Case Presentations in Primary Immune Deficiency Diseases

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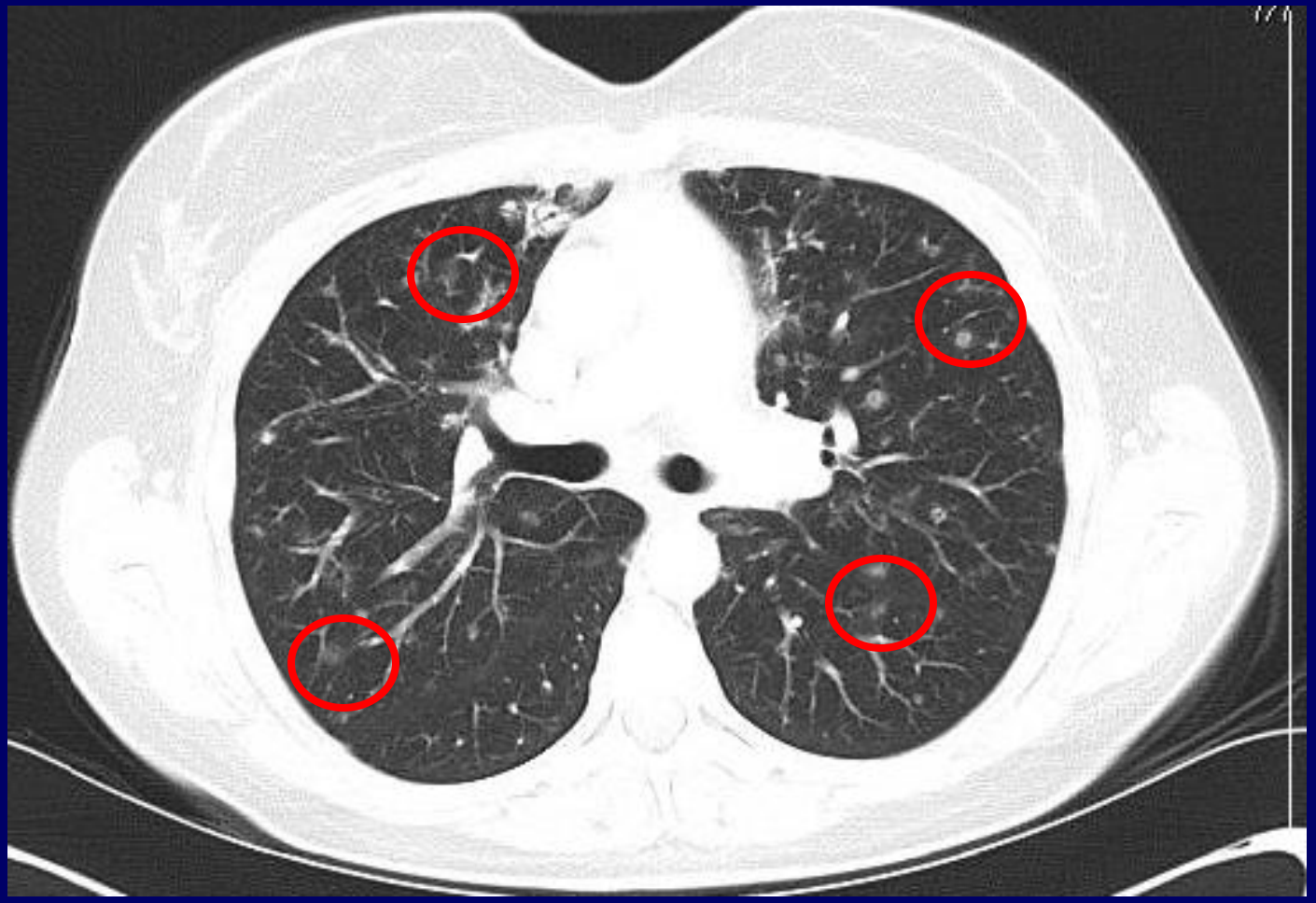
COPD and recurrent infections

- 42 WF non- smoker with diagnosis of COPD
- Chronic sinusitus, recurrent bacterial pneumonia requiring treatment with IV antibiotics
- FEV1- 64% predicted with little reversibility
- History of thrombocytopenia and splenomegaly

Bilateral, diffusely distributed nodules in lung and liver, mediastinal lymphadenopathy, bronchiectasis biopsies shows non-caseating granuloma



The Specialists

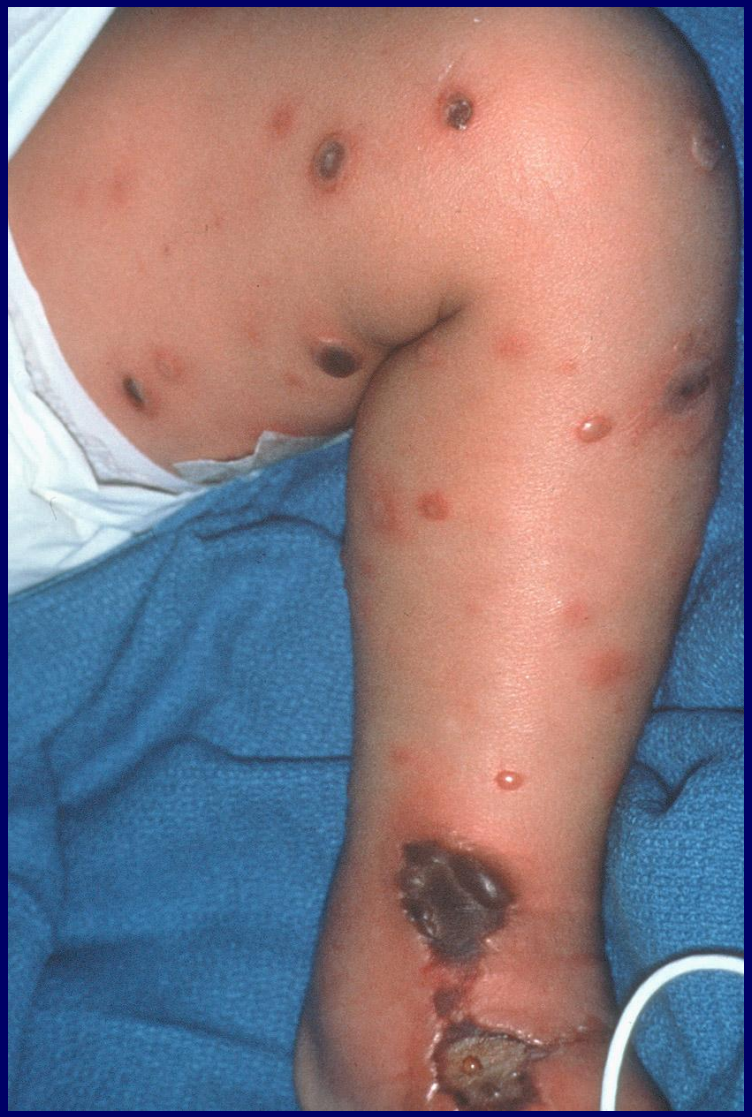
- **What does this patient have?**
  - **Her Rheumatologist said sarcoidosis.**
  - **Her oncologist suspected cancer.**
  - **Her pulmonologist said COPD.**
  - **She said “*to H#&!* with you guys!*”**

Immunology Evaluation

- **After nearly ten years of persistent symptoms and progressive bronchiectasis an immune evaluation was performed.**
- **Immuneglobulins Levels**
  - **IgG 154 (613-1295 mg/dl)**
  - **IgA < 5 (69-309 mg/dl)**
  - **IgM 10 (53-334 mg-dl)**
- **Low T cell numbers, inverted CD4/CD8 ratio**
- **No functional antibody titers to tetanus, diptheria, or pneumococcal polysaccharide**
- **HIV antibody testing was negative**
- **B cell enumeration was normal at 15%**

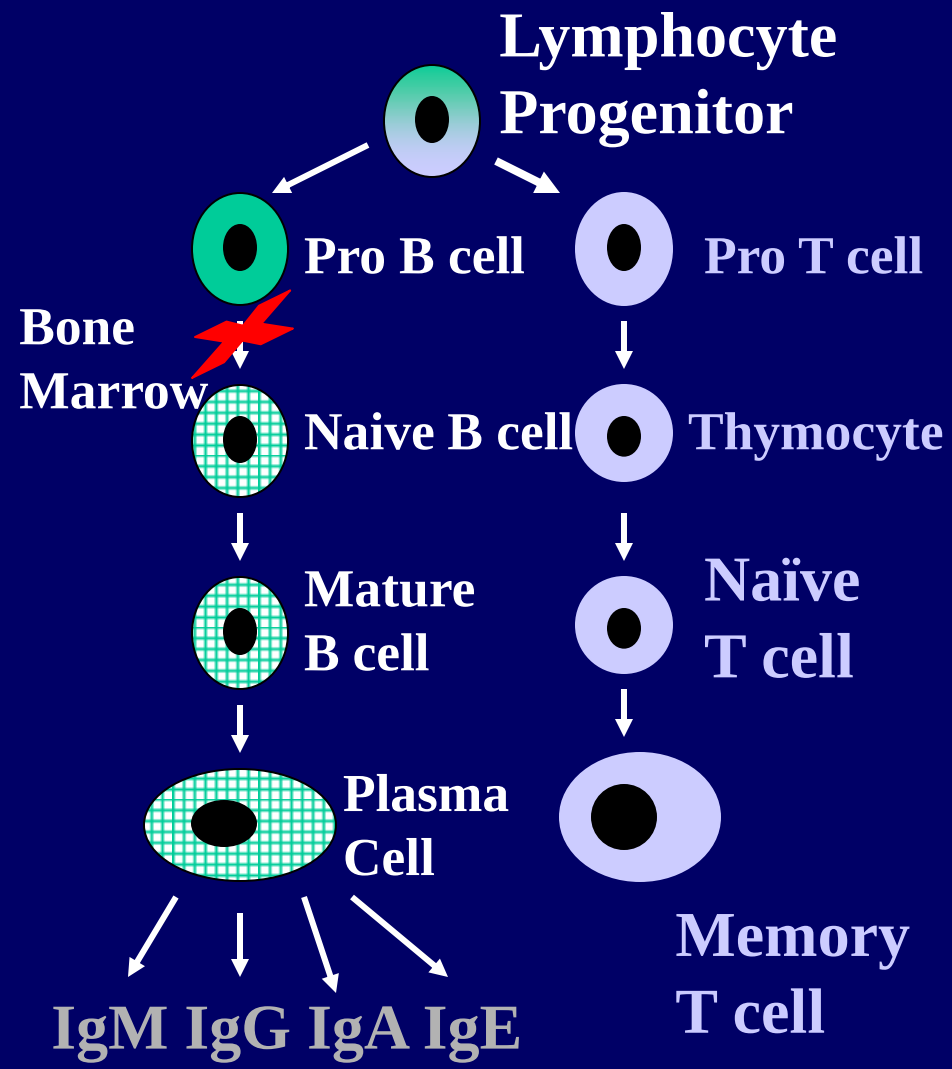
- **<u>DIAGNOSIS</u>: Common Variable Immunodeficiency**

Pseudomonas Sepsis



- 15 mo male in good health until age 12 mo
- 3 episodes of OM
- Initial hospitalization for fever, pneumonia, meningitis, and illustrated rash
- Cultures positive for *Pseudomonas aeruginosa*
- Leukocytosis with PMN predominance

X-linked Agammaglobulinemia



- Maturation arrest in Pre-B cell development
- No Circulating CD19 or CD20 B lymphocytes
- All Immunoglobulins decreased
- T cell Development is Normal
- Mutation in B cell specific *Src* associated tyrosine kinase (BTK)

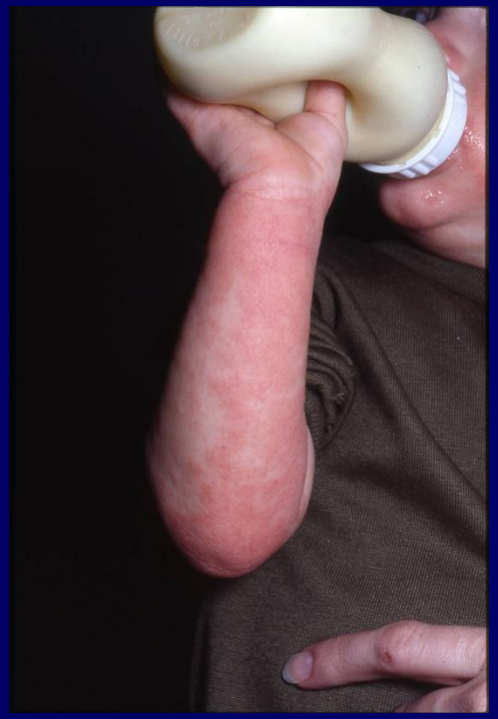
Infant with Neutropenia, Fever, and Spenomegaly

- **The 14 mo with thrombocytopenia, neutropenia, autoimmune hemolytic anemia with fever, enlarged liver and spleen, “silver” hair, and abnormally light skin.**
- **Serum ferritin level 10,000**

Griscelli Syndrome with Hemophagocytic Lymphohistiocytosis

Diagnostic Criteria for HLH

- Fever, splenomegaly,
- Cytopenia (Hb, plts, neutrophils)
- Hypertriglyceridemia or hypofibrinogeneia
- Hemophagocytosits (BM, Liver, LN, or CSF)
- Low NK activity
- Elevated ferritin (>500 mg/L)
- Abnormal sIL-2R in plasma



18 mo male with eczema, chronic OM, polyarticular arthritis with this immunoglobulin profile:

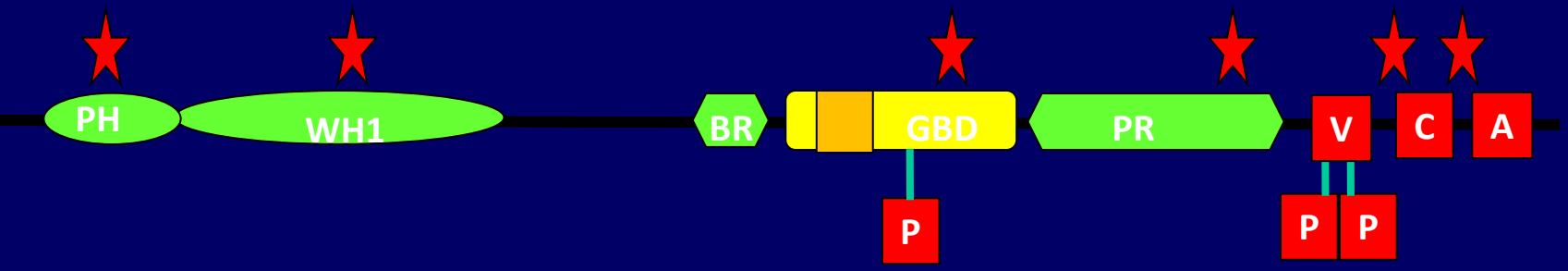
	Patient	Normal levels for age
IgG	445	383- 1030 mg/DL
IgA	255	27- 169 mg/DL
IgM	10	28- 113 mg/DL
IgE	335	0-180 IU/ml

You would expect which of the following laboratory findings in this child?

a) elevated serum creatinine
b) abnormal serum aldolase level (>15 mg/DL)
c) positive HIV ELISA
d) platelet count of <20,000/ul

Wiskott Aldrich Syndrome

Clinical phenotypes correlate with genotype in WAS:



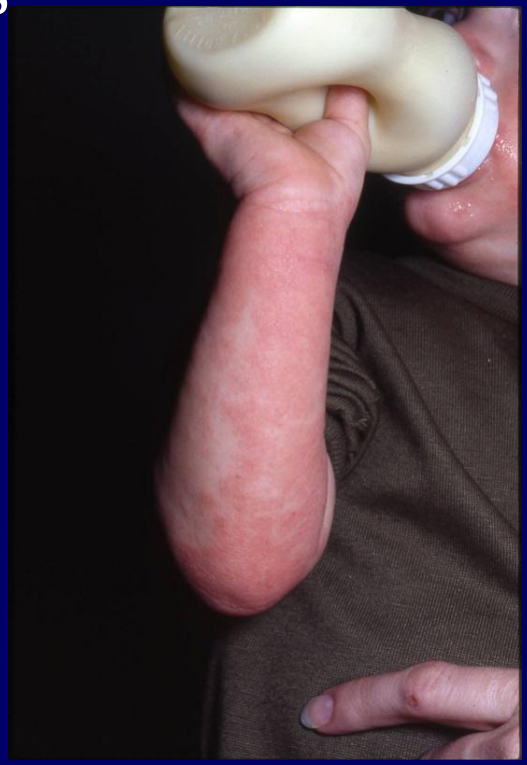
Four Clinical Phenotypes resulting from mutations of WAS:

Wiskott Aldrich Syndrome

X-Linked Thrombocytopenia

Intermittent XLT

X-Linked Neutropenia

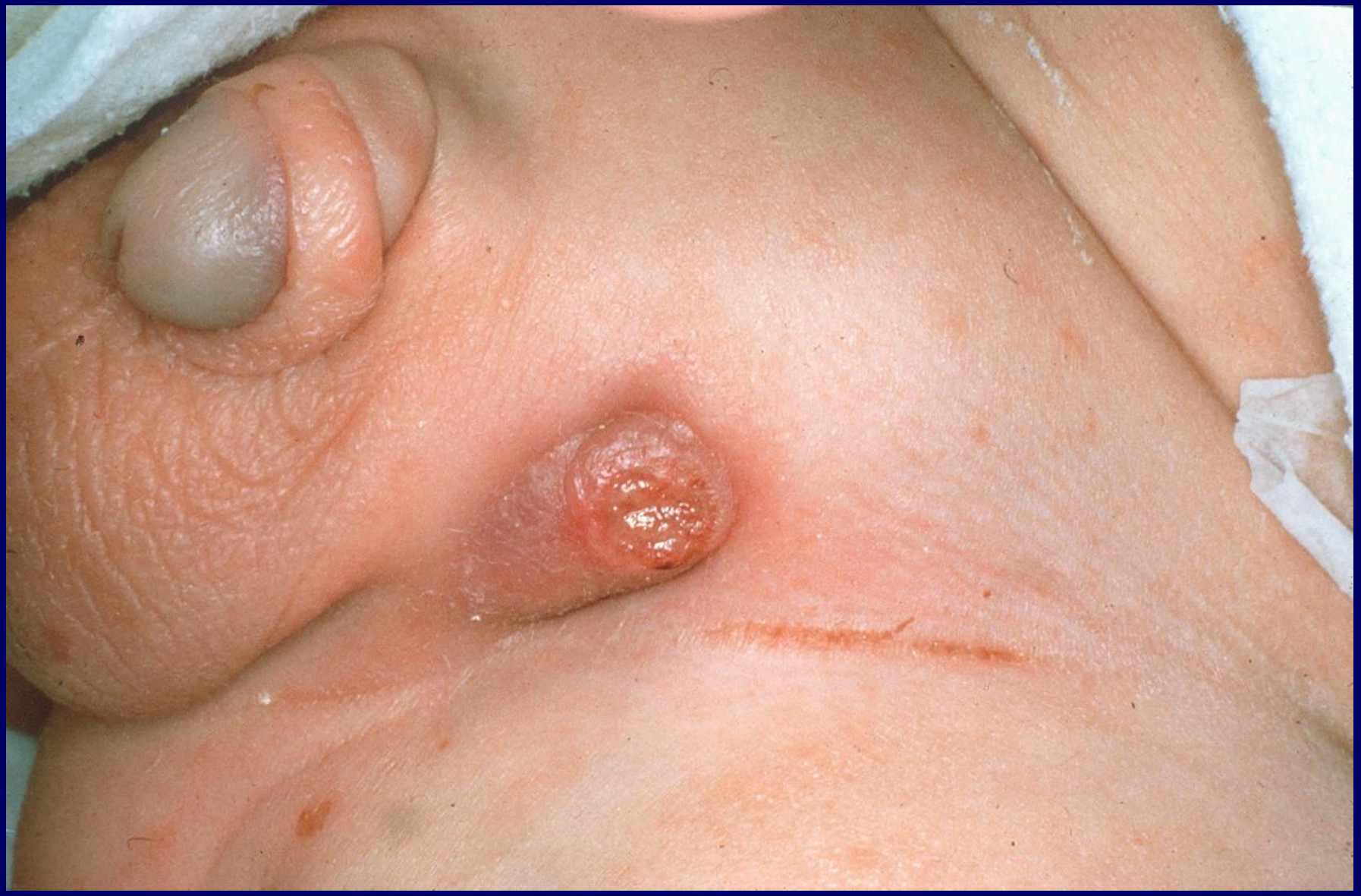


Mutations mostly exonic and distributed across gene

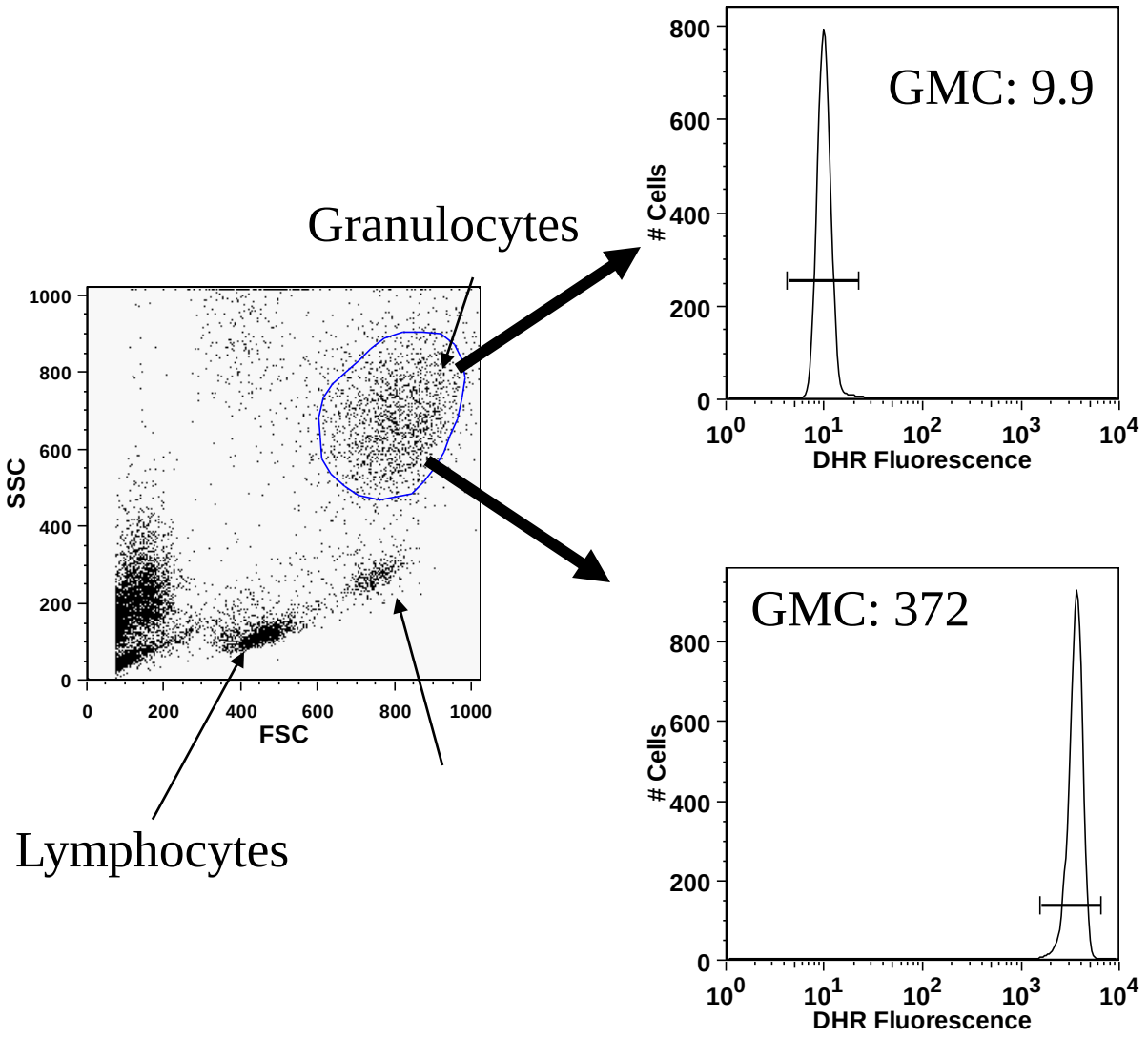
Effect on protein expression *generally* correlates with phenotype severity

- **Milder: some protein expressed**
- **Severe: no protein expressed**

Staph aureus Lymphadenitis



Analysis of Granulocyte Respiratory Burst Using Dihydrorhodamine (DHR)

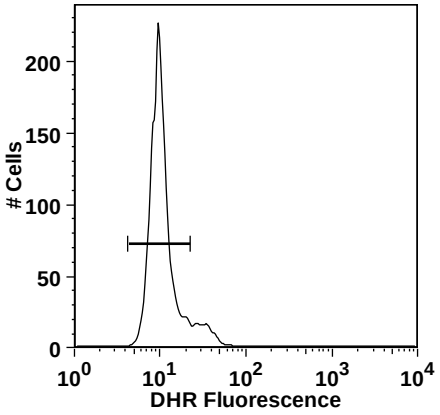
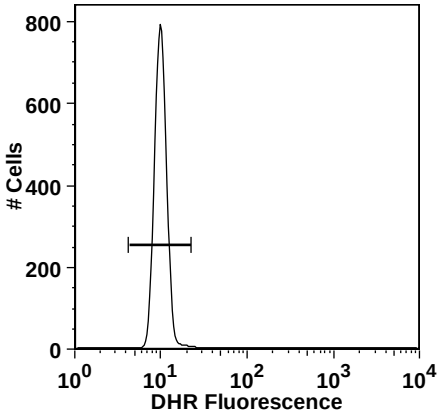
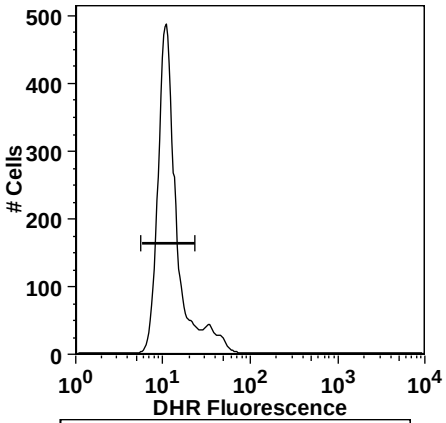
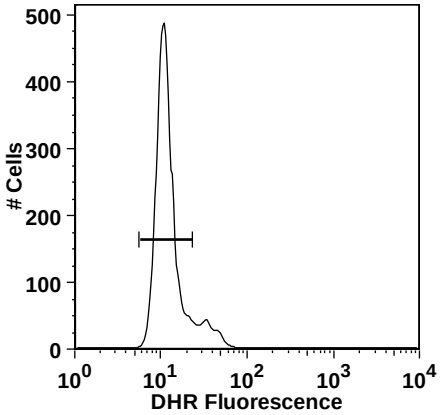
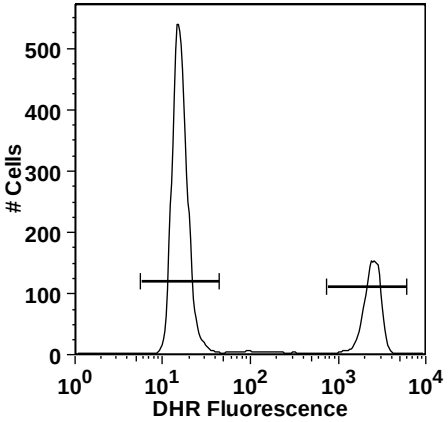
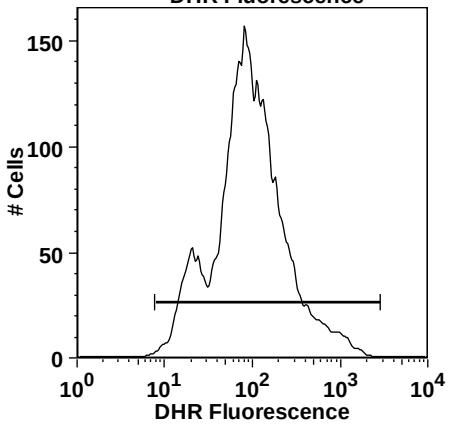


Unstimulated cells

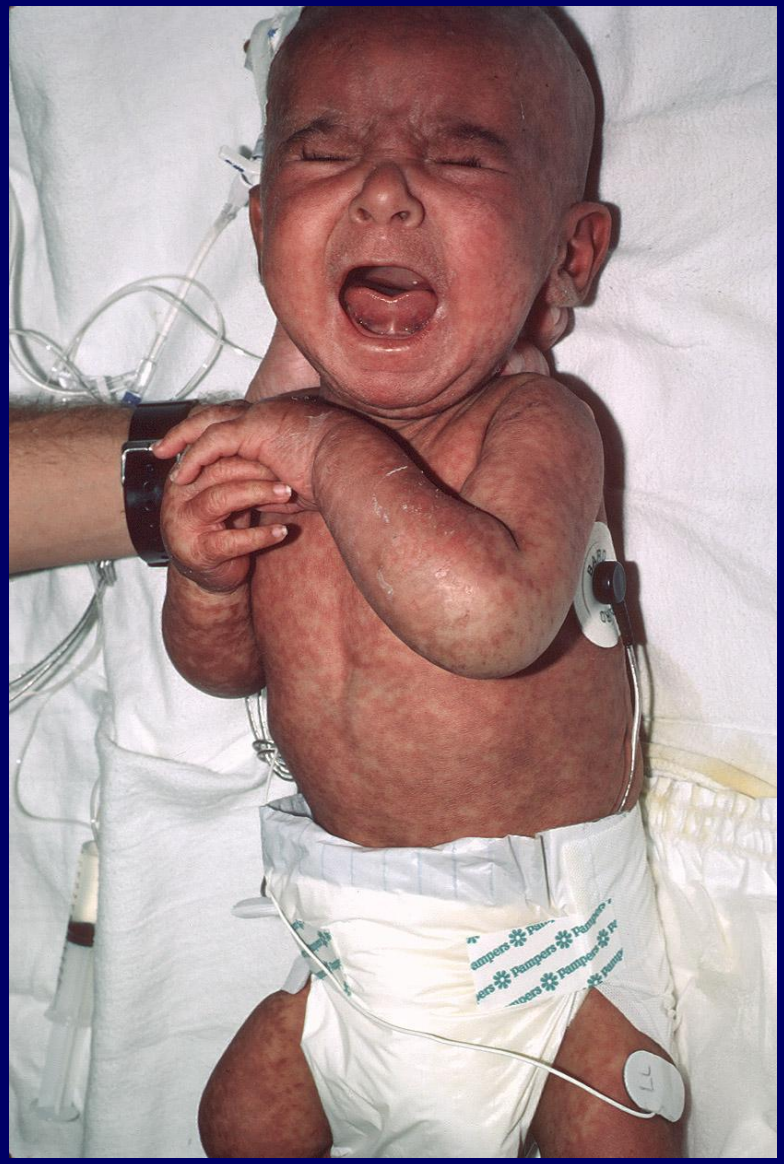
Stimulated with PMA
SI = 376
(Normal ≥ 100)

Stimulation Index (SI) = non-stimulated GMC ÷stimulated GMC

ABNORMAL DHR RESULTS

	***gp*$^{91-}$ (X-linked)**	***gp*$^{91-}$ (female carrier)**	***p*$^{47-/-}$**
Non-Stimulated			
PMA Stimulated			
	SI = 1.1	**peak #1 SI = 1.5** **peak #2 SI = 248**	**SI = 9.1**

Severe Combined Immune Deficiency

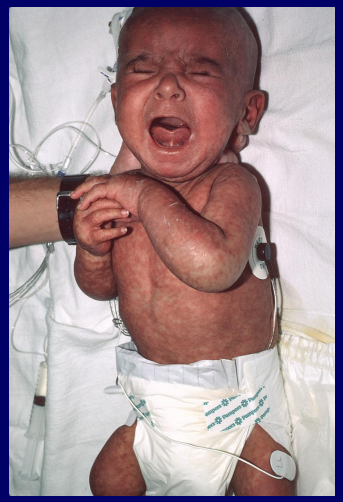


- PCP
- Failure to thrive
- Rash and Hepatitis following transfusion
- Normal total WBC
- Severe Lymphopenia

SCID: ADA Deficiency
(Defective Purine Salvage Pathway)

NORMAL:

(toxic metabolite)
deoxyAdenosine
+
Normal ADA
↓
Deoxyinosine
NON-toxic

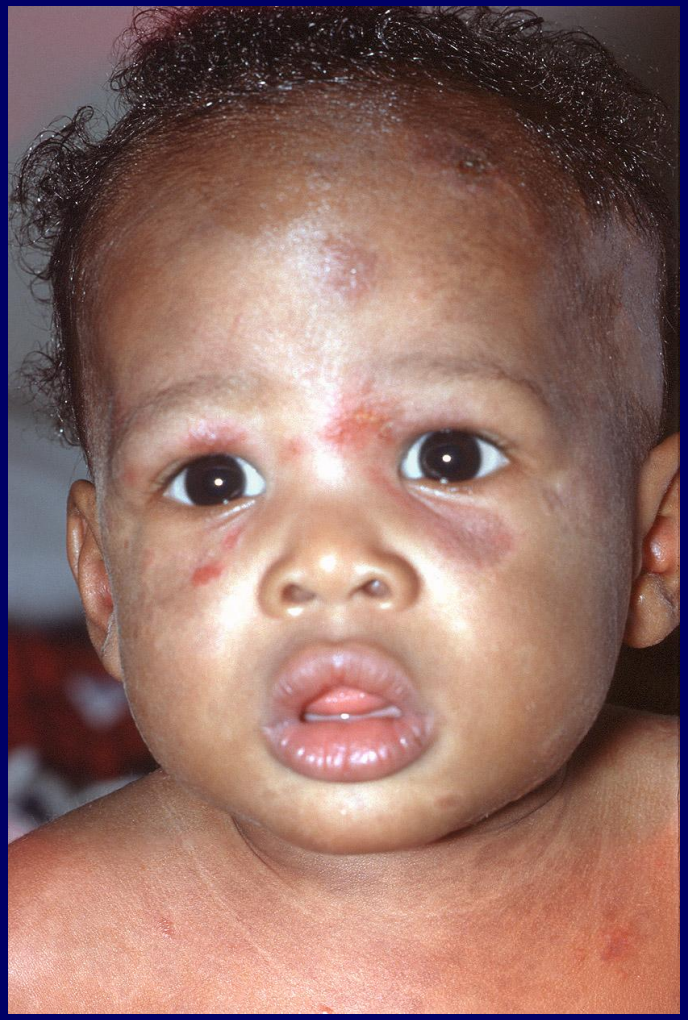


Adenosine deaminase deficiency:

(toxic metabolite)
deoxyAdenosine
+
ADA deficiency
↓
accumulation of
deoxyadenosine
lymphocyte death

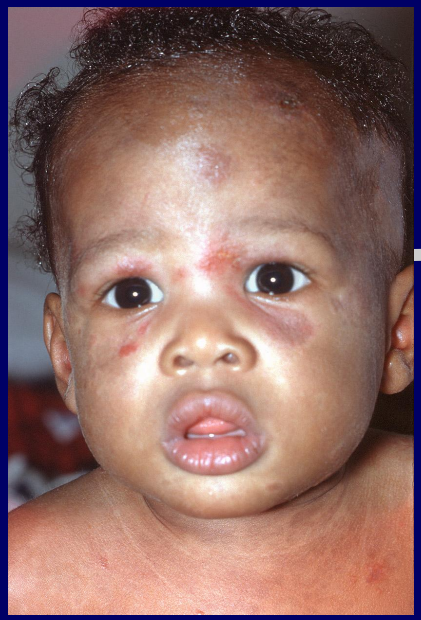
Absent T , B, or NK Cells

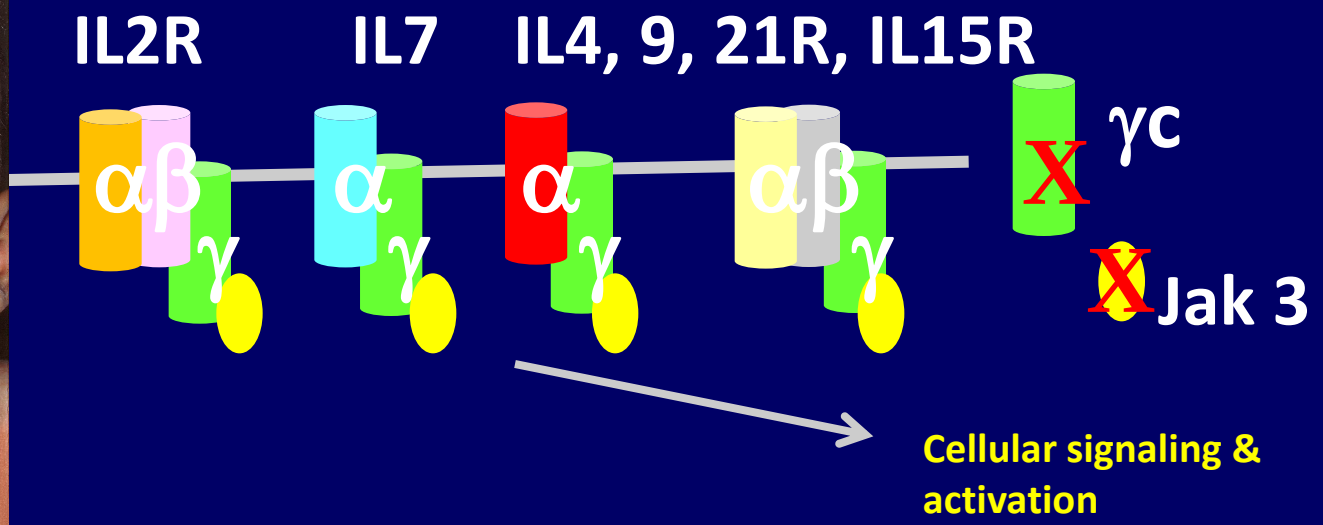
Rash in a 4 mo old



- Failure to thrive
- Skin Biopsy shows perivascular lymphocytic infiltrate
- What are these cells telling you?

SCID with nonfunctional B cells: X-linked (γc) and Jak3





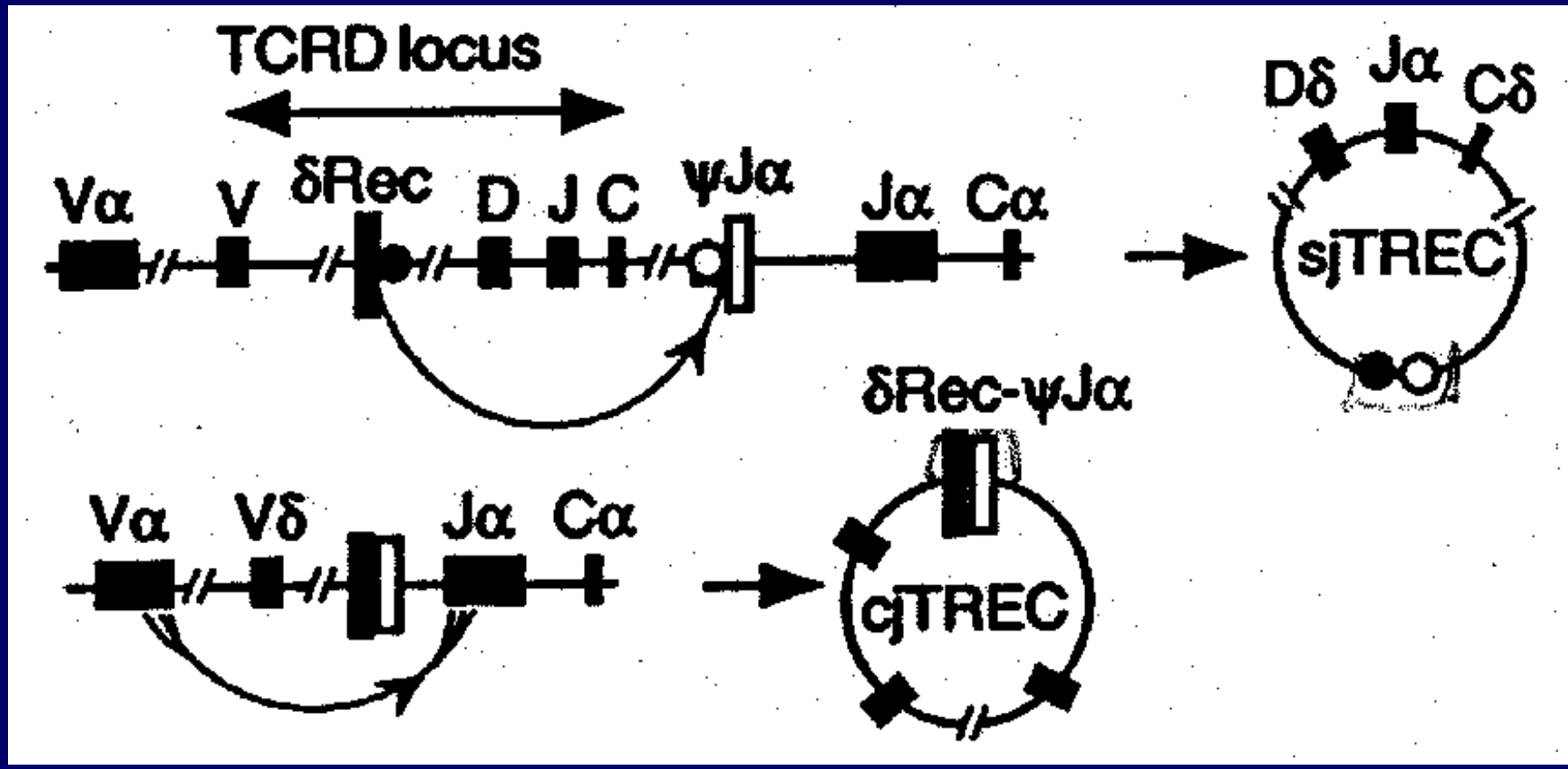
- Receptors for IL-2, 4, 7, 9, 15, 21 share common γ chain (γc)
- Jak 3 is involved in intracellular signaling through γc
- Mutations in common γ chain cause X linked SCID (44%)
- Mutations in Jak 3 cause an autosomal recessive SCID (6%)
- Intracellular signaling through γc and Jak 3 important in T cell and NK cell development
- Phenotype is T-,NK-,B+ SCID for both of these forms

Adapted from: R. Buckley, Primary Cellular Immunodeficiencies. JACI May 2002.

T/B/NK Phenotypes in SCID

Phenotype	Defect	Genetics
$T^-/ B^-/ NK^-$	ADA Deficiency	AR
$T^-/ B^-/ NK^+$	RAG Deficiency	AR
	Artemis	AR
$T^-/ B^+/ NK^-$	γc IL-2R	X-linked
	Jak3	AR
$T^-/ B^+/ NK^+$	IL-7άR	AR
	CD3 δεζ TCR	AR
	Complete Di George	AD

TREC


TCRD locus
Vα
V
δRec
D
J
C
ψJα
Jα
Cα
Dδ
Jα
Cδ
sjTREC
δRec-ψJα
Vα
Vδ
Jα
Cα
cjTREC

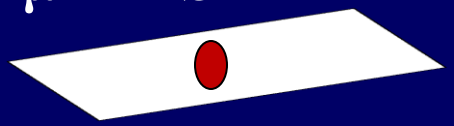
TREC Assay for NBS

Baker, et al, JACI 2009

Screening
all infants

blood
drop

3 µl DBS



Guthrie
Card

3.2 mm punch

DNA extraction

RT-qPCR
δRecψJαTREC primers
β actin control

40 cycle Amplification

Median TRECs 827 copies
Cutoff for SCID <25 copies

T cell Deficiencies with abnomal TREC levels

- SCID subtypes: ADA, RAG1, Artemis, Jak3, γcIL-2R (x-linked SCID), IL-7Rα, ζTCR, Zap70, reticular dysgenesis, CHH
- Non-SCID subtypes with low TREC: 22q Deletion Syndrome (DiGeorge), other thymic defects (CHARGE), Idiopathic T cell lymphopenia, extravascular T cells (chylothorax)