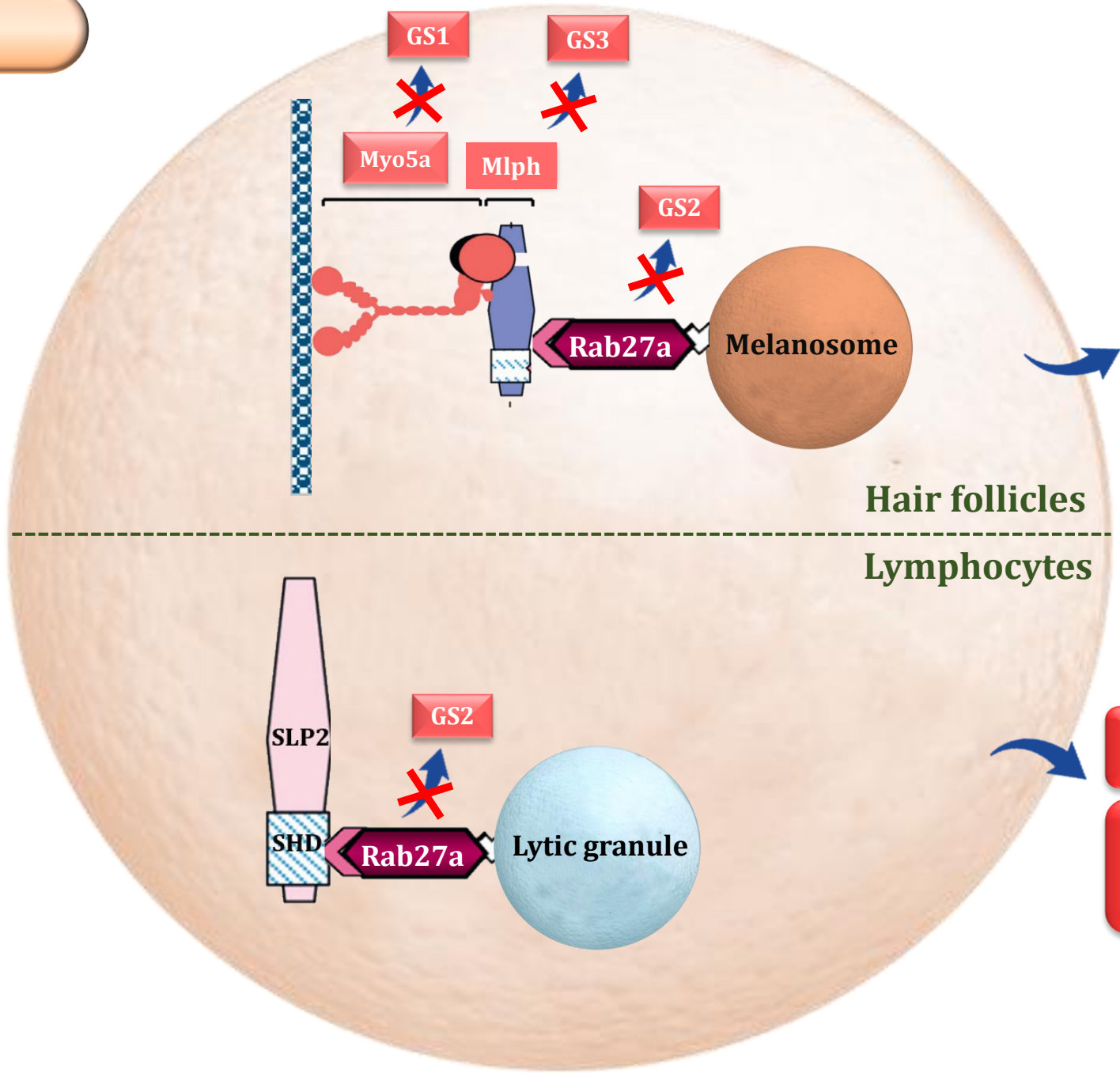


CHS: LYST Mutation





Griscelli syndrome (GS)

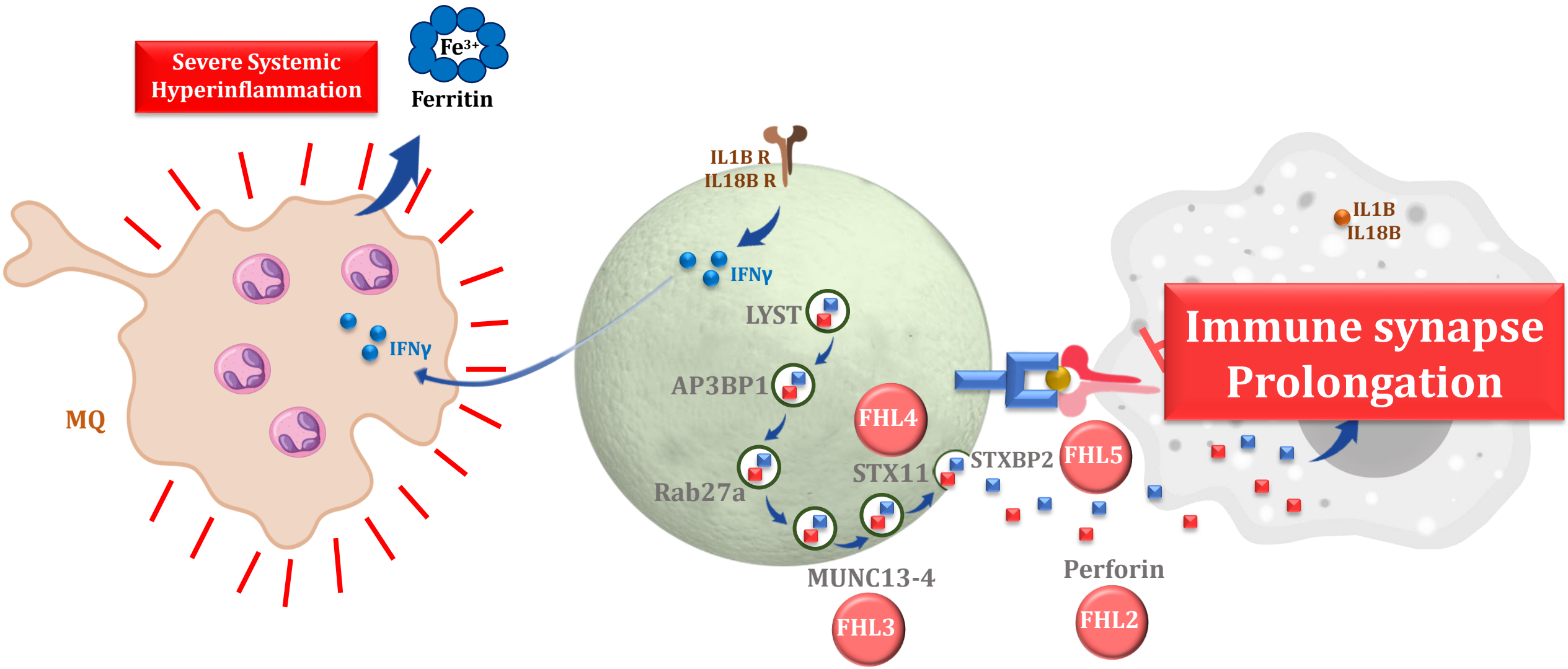


Hypopigmentation

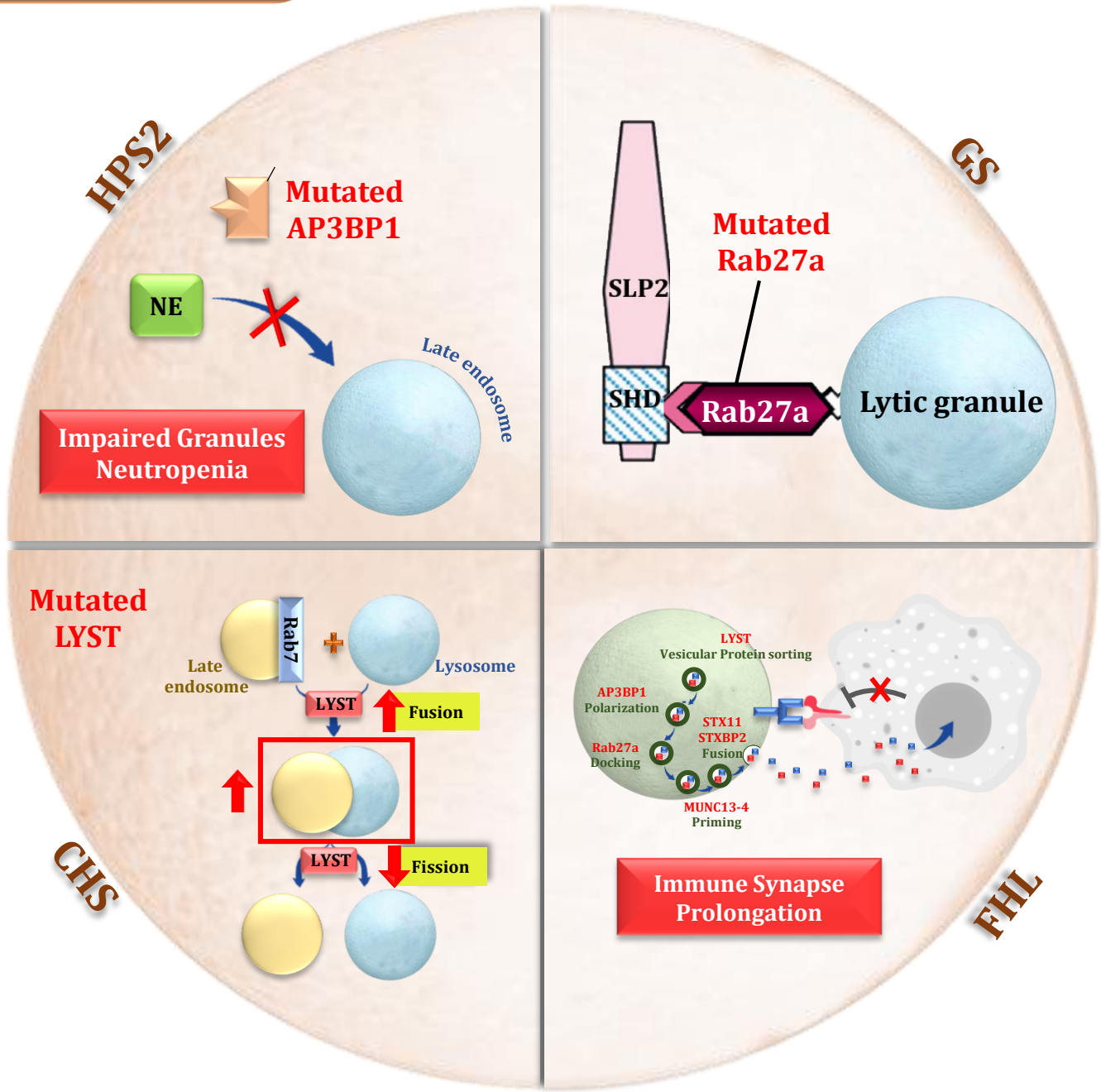
Hypopigmentation

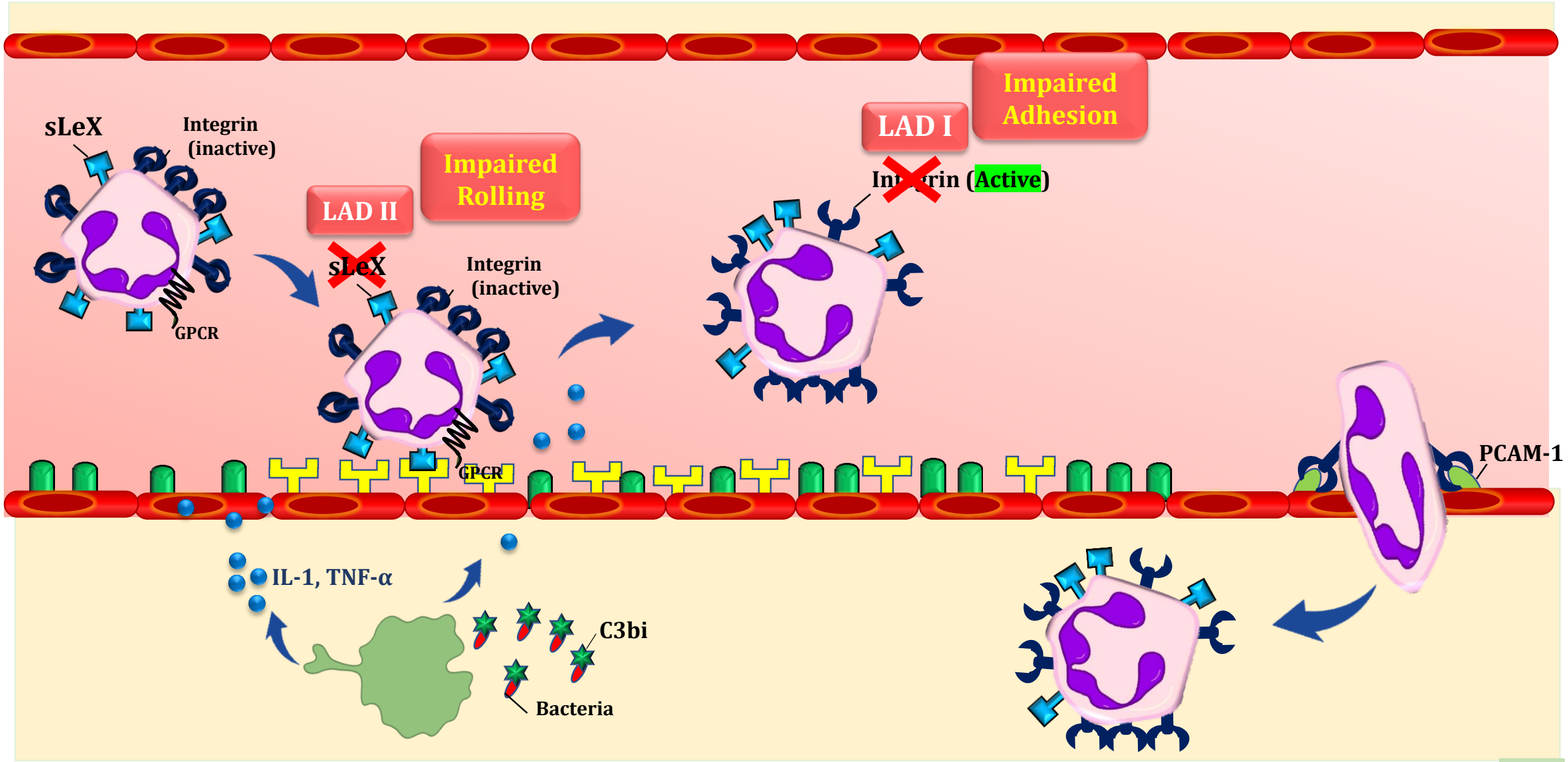
Hemophagocytic syndrome

Familial Hemophagocytic Lymphohistiocytosis (FHL)

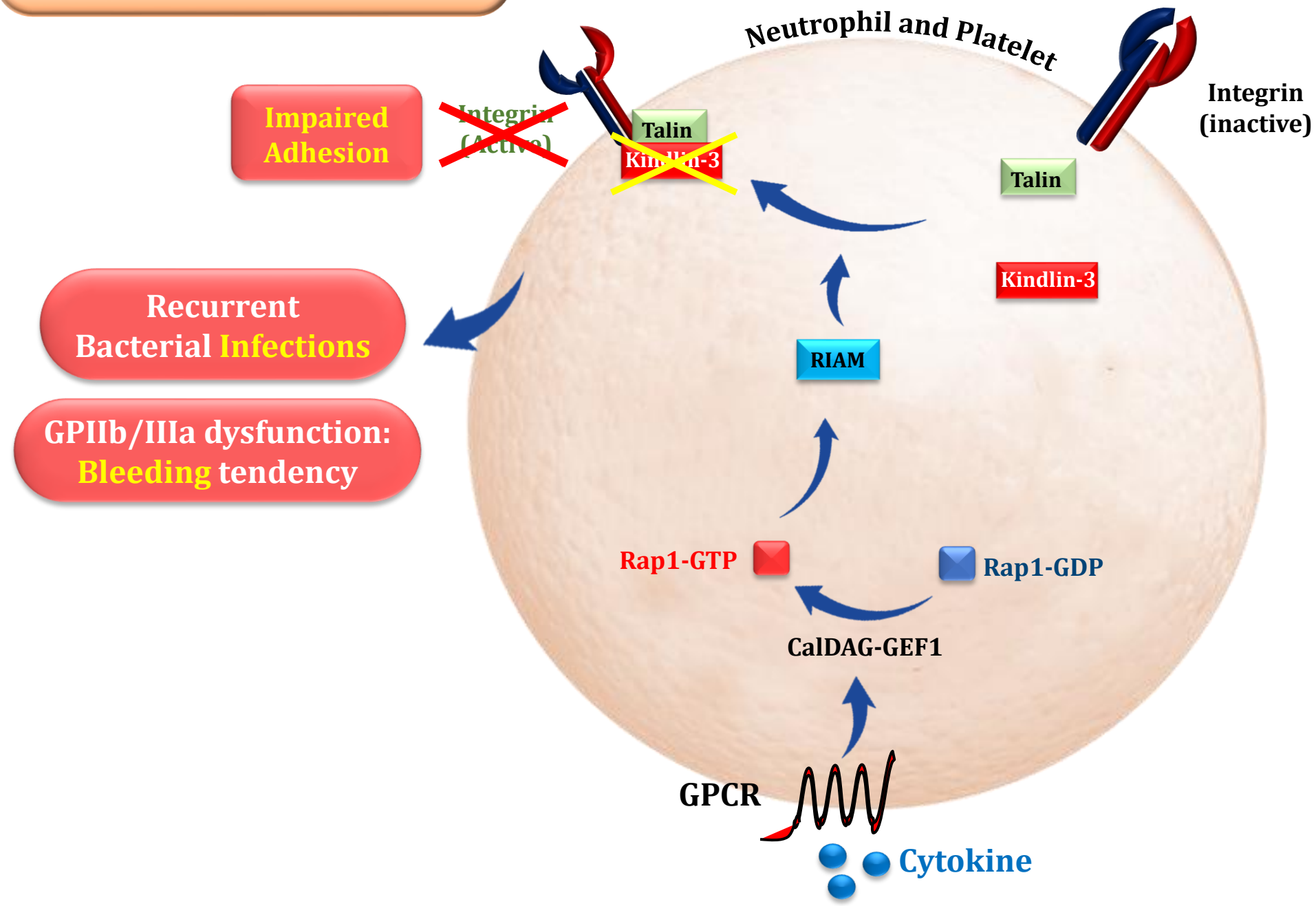


Degranulation Abnormalities **in Summary**




sLeX
Integrin
(inactive)
GPCR
LAD II
Impaired
Rolling
sLeX
Integrin
(inactive)
GPCR
LAD I
Impaired
Adhesion
Integrin (Active)
PCAM-1
IL-1, TNF-α
C3bi
Bacteria

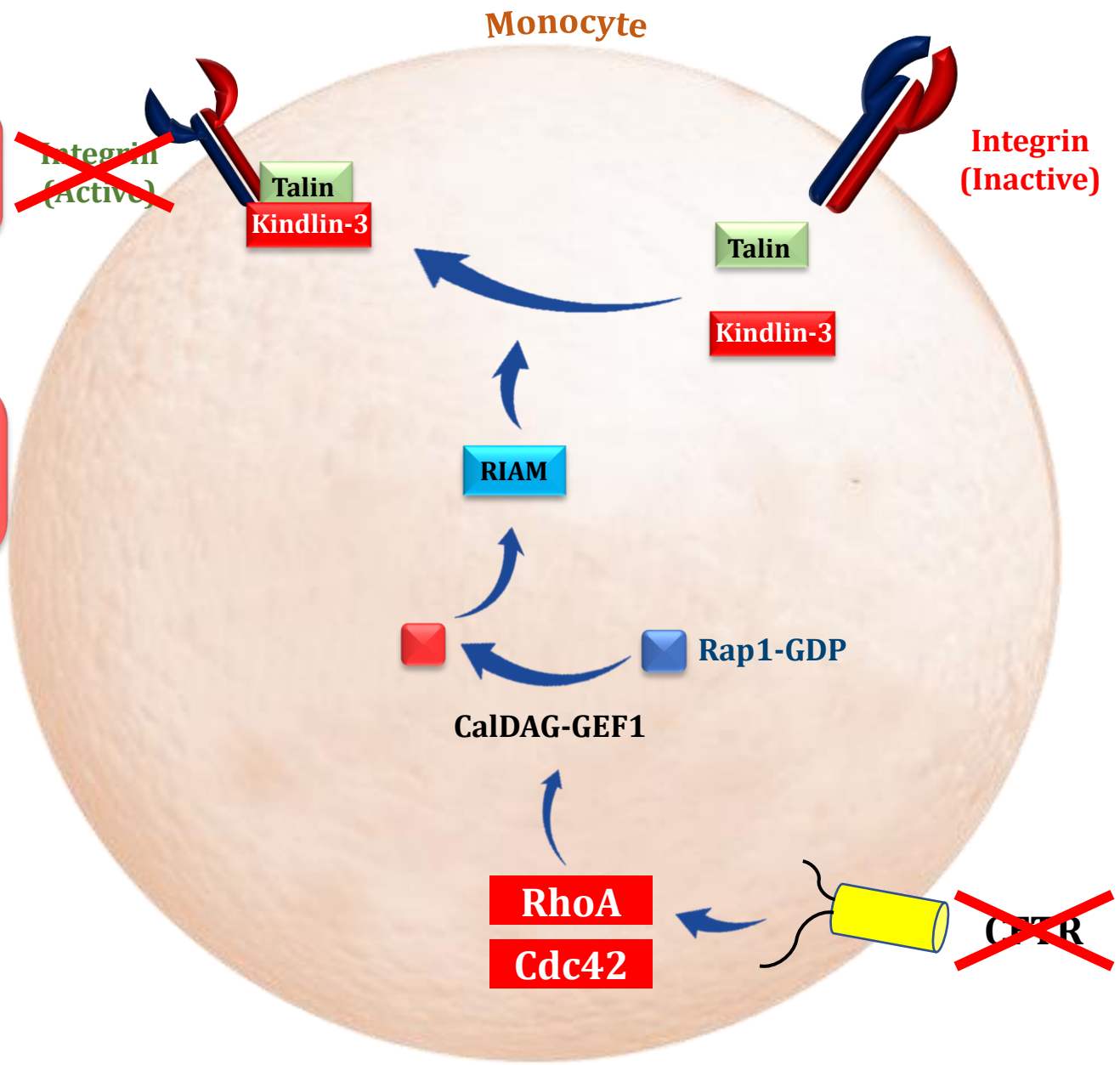
LAD III: KINDLIN3 Mutation



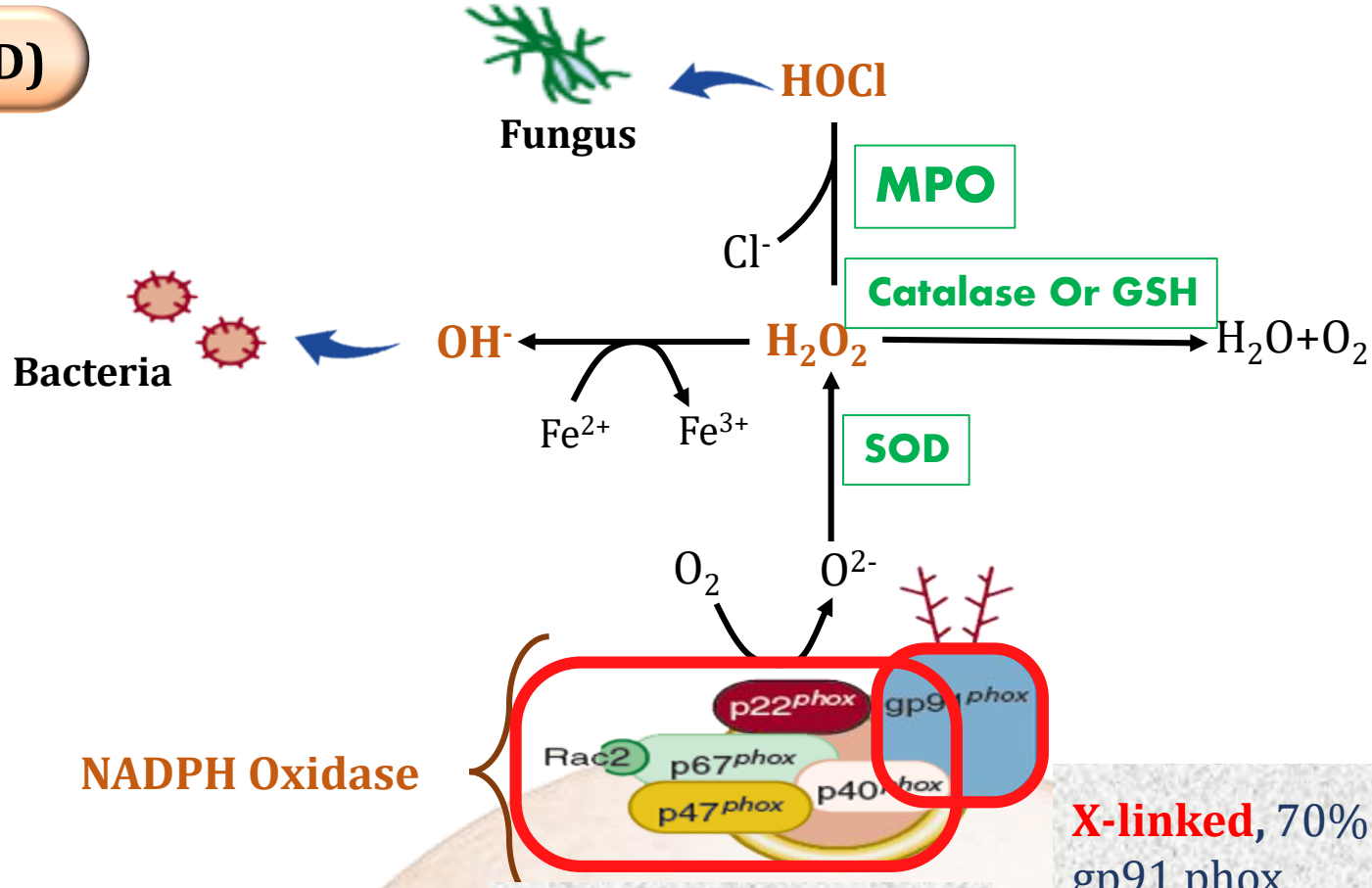
LAD IV: CFTR Mutation

Impaired Int Adhesion
In Mon of CF patients

- Impaired phagocytosis
- Impaired Ag presentation
- ...



Chronic Granulomatous Disease (CGD)

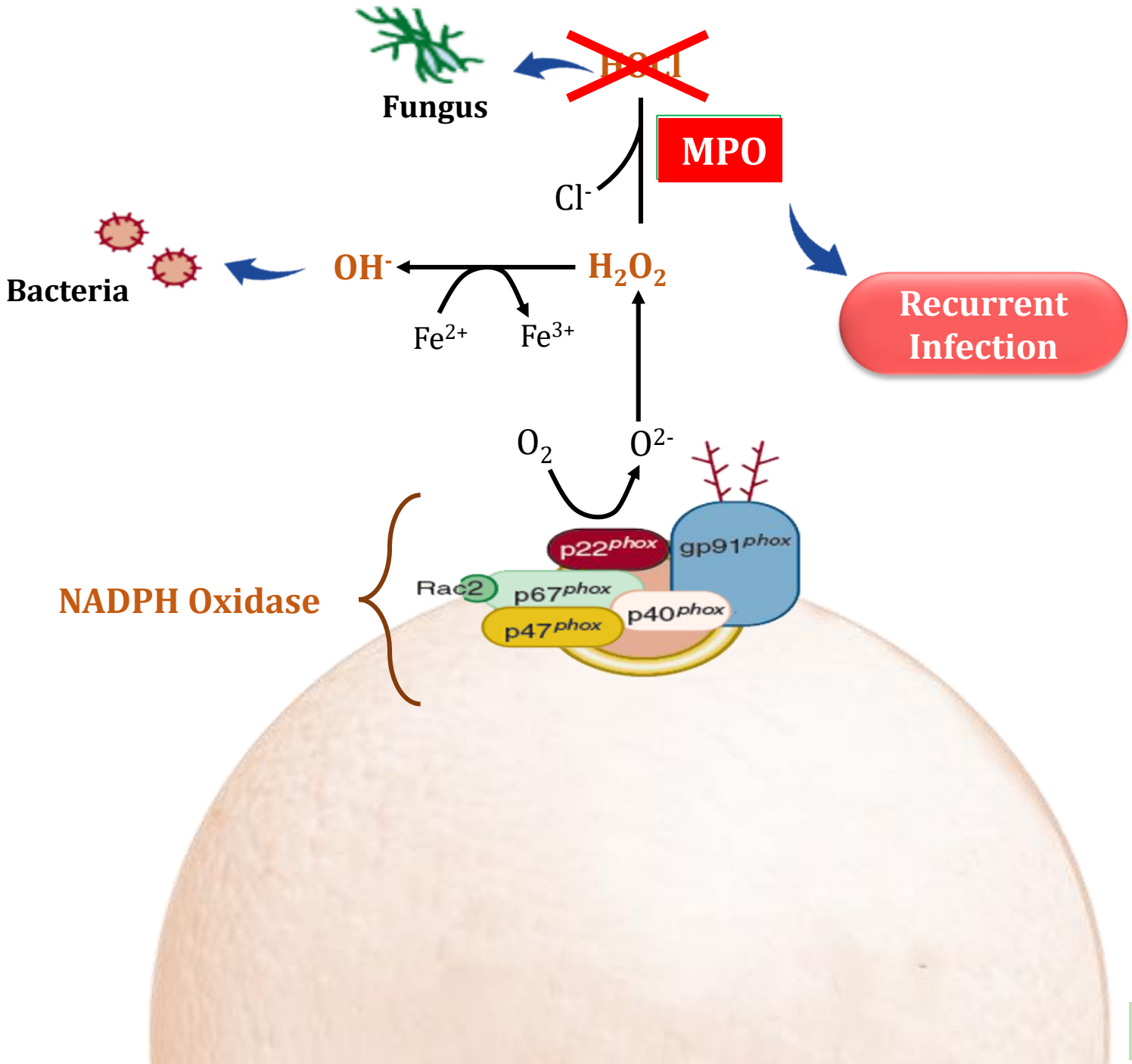


X-linked, 70%
gp91 phox

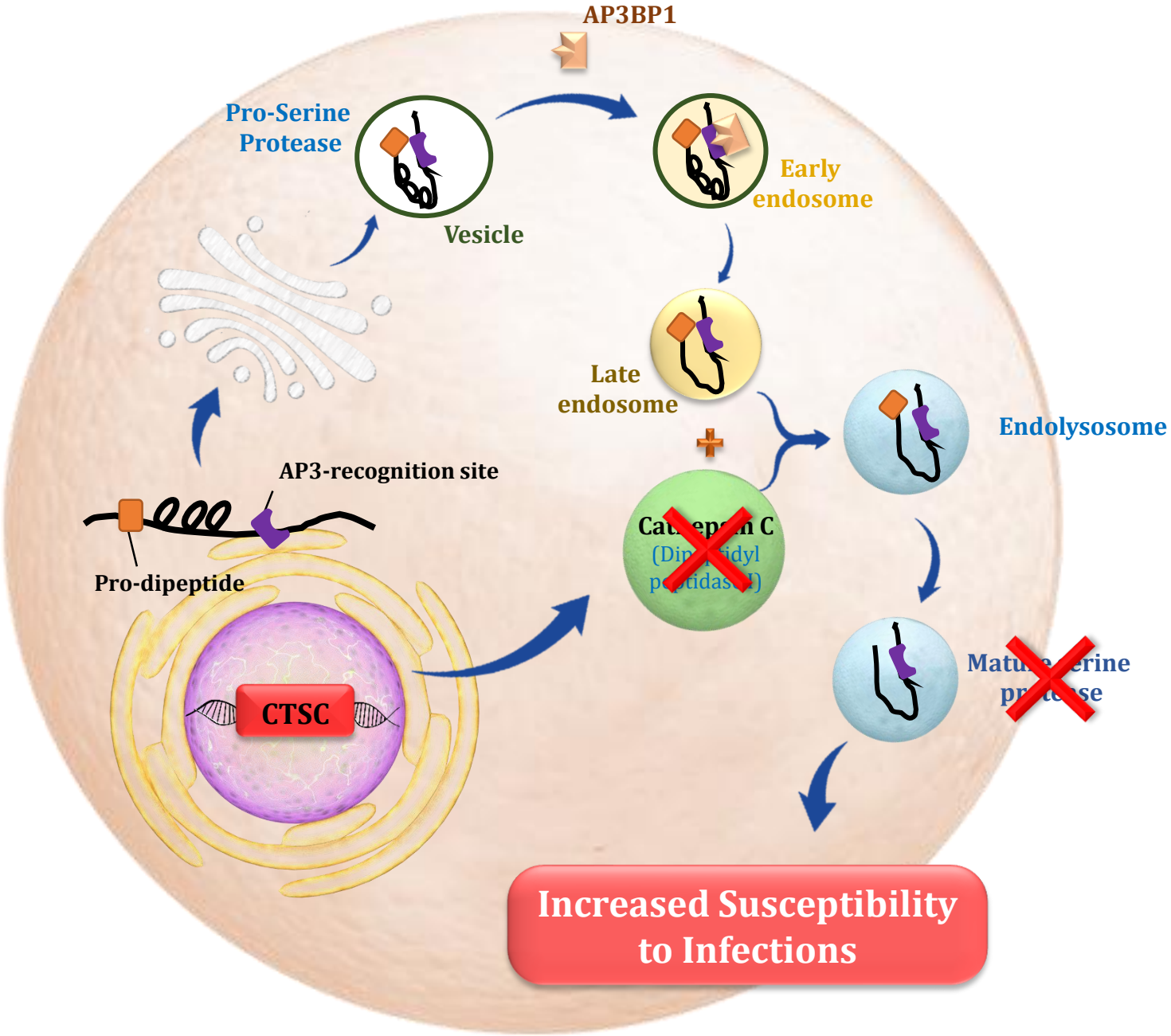
Autosomal Recessive:
p22phox
P47phox
P67phox
p40phox

Recurrent Infection

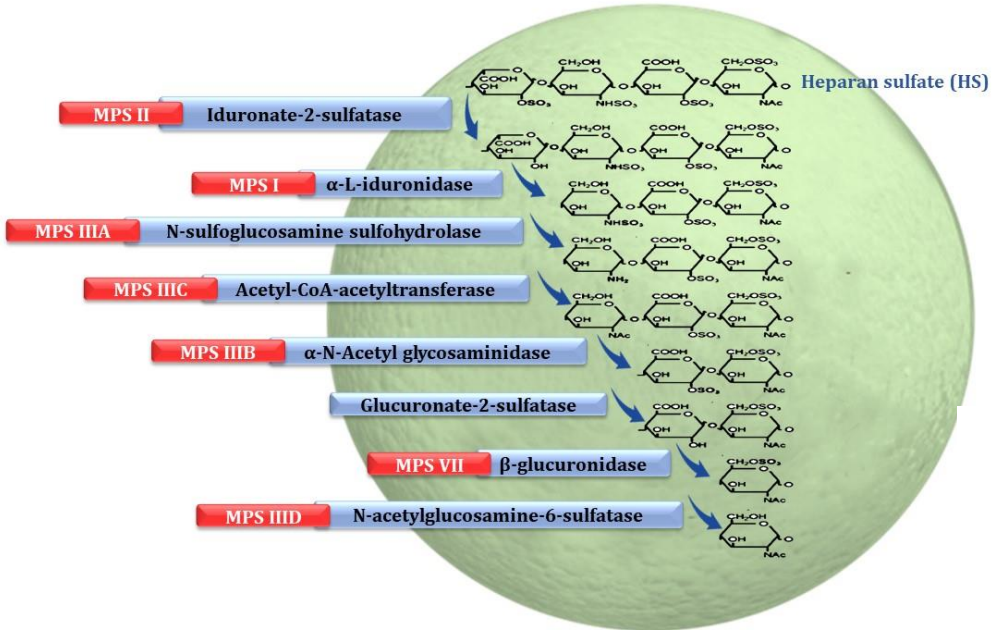
Myeloperoxidase Deficiency

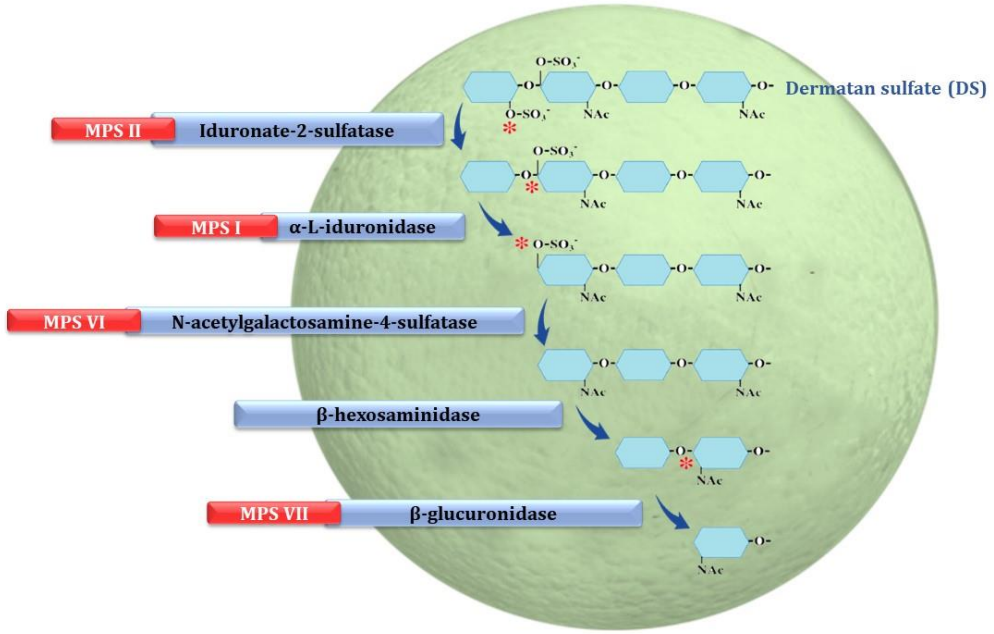


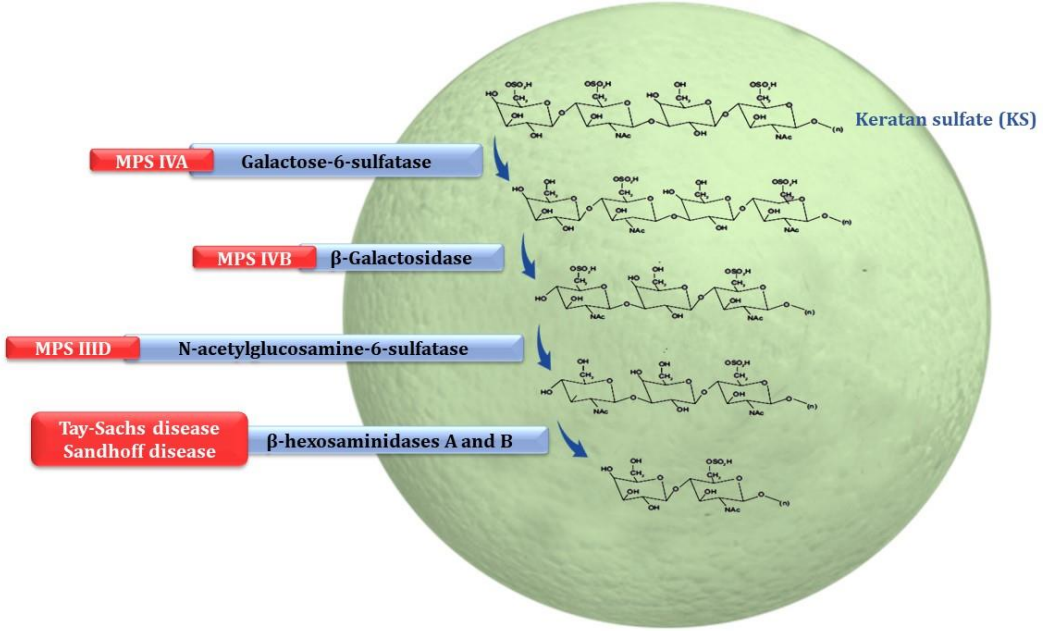
Papillon Lefevre syndrome: CTSC Mutation



Mucopolysaccharidoses



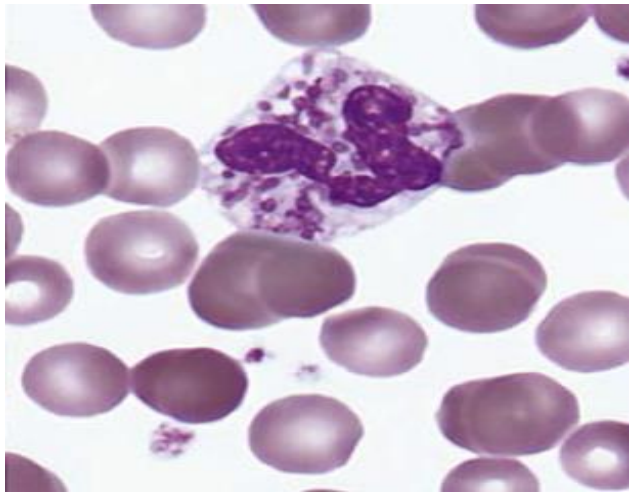


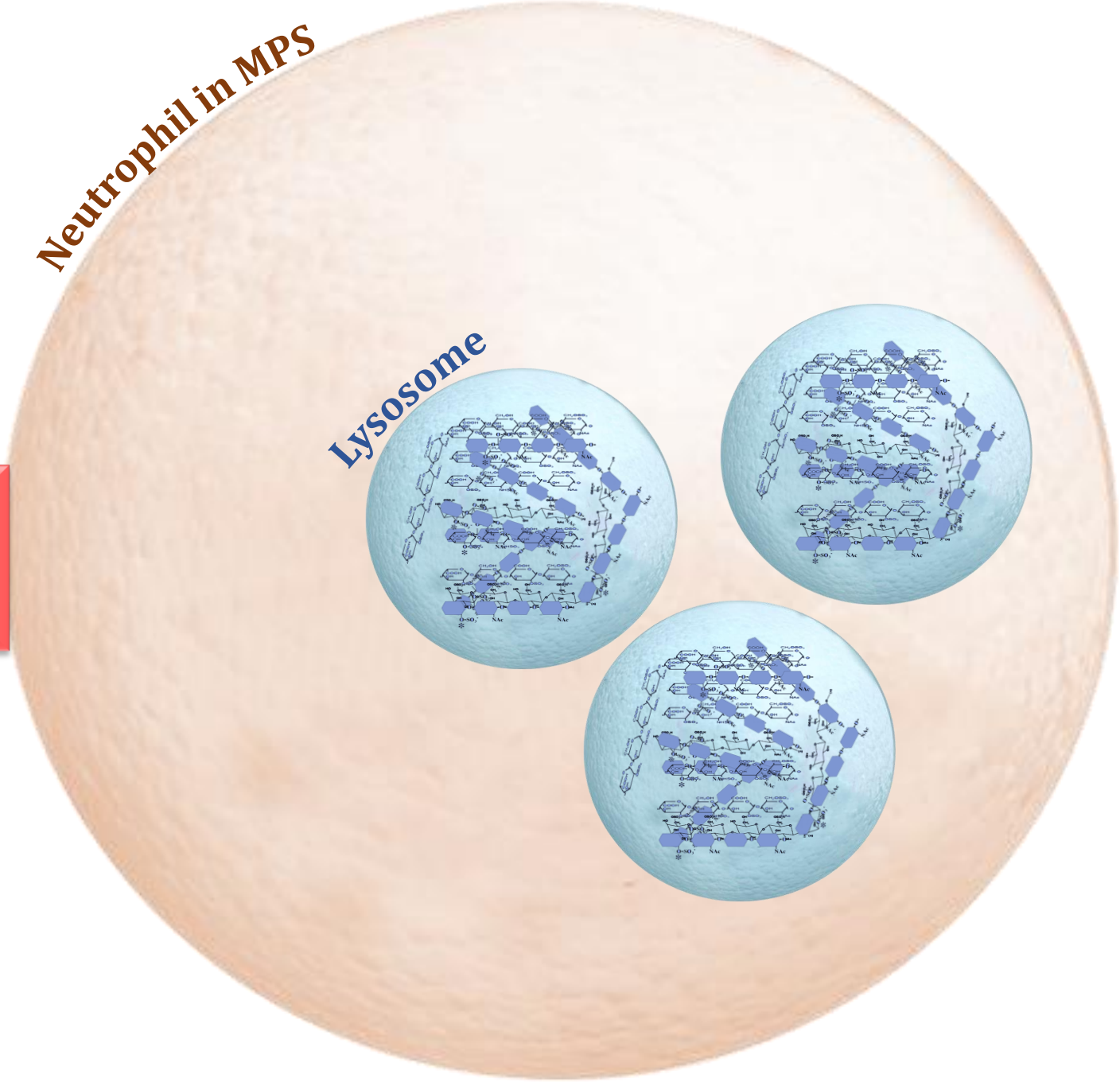


Alder–Reilly Anomaly

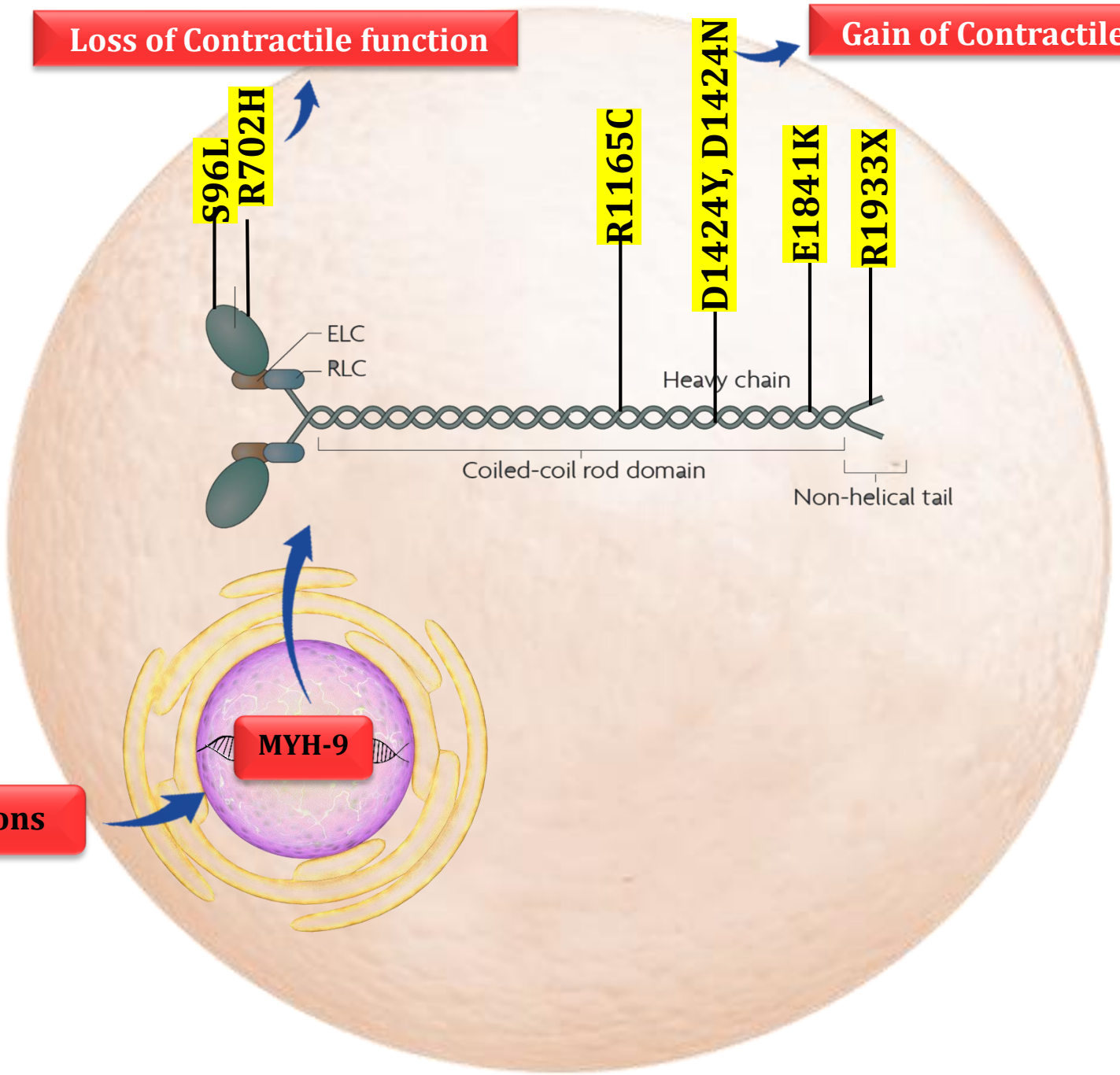
Partially-digested Mucopolysaccharides

- Physical Abnormalities
- Cognitive Problems
- Shortened Survival



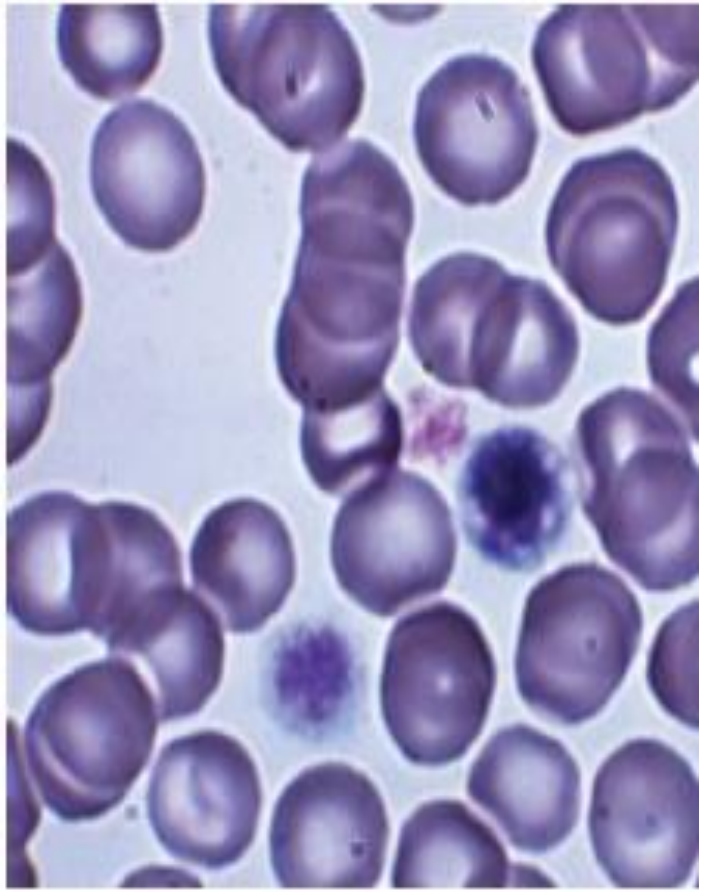


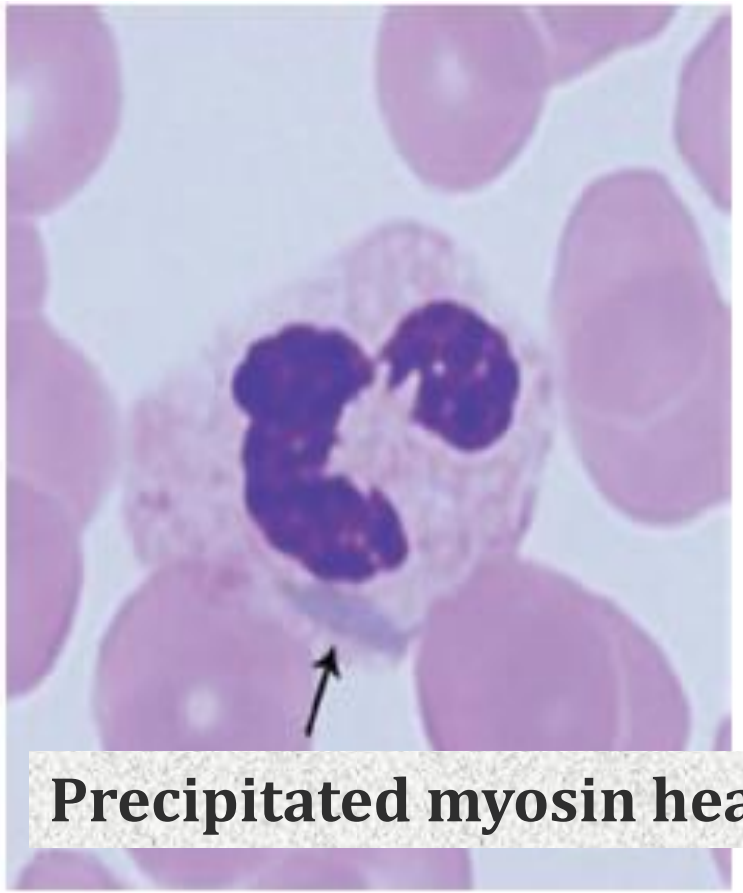
MYH9-related disorders



>80 different mutations

MYH9-related disorders





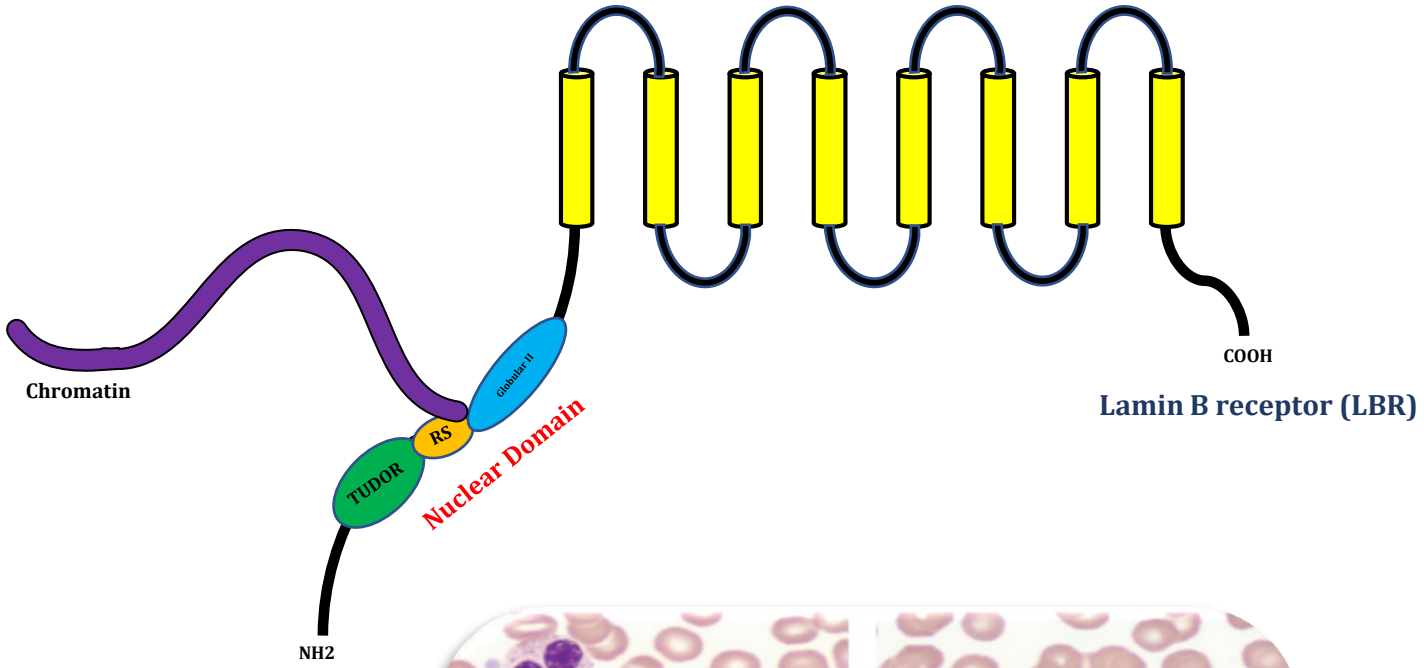
Precipitated myosin heavy chains

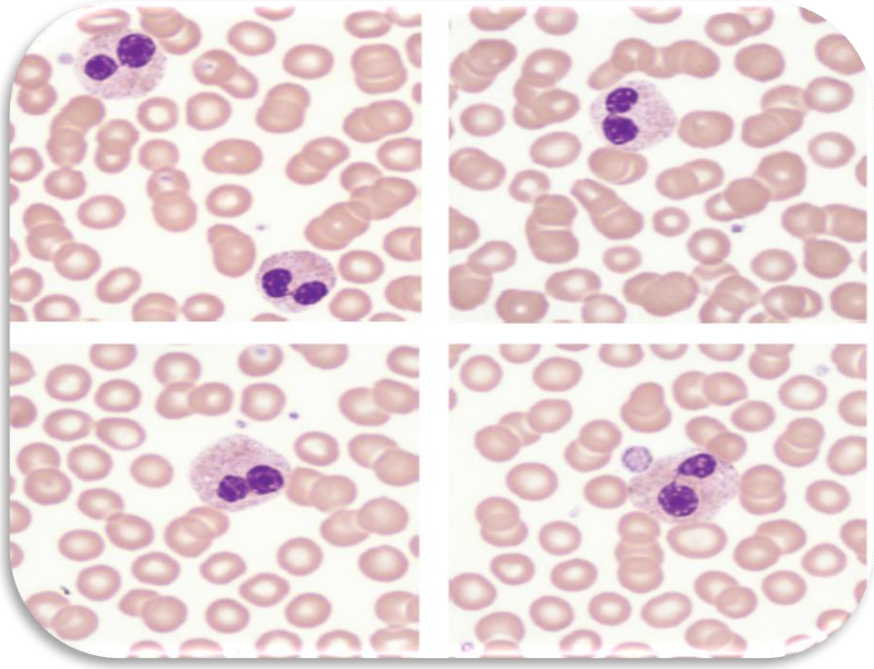
Giant Plt and Döhle-like inclusion bodies in Neutrophil

Pelger–Huët anomaly (PHA)

LBR gene Defects (Nuclear domain)

Hypo-Segmentation in Neutrophils

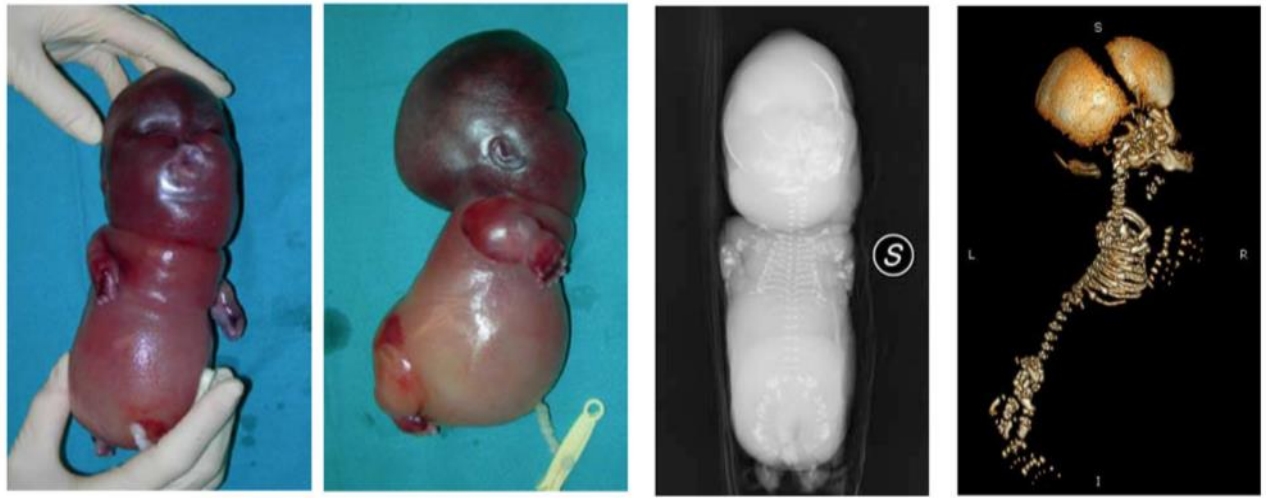




Greenberg Skeletal Dysplasia

Homozygous mutations;

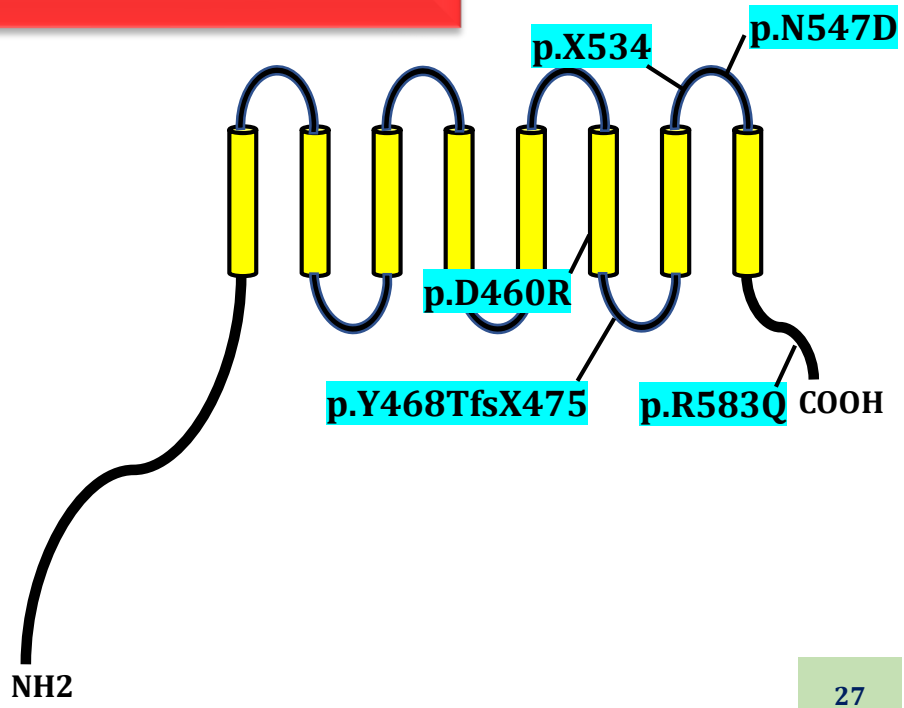
- c.1379 A>G (p.D460R)
- c.1492delT (p.Y468TfsX475)
- c.1599-1605TCTTCTA⇨CTAGAAG (p.X534)
- c.1639A>G (p.N547D)
- c.1748G.A (p.R583Q)



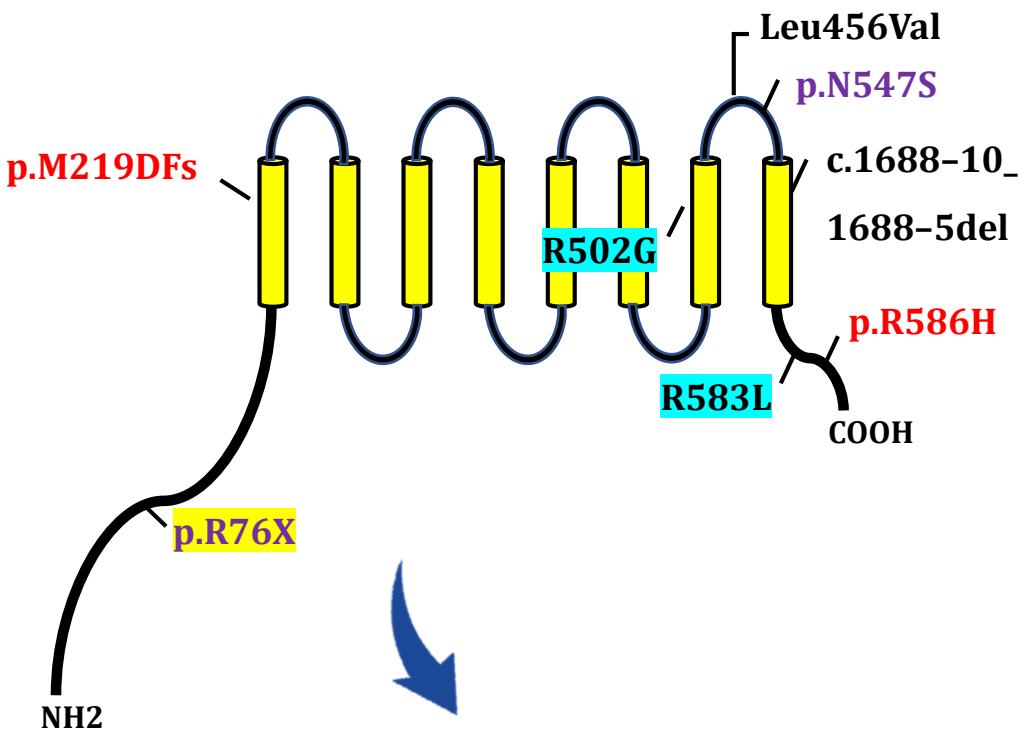
Impaired Fetal Development

Loss of Sterol Reductase Activity

Impaired Embryonic Hedgehog Pathway



Pelger-Huët Anomaly with mild Skeletal anomalies (PHASK)



Mild (Non-lethal) Skeletal Abnormalities with or without Bilobed Neutrophil Nuclei