Non-Infectious Presentations and Complications of Immunodeficiency: A New Era of Immune Defects

Jennifer Leiding, MD
Associate Professor
Division of Allergy and Immunology
Department of Pediatrics
University of South Florida
jleiding@health.usf.edu

Disclosures

- Horizon Pharma – Speaker and Consultant
- CSL-Behring – Speaker and Consultant
- All Children's Foundation – Grant support
- USF – grant support

Learning Objectives

- 1. Identify new rare defects of the immune system that cause immunodeficiency.
- 2. Understand non-infectious presentations and manifestations of primary immunodeficiency.
- 3. Describe the evaluation of patients with immunodysregulatory diseases.

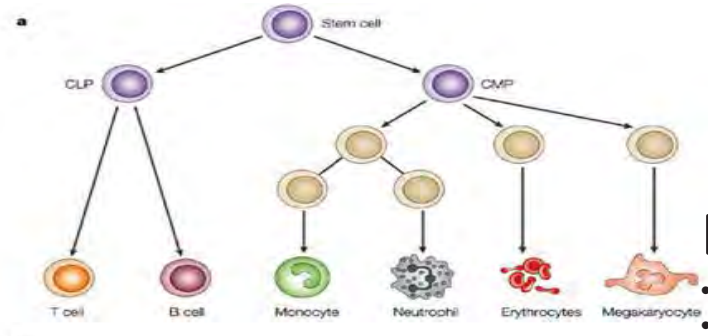
The Immune System

- What does it do?
  - Recognizes pathogens (non-self)
  - Organizes a defense response
  - Facilitates pathogen destruction and elimination

The Immune System

1. Innate
   - Present from birth
   - Specificity is “pre-programmed”
   - Includes non-immunological cells (e.g. skin and cilia)
2. Adaptive
   - Develops during life with exposure to infection (memory)
   - Increases affinity with experience (specificity)
   - Two compartments:
     - Cellular- Mediated by cells
     - Humoral-Mediated by soluble factors
   - Memory and Specificity are key features

Lymphocytes



T cells

- Develop in the thymus
- Mediate specific cellular immunity, kill infected cells
- Provide help to B cells for antibody production
- Regulate immune responses through cytokine secretion

B cells

- Develop in the Bone marrow
- Mediate humoral specific immunity by producing antibodies

Neutrophils

- Average count is 5000/ul
- Make approximately 10^{11} per day
- Most are in the bone marrow
- Can go up 10 fold in emergencies
- Circulating half life is about 7 hours

Molecular biology of PIDD

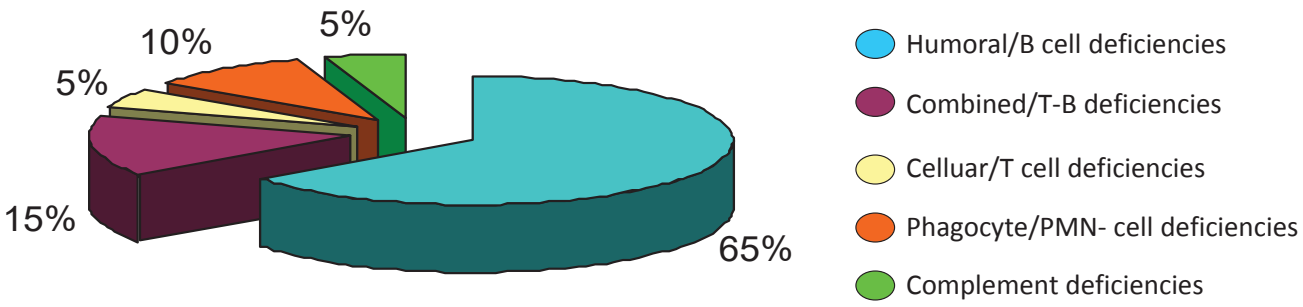
- Over 300 genetic abnormalities described for primary immune deficiencies

Primary Immunodeficiencies

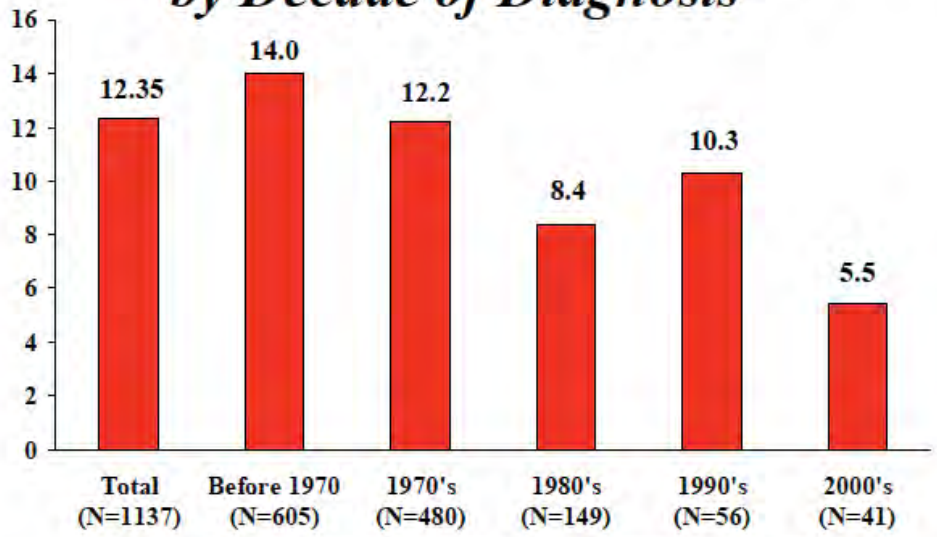
Epidemiology

- Incidence: 1/1,200-20,000 (2:1, ♂:♀)

- Distribution:



Average Number of Years to Diagnosis by Decade of Diagnosis



Q9. At what age was that person first diagnosed with a primary immunodeficiency disease? Q8. At what age (in years) did these repeated, serious or unusual infections begin? (Base: Infection prior to diagnosis- N = 1,218; 81 cases missing data to Q8 or Q9).

10 Warning Signs of Immunodeficiency*

1. Eight or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or elsewhere on skin, after age 1.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections.
10. A family history of Primary Immunodeficiency.

*The Jeffrey Modell Foundation, Inc.

Infections in PIDD

- Unusual
  - Opportunisitic, fungal, viral
- Severe
  - Deep, blood borne
- Chronic
  - Poor response to therapy, recurring

Antibody Deficiency

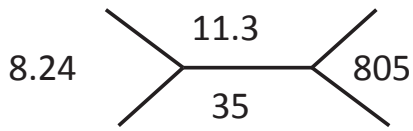
- Still by far the most common
- Recurrent sinopulmonary infections
- Susceptibility to GI infections
- Often managed with immunoglobulin supplementation

The Concept of Immune Dysregulation

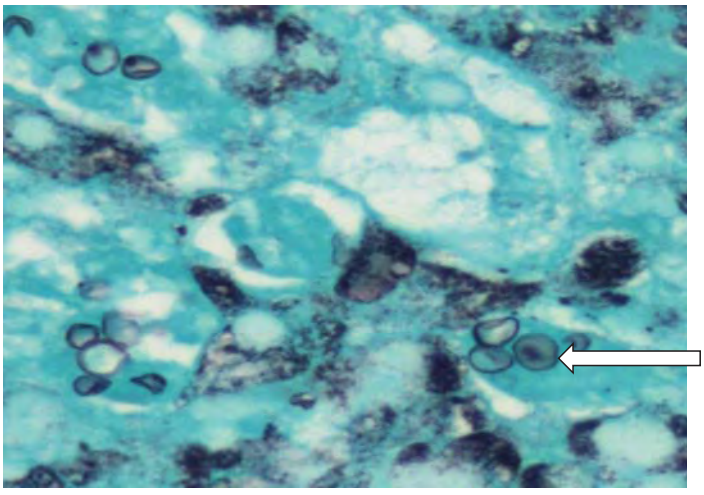
- The immune system – Not just to fight infections
  - Prevention of autoimmunity
  - Cancer surveillance
  - Host – microbial interactions / symbiosis
- Quality matters more than quantity
- Too much of anything is bad

Case 1

- 12m male with
  - Chronic diarrhea
  - Chronic cough
  - Failure to thrive
  - Elevated liver enzymes



- Differential
  - PMN 88%
  - Eos 2%
  - Lymphs 2%
  - Monos 8%
- ALC = 165



PJP on micrograph of liver biopsy

SCID – Molecular Causes and Phenotypes

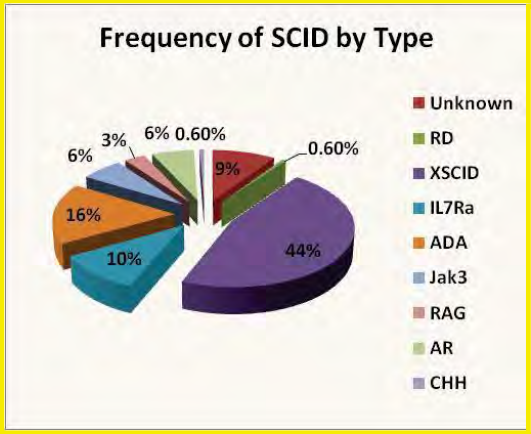


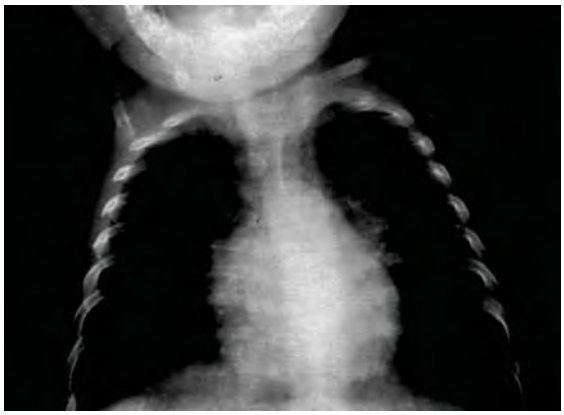
TABLE II. Molecular causes of SCID and characteristic lymphocyte phenotypes

	Lymphocyte phenotype
X-linked SCID	
(1) γc gene mutations	T(−),B(+),NK(−)
Autosomal Recessive SCID	
(1) *ADA* gene mutations	T(−),B(−),NK(−)
(2) *Jak3* gene mutations	T(−),B(+),NK(−)
(3) *IL7Rα*-chain gene mutations	T(−),B(+),NK(+)
(4) *RAG1* or *RAG2* mutations	T(−),B(−),NK(+)
(5) Artemis mutations	T(−),B(−),NK(+)
(6) *CD45* gene mutations	T(−),B+

Buckley et al. Primary Cellular Immunodeficiencies JACI 2002

Common Clinical Phenotype, Variable Genotype

- Failure to thrive, diarrhea
- Recurrent Opportunistic Infections
  - Fungi – Candida
  - Viruses – parainfluenza virus, CMV, adenovirus
- Absence of T cells
- Specific gene defect defines impact on B and NK cell development



Gennery 2001 *J Clin Path*

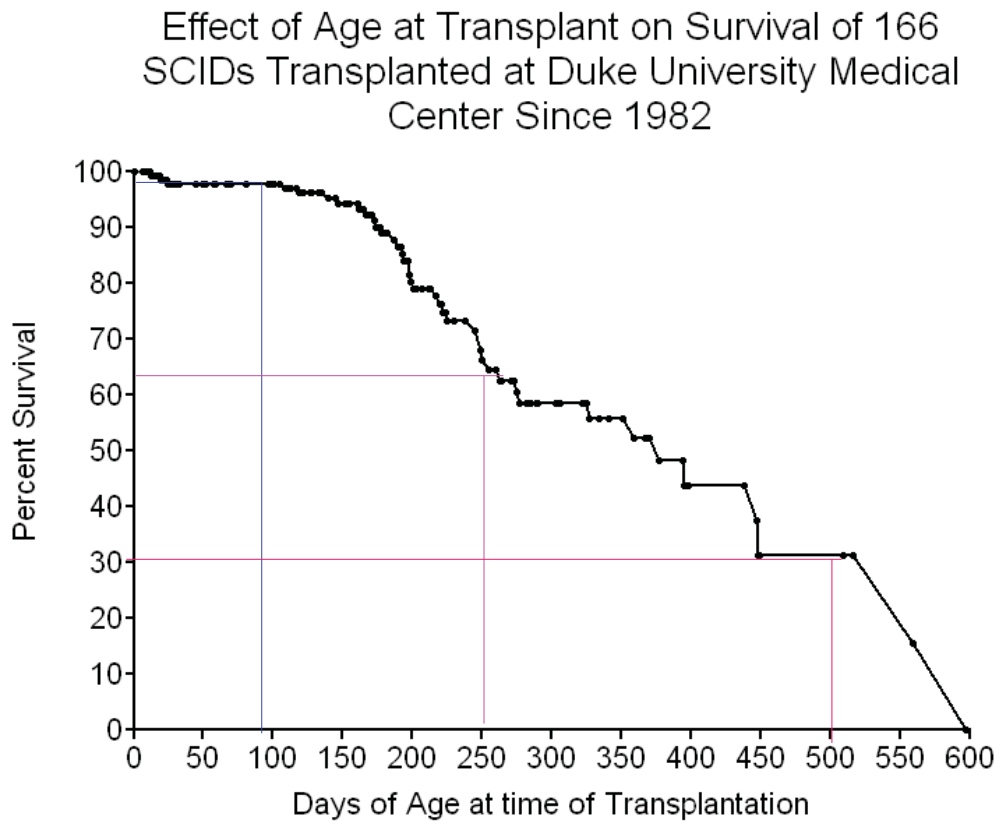
Treatment of SCID: Immunologic Emergency

Curative:

- Stem cell transplantation

Adjuvant:

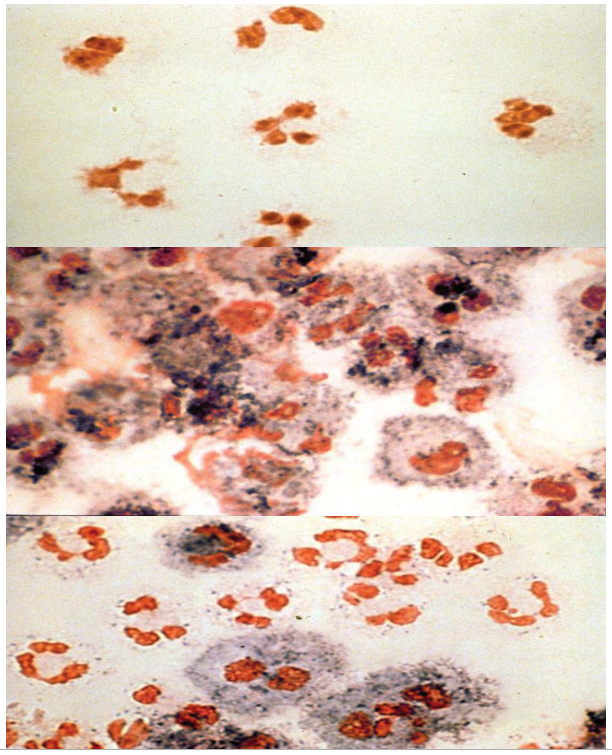
- Enzyme replacement (PEG-ADA)
- Gene therapy (ADA, XL-SCID)
- IVIG
- Avoidance live viral vaccines
- Irradiation of blood products
- CMV negative blood products only
- Prophylactic antibiotics (Bactrim for PJP)
- Protective isolation



Case 2

- 2m male presents with 1 day of fever and erythema, discharge, and swelling at site of heelstick.
- Culture + *Serratia marcesens*
- 1 month later develops bilateral cervical lymphadenitis
- Cultures + *Klebsiella oxytoca*
- He is growing well and has no other positive family history.

The NBT Fallen out of Favor

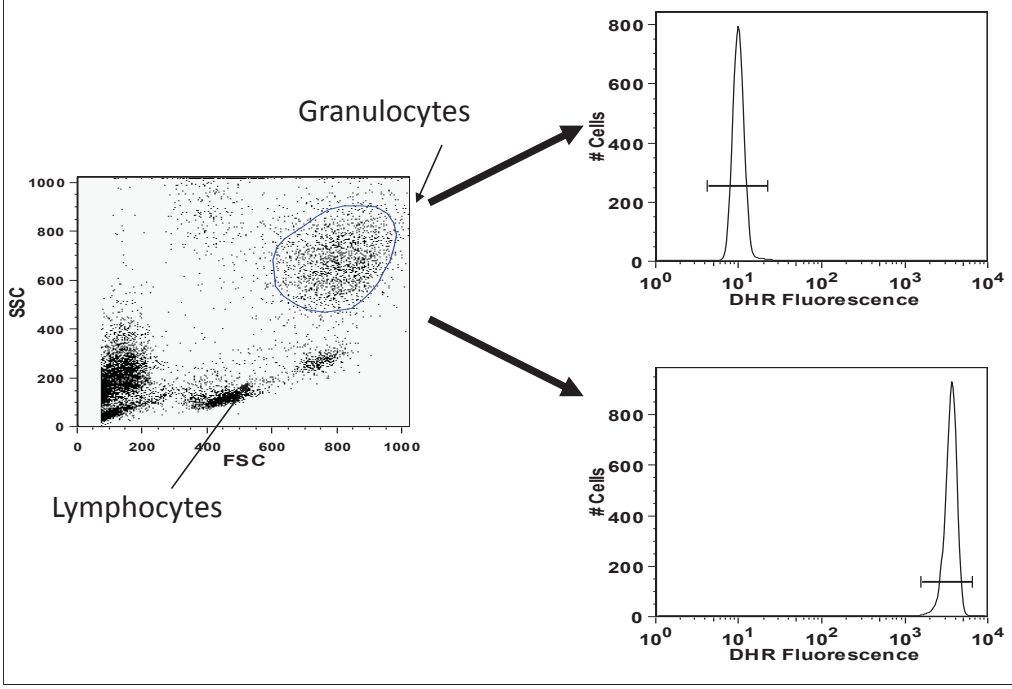


CGD PATIENT

NORMAL

X-CGD CARRIER
(Lyonization)

Flow Cytometry Analysis of Granulocyte Respiratory Burst Using Dihydrorhodamine

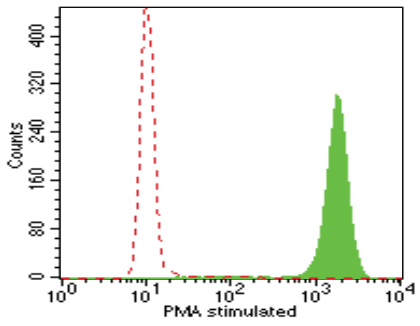


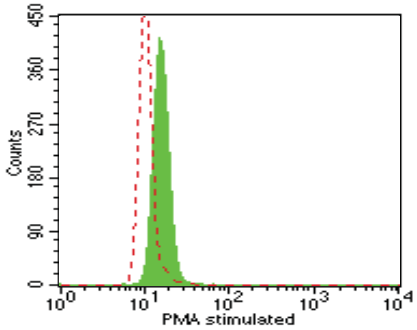
Unstimulated cells

Stimulated with PMA
SI = 376
(Normal ≥ 100)

DHR Assay to Diagnose CGD

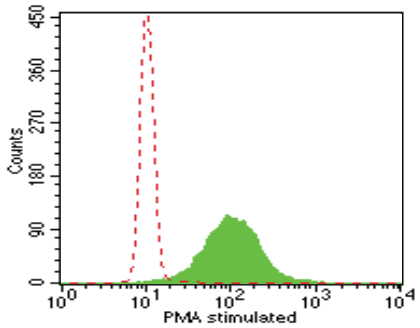
Normal

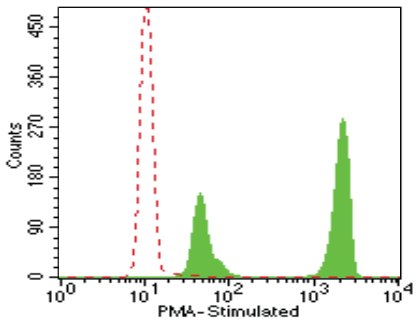




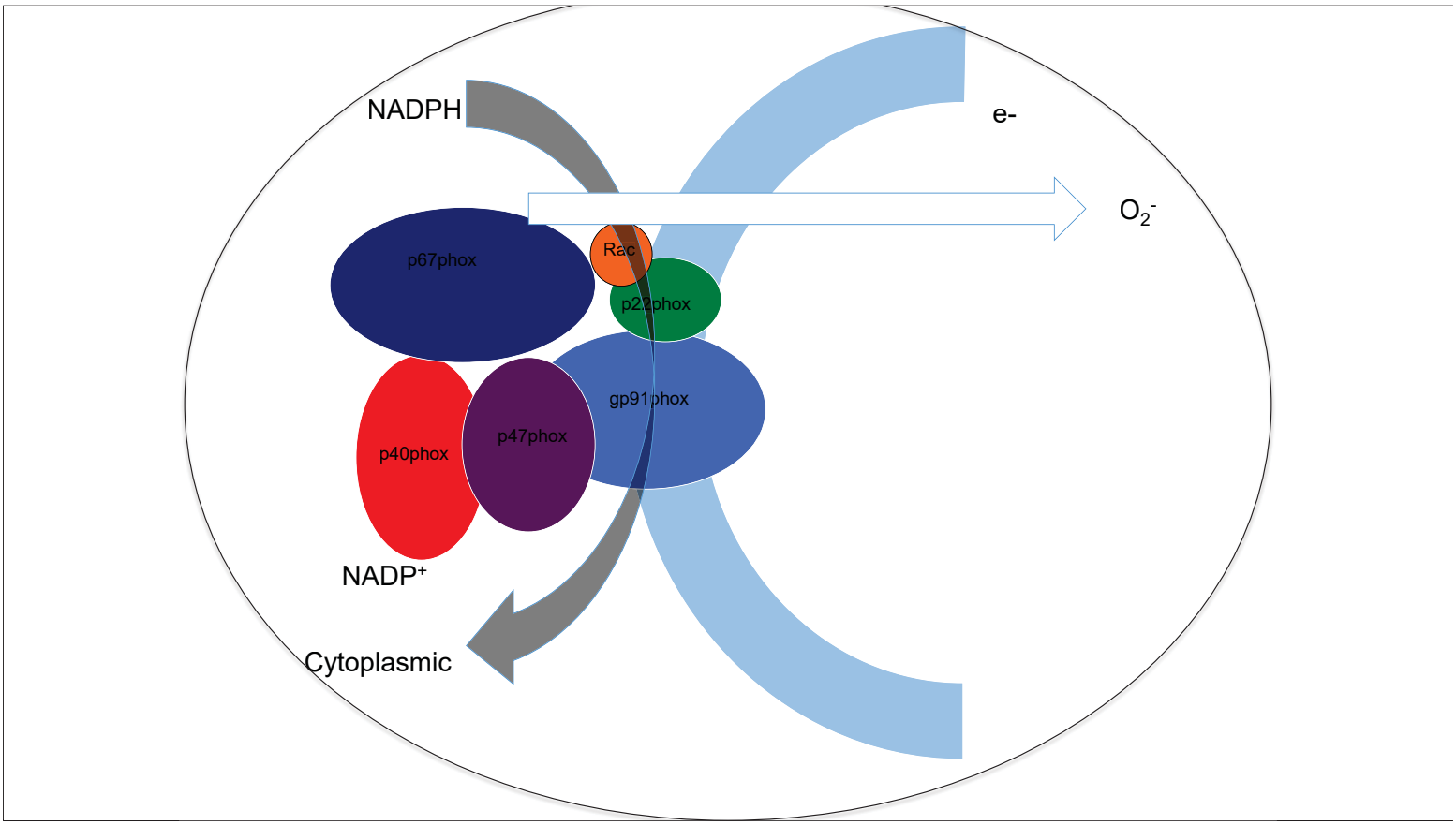
Phox[91] deficient CGD (X-linked)

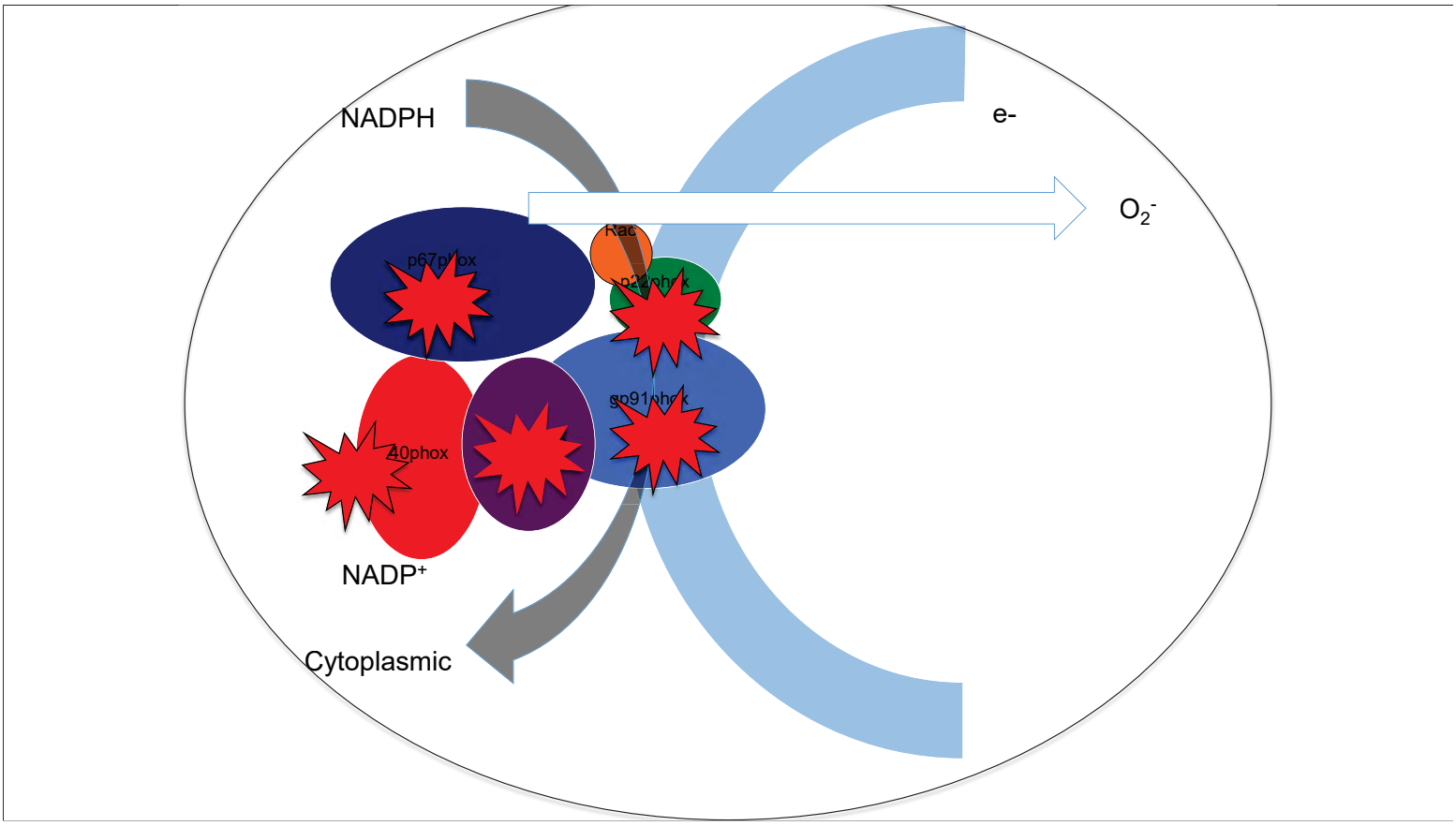
AR deficient CGD





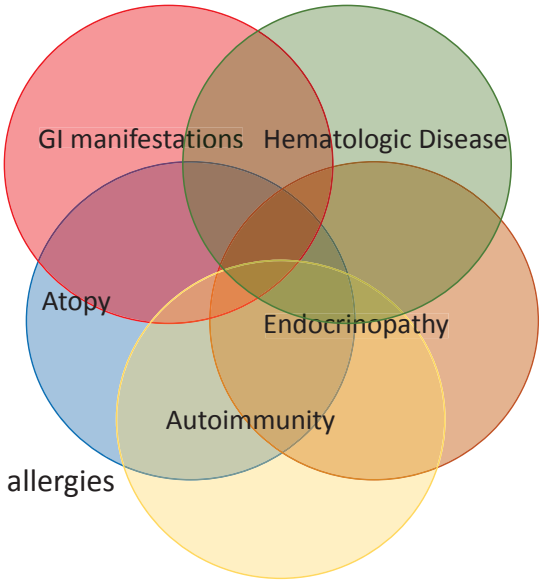
X-linked CGD carrier


NADPH
e-
O_2^-
p67phox
Rac
p22phox
gp91phox
p40phox
p47phox
$NADP^+$
Cytoplasmic


NADPH
e-
O_2^-
Rac
$NADP^+$
Cytoplasmic

Other Problems in PIDD

- Failure to Thrive
- Enteropathy
- Colitis
- Autoimmunity
- Hematologic Disorders
  - Neutropenia, anemia, thrombocytopenia
  - Lymphoproliferative disease
  - Splenomegaly
- Atopy
  - Severe eczema, food allergies, environmental allergies
- Endocrinopathies
- Dysmorphic features



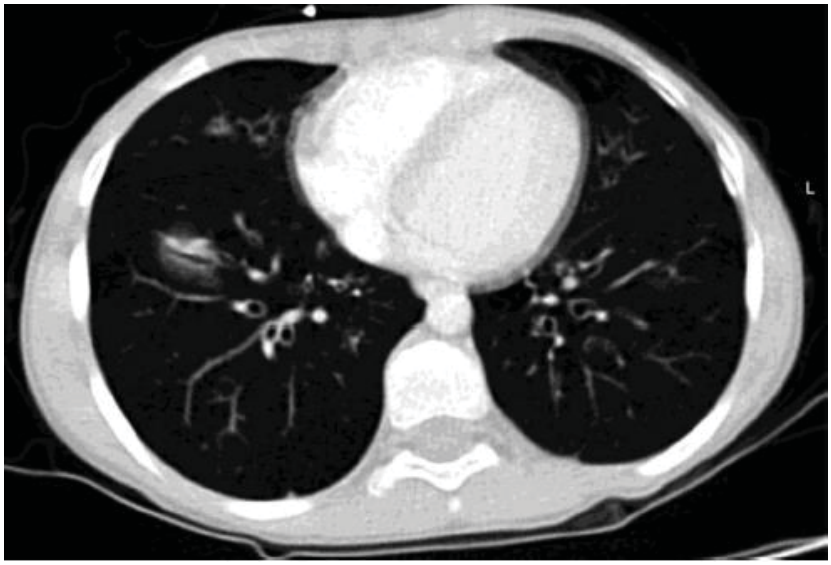
What this gives you

Unusual Presentations of Common PIDDs

Brand New Diseases

Case 3

- 10yo female with oxygen dependent lung disease
  - Bronchiectasis secondary to chronic asthma
  - Recurrent pulmonary infections
  - Digital clubbing
  - Recurrent ear infections
  - Failure to thrive

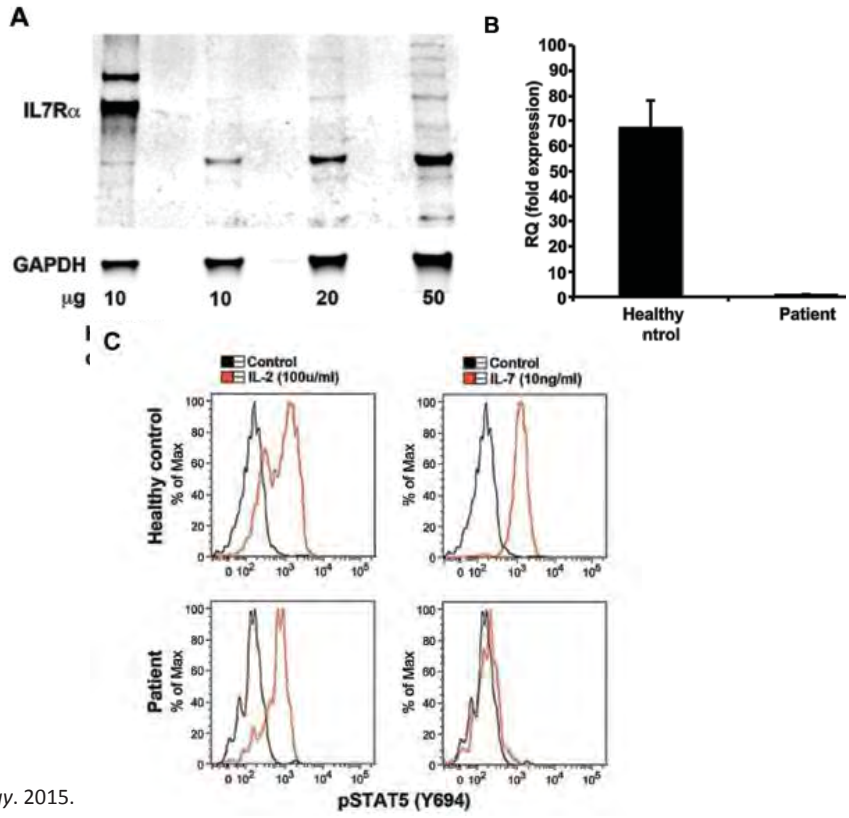


Leiding JW et al. *Annals of Allergy, Asthma, and Immunology*. 2015.

Case 3: SCID

Table 1
Immunologic evaluation of patient

IgG (mg/dL) (608–1,572)	783
IgA (mg/dL) (45–236)	896
IgM (mg/dL) (52–242)	183
IgE (IU/mL) (<25)	<2
Tetanus titer (IU/mL) (>0.1)	0.59
Diphtheria titer (IU/mL) (>0.1)	0.07
Post-pneumococcal titer (IU/mL) (>1.3)	>50% serotypes protective
Absolute lymphocyte count cells/μL (1,900–3,700)	363
Absolute $CD3^+$ cells/μL (1,200–2,600)	70
Absolute $CD4^+$ cells/μL (650–1,500)	35
Absolute $CD8^+$ cells/μL (370–1,100)	18
Absolute $CD19^+$ cells/μL (270–860)[a]	62
Absolute $CD56^+$ cells/μL (100–480)	224
$CD4^+CD45RA^+$ (51%–67%)	2%
$CD4^+CD45RO^+$ (33%–49%)	98%
Lymphocyte stimulation to mitogens (counts/min)	
Phytohemagglutinin (>93,000)	4,904
Concanavalin A (>76,000)	10,127
Pokeweed (>85,000)	31,207
Lymphocyte stimulation to antigens (SI)	
Tetanus (>3)	13.1
Candida (>3)	1.7



Leiding JW et al. *Annals of Allergy, Asthma, and Immunology*. 2015.

SCID – Molecular Causes and Phenotypes

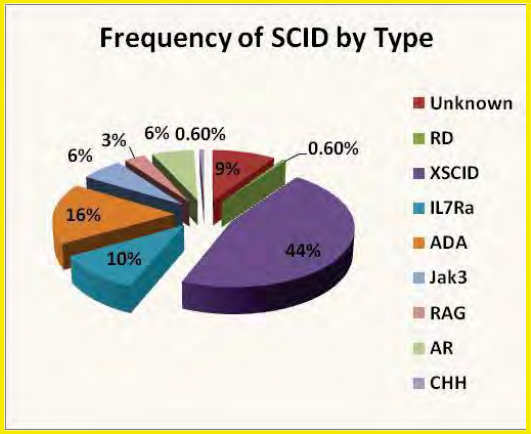
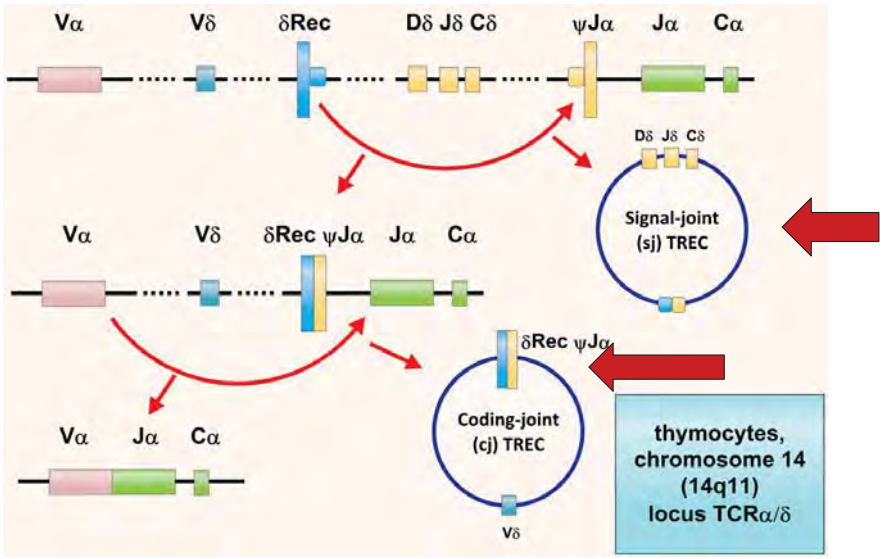


TABLE II. Molecular causes of SCID and characteristic lymphocyte phenotypes

	Lymphocyte phenotype
X-linked SCID	
(1) γc gene mutations	T(−),B(+),NK(−)
Autosomal Recessive SCID	
(1) *ADA* gene mutations	T(−),B(−),NK(−)
(2) *Jak3* gene mutations	T(−),B(+),NK(−)
(3) *IL7Rα*-chain gene mutations	T(−),B(+),NK(+)
(4) *RAG1* or *RAG2* mutations	T(−),B(−),NK(+)
(5) Artemis mutations	T(−),B(−),NK(+)
(6) *CD45* gene mutations	T(−),B+

Buckley et al. Primary Cellular Immunodeficiencies JACI 2002

T cell Receptor Excision circle (TREC)



New Classification of SCID

Classic SCID

CD3 <300 cells/mm3 and PHA <10% control

Leaky SCID

CD3 300-1500 cells/mm3, PHA 10-30% control, no maternal T cell engraftment

Variant SCID

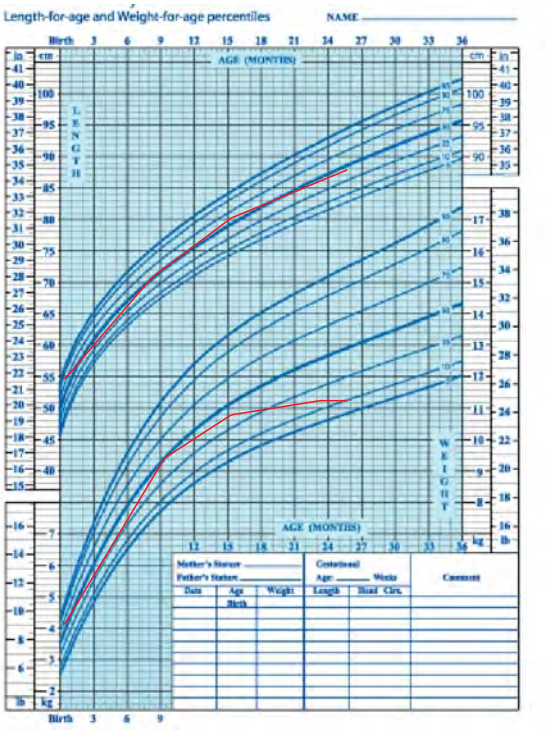
CD3 300-1500 cells/mm3 with impaired function, no maternal T cells found, no genotype found.

Idiopathic Lymphopenia

CD3 300-1500 cells/mm3, Normal PHA, no maternal T cell engraftment, no known genetic cause of SCID

Case 4

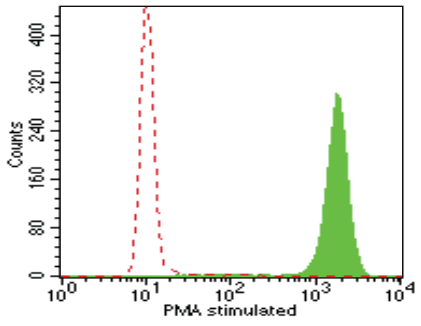
- 2 y.o. Caucasian male presents to the pediatrician for several weeks of diarrhea
  - Possible fever the first week
  - Intermittent abdominal pain
  - Loose stools, 3-4 per day
  - No frank blood
  - Decreased appetite, but drinking well
- **PMH:** wheezes with viral URIs, left
- **Family Hx:** maternal cousin with inflammatory bowel disease

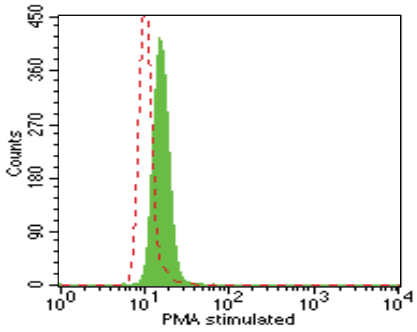


CBC with differential- normal
CMP- albumin 2.9
ESR 12, CRP 2.6
Stool culture: negative
Ova & parasites: negative

DHR Assay to Diagnose CGD

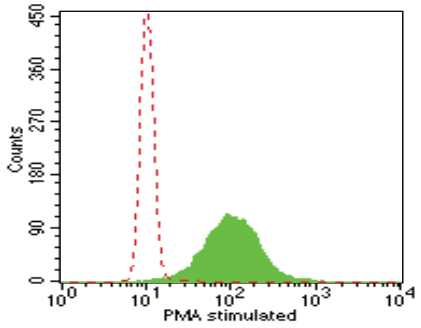
Normal

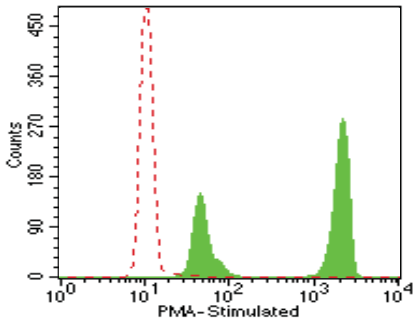




Phox^{91} deficient CGD (X-linked)

AR deficient CGD





X-linked CGD carrier

Types of CGD

XL – *CYBB*, gp91^{phox}	70%
Female carriers	
AR – *NCF1*, p47^{phox}	20%
1/250 are carrier	
NCF2, p67^{phox}	6%
CYBA, p22^{phox}	6%

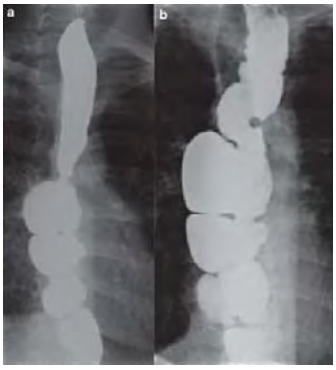
CGD Infections

Staph aureus	liver, lymph nodes, osteo
Serratia marsescens	skin, lung, lymph nodes
Burkholderia spp.	pneumonia, bacteremia
Nocardia spp.	pneumonia, brain, liver
Aspergillus spp.	lung, esp. miliary, spine
Salmonella spp.	sepsis, diarrhea, osteo
BCG	lymph node, rarely disseminates

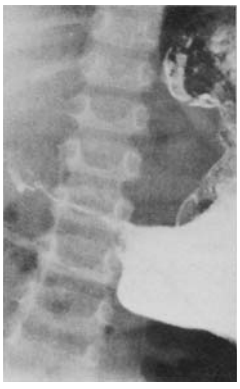
Others more rare:

Chromobacterium violaceum *(brackish water, e.g. Disney World)*
Francisella philomiragia *(brackish water, Chesapeake Bay)*
Granulibacter bethesdensis *(widespread)*
Methylobacter extorquens

Granulomatous Complications

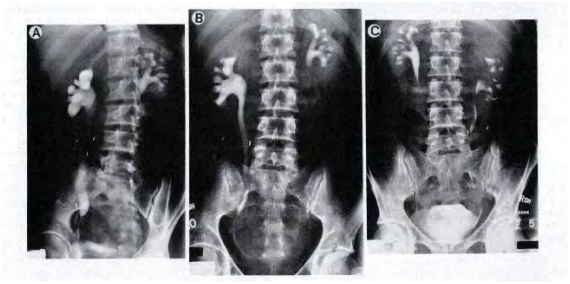


Laskey H. 2009. *Am J Gastro*.



Chin T. 1987. *J Pediatrics*.

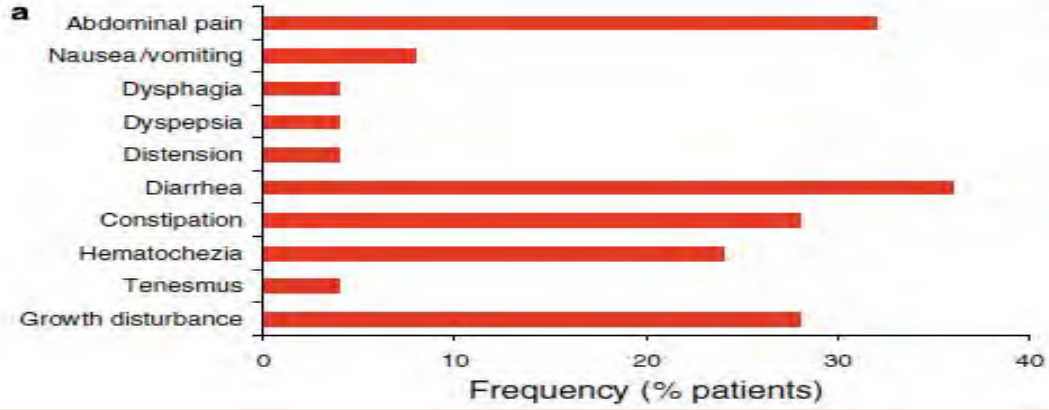
Esophageal Strictures
Gastric Outlet obstruction
Vesicoureteral Reflux



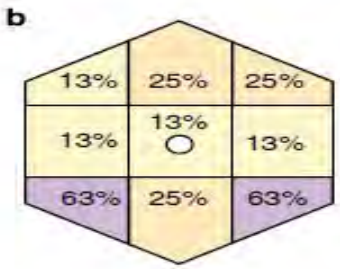
Walther M. 1992. *J Urol.*

Inflammatory Bowel Disease in CGD

Frequency of symptoms in the preceding 3 years



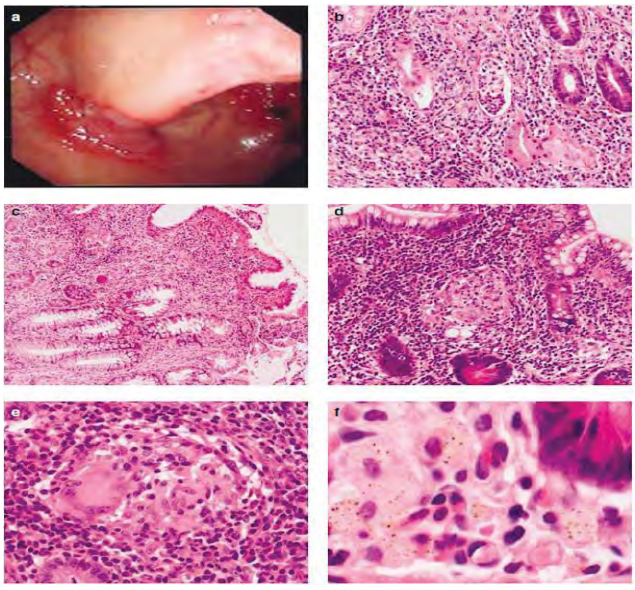
Location of abdominal pain



16 (64.0 %) were documented as experiencing at least one symptom relating to the gastrointestinal tract in the preceding 3 years

Marks. 2009. *Am J Gastro*.

Inflammatory Bowel Disease in CGD



Marks. 2009. *Am J Gastro.*

a. Colonic inflammation and ulceration
b. Colonic mucosa with active inflammation and withered crypts
c. Active chronic colitis with architecture distortion
d, e. epitheliod granuloma with Langerhan's type giant cells
f. **Pigment laden macrophages in noninflamed regions******

Diagnosis of CGD-colitis

- Subjective complaints
- Weight loss, microcytic anemia, hypoalbuminemia
- Antimicrobial panels: ASCA IgG, ASCA IgA, anti-OMPC, anti-I2, and anti-CBir1 present at high levels and not predictive of colitis.
- Routine screening of CGD in patients with colitis is not high yield.

Yu 2011 *Clin Immuno*
Jaggi 2012 *J Clin Immunol*

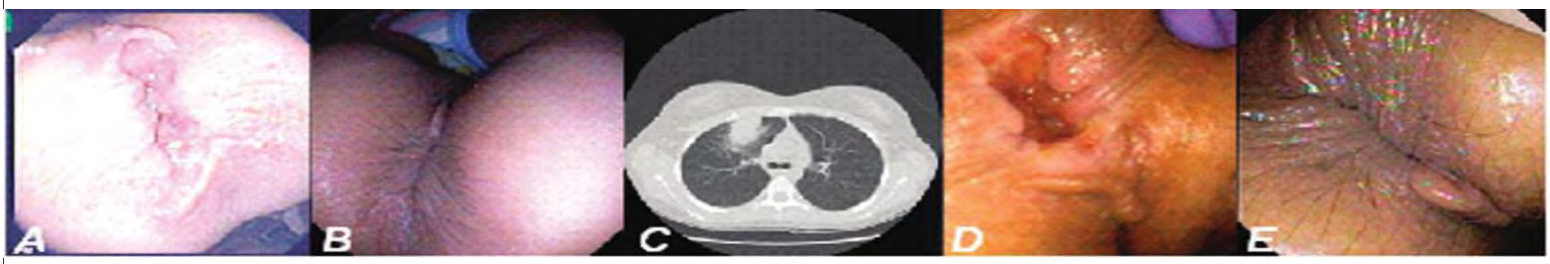
Management of CGD-colitis

- Steroids
- Metronidazole, 6-MP, salicylic acid derivatives, mesalamine.
- Surgery

Leiding JW and Holland SM . *GeneReviews*. 2015

Complications of Tumor Necrosis Factor–α Blockade in Chronic Granulomatous Disease–Related Colitis

Gulbu Uzel,[1] Jordan S. Orange,[2] Nina Poliak,[2] Beatriz E. Marciano,[1] Theo Heller,[2] and Steven M. Holland[1]



Pre post infection flare restart

5 Patients
Severe infections after 3 to 12 infusions
2 Deaths despite prophylaxis

Uzel 2010 *CID*

Case 4

- 3m male with severe failure to thrive, profound diarrhea and weight loss.
- Eczematous dermatitis
- Developed type 1 diabetes with +anti-insulin antibodies
- Developed hypothyroidism with +anti-TPO antibodies
- Developed Coomb's postive hemolytic anemia
- No infections
- Immune evaluation is normal with the exception of low Treg cells

IPEX: Immunodeficiency Polyendocrinopathy Enteropathy X linked

Mutation in FOXP3

↓

Lack of CD4+ CD25+FOXP3+ Regulatory T cells

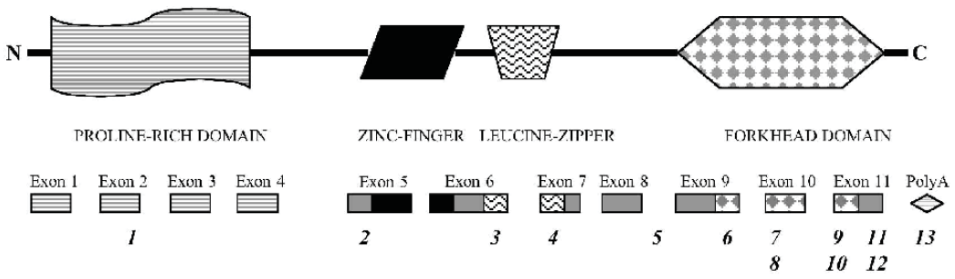
↓

CD4+CD25+ Tregs are critical for the maintenance of peripheral immunological tolerance

Synopsis:

Inheritance	X linked recessive
GI	Diarrhea,secretory Enteropathy Ileus Villous atrophy Chronic inflammation
Skin	Eczema/Atopy
Hematology	Hemolytic anemia Autoimmune thrombocytopenia
Immunology	Immune dysregulation Variable autoimmune diorders Lymphadenopathy autoantibodies
Molecular basis	Mutation in FOXP3
Endocrine	DM, thyroid

FOXP3 Protein



FOXP3: Transcription factor responsible for development of Treg

Mutations can occur throughout the gene, more reported in the "forkhead" domain

Gambineri, et al Curr Opin Rheum 2003

Treatment

- Immunosuppression
  - Steroids, sirolimus, tacrolimus
- Bone Marrow Transplant

Enteropathy in PIDD

- Chronic diarrhea and weight loss
- Failure to thrive
- Celiac like
- Autoimmune enteropathy
- Granulomas
- Lymphocytic infiltrate

Endocrinopathy in PIDD

- Type 1 diabetes mellitus
- Thyroid disease
- Addison's disease
- Hyperparathyroidism
- Gonadal failure
- Growth hormone deficiency

Case 5 Hyper IgE at its worst

- 3yo male with
  - severe allergic rhinitis
  - asthma
  - severe eczema
  - food allergies – milk, egg, tree nuts, sesame
  - Recurrent URI's
  - Recurrent otitis media
  - 2 pneumonias
- Total IgE >3000

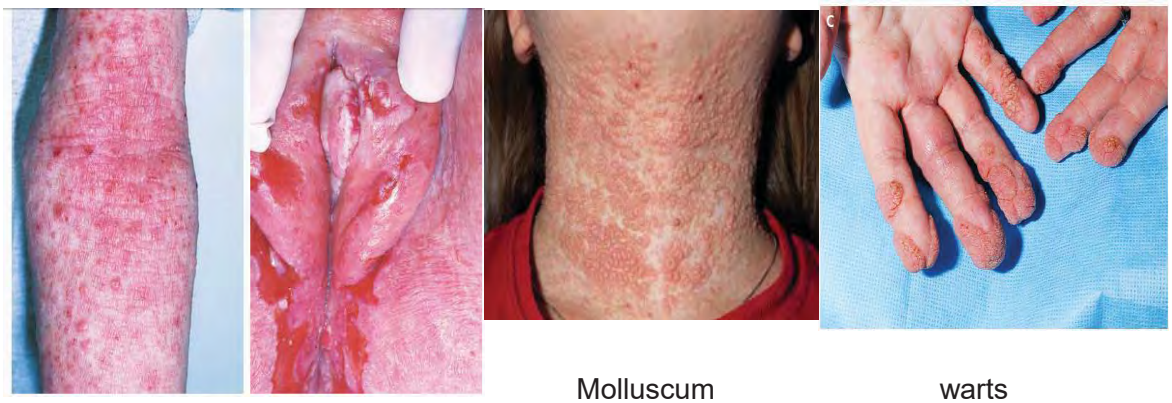
Hyper-IgE Syndromes

- Autosomal Dominant Hyper IgE Syndrome
  - AD-HIES
  - Job's Syndrome
  - STAT3 deficiency
  - Loss of Function in STAT3 (LOF-STAT3)
- Autosomal Recessive Hyper IgE Syndrome
  - AR-HIES
  - DOCK8 deficiency

Autosomal Recessive HIES – Combined Immunodeficiency with *DOCK8* Mutations

- Dedicator of cytokinesis 8 protein
- Recurrent sinopulmonary tract infections
- Recurrent cutaneous viral infections
- Severe atopy with elevated serum IgE levels and hyper-eosinophilia
- Immunology
  - Low numbers of T-cell and B-cells
  - Low serum IgM, variable IgG antibody responses
  - Decreased numbers and function of Th17 cells

Dermatitis and Viral Infections of the Skin in DOCK8 PIDD



AD | Herpes simplex | Molluscum | warts

Zhang et al NEJM 2009

High IgE without Atopy

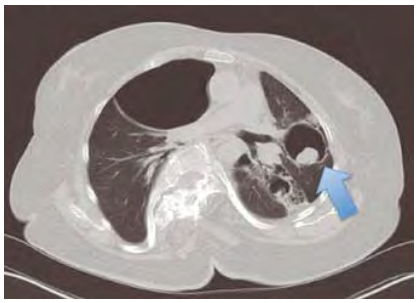
- 18 yo female admitted for Herpes zoster involving V1 and V2 of the trigeminal nerve.
- History of:
  - Pneumonia as a child associated with pneumatocele development
  - Retained primary teeth
  - Mother died of *Aspergillus* pneumonia
  - IgE as high as 13,000 IU/ml

AD-HIES / Job's Syndrome

- Recurrent pneumonia
- Recurrent boils
- eosinophilia
- markedly increased serum IgE (>10,000 IU/ml)
- eczema
- Distinct abnormities of connective tissue

Schimke et al JACI 2010
Woellner et al JACI 2010

AD-HIES / Job's Syndrome



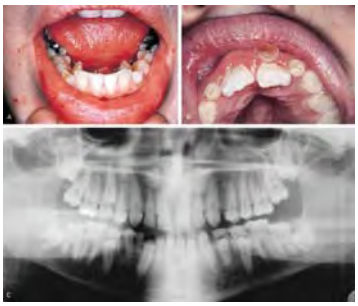


Table 1. Clinical features of hyper-IgE syndrome

Immunologic (% frequency)	Nonimmunologic (% frequency)
Eczema (100)	Intraoral lesions (93)
Peak serum IgE > 2,000 IU/mL (97)	Characteristic facies (83)
Eosinophilia (93)	Minimal trauma fractures (71)
Boils (87)	Coronary artery tourtuosity or dilation (70)
Recurrent pneumonias (87)	Focal brain hyperintensities (70)
Mucocutaneous candidiasis (83)	Hyperextensibility (68)
Newborn rash (81)	Scoliosis (63)
	Retained primary teeth (>60)
	Hypertension (54)
	Coronary aneurysms (37)
	Chiari I malformation (18)
	Degenerative joint disease (unknown)
	Craniosynostosis (unknown)

Grimbacher et al NEJM 1999
Sowerwine KJ Ann NY Acad Sci 2012

What is all the STAT about?

11 year old female with autoimmune hepatitis

- Autoimmune hepatitis
  - Treated with tacrolimus, cellcept, remicaide, rapamycin, rituximab, cytoxan
  - Cadaveric liver transplantation 2013.
  - New liver is failing with chronic ascites, portal hypertension, and severe electrolyte abnormalities
- Celiac disease, ulcerative colitis
- Growth failure
- Also had history of T and B cell lymphopenia and profound hypogammaglobulinemia.
- Thrombocytopenia post liver transplant
- Mom- looks very small. No real medical history.

Labs

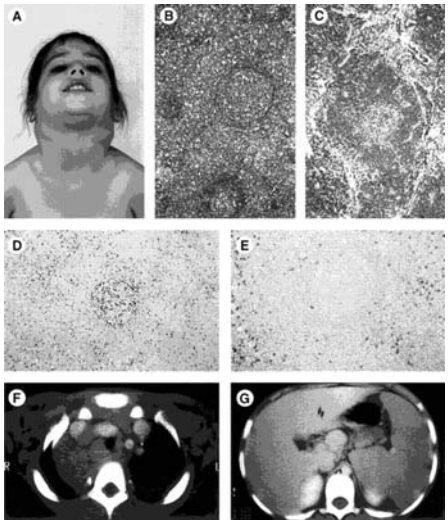
- Bone marrow biopsy –myelodysplasia
- Intermittently neutropenic and intermittently thrombocytopenic.

IgG 497
IgA 107
IgM 71 mg/dl

CD3+ 645
CD4+ 74
CD8+ 494
CD19+ 2
CD56+ 22 cells/mm^3
DNT's (CD4-CD8-) 77 (12%)

Double Negative T cells

- CD4+CD8+ → CD4+CD8- or CD4-CD8+ → CD4-CD8-



Mother becomes a patient

- Fatigue and unintentional weight loss
- Growth failure, on growth hormone as a child
- Enteropathy as a child
- Colitis as a child
- Enlarged spleen, cervical and axillary adenopathy

- WBC 3.4 ANC 2489 ALC 731
- IgG 350, IgA 80, IgM 106, IgE <2, albumin 2.8
- S. pneumoniae titers 20/23
- VZV IgG 4.79
- Diptheria IgG 0.19 tetanus IgG 1.80
- Rubella <0.9, mumps 0.9, measles 0.9
- CD3+ 383 CD4+ 216 CD8+ 153 CD19 +238 CD56+ 20 cells/mm^3
- DNT's (CD4-CD8-) 52 (14%)

Lymphoproliferative Disease

- Splenomegaly
- CD4-CD8- $\gamma\delta$ T cell population
- Cervical and inguinal lymphadenopathy

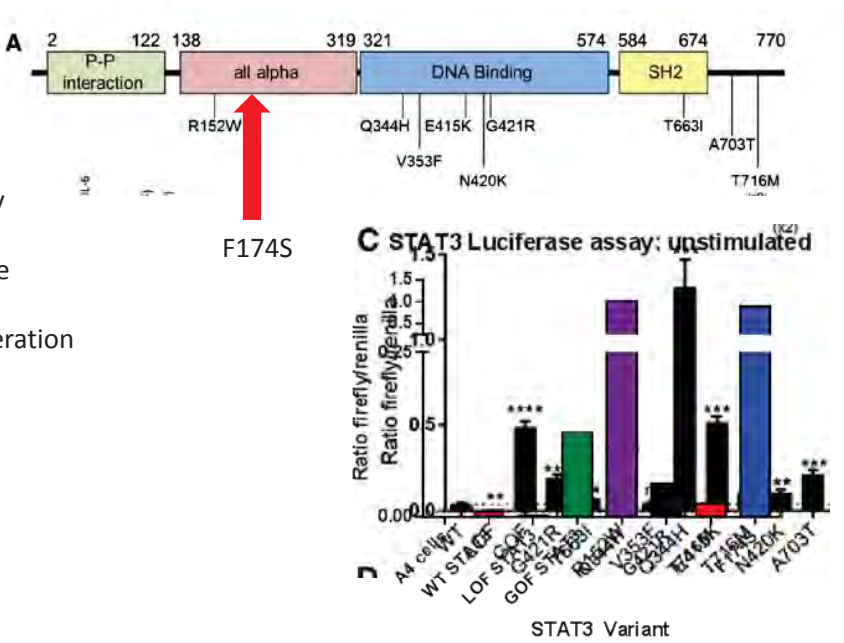
Age 44y – weight 39.4kg, height 139.5cm (4.5 feet)

[redacted]

At age 13y – 17.9kg, 97cm (a little over 3 feet)

[redacted]

GOF-STAT3 mutations



F174S

Autoimmunity
Enteropathy
Growth Failure
Infections
Lymphoproliferation

Milner J. et al. *Blood*. 2015.
Cooper Lab, Washington University

LOF-STAT3 vs GOF-STAT3

Same gene, Different Phenotype

LOF-STAT3

Autosomal dominant HyperIgE syndrome

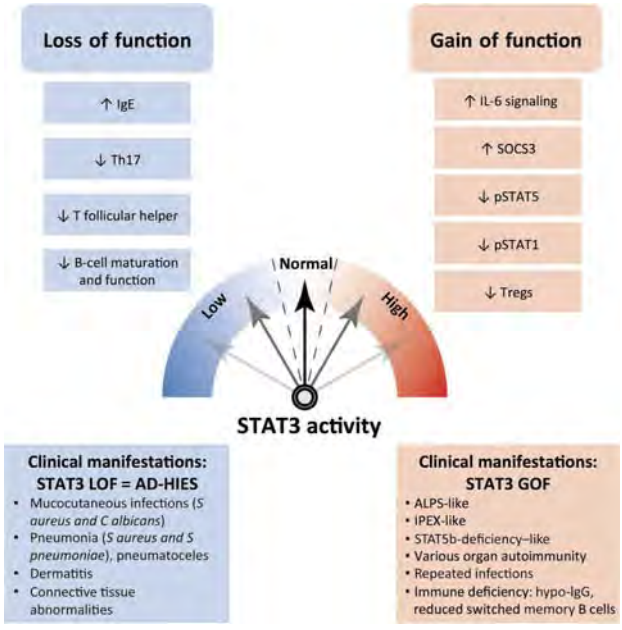
- eczema
- pneumonias with pneumatoceles
- abscesses
- characteristic face
- Mucocutaneous fungi
- retained primary teeth

GOF-STAT3

- enteropathy
- growth failure
- autoimmunity
- lymphoproliferation
- malignancy

Combined immune defect – lymphopenia, hypogammaglobulinemia

Both LOF and GOF STAT3 mutations have significant clinical consequences.



Elie Haddad Blood 2015;125:583-584

blood

Case – 21yo female with Mucocutaneous Candidiasis and fungating hand granuloma

- Initially presented at age 3 yrs with recurrent mucocutaneous candidiasis
- Intermittent leukopenia and neutropenia

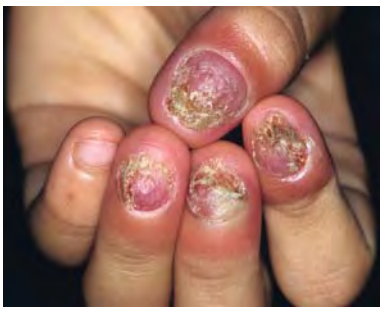
[redacted]

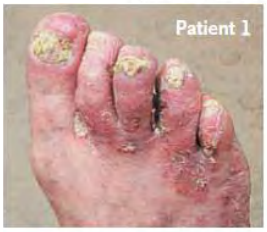
[redacted]

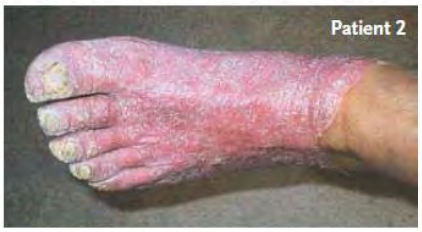
NEJM 2011 ORIGINAL ARTICLE

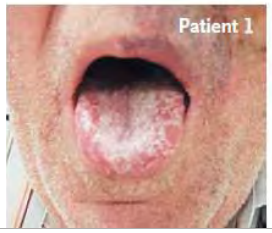
STAT1 Mutations in Autosomal Dominant Chronic Mucocutaneous Candidiasis

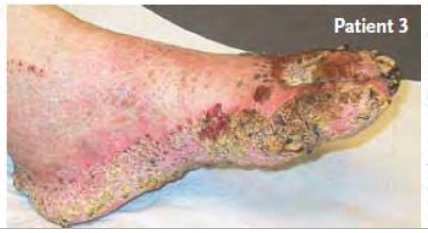
Frank L. van de Veerdonk, M.D., Ph.D., Theo S. Plantinga, Ph.D., Alexander Hoischen, Ph.D., Sanne P. Smeekens, M.Sc., Leo A.B. Joosten, Ph.D., Christian Gilissen, Ph.D., Peer Arts, Ph.D., Diana C. Rosentul, M.Sc., Andrew J. Carmichael, M.D., Chantal A.A. Smits-van der Graaf, M.D., Ph.D., Bart Jan Kullberg, M.D., Ph.D., Jos W.M. van der Meer, M.D., Ph.D., Desa Lilic, M.D., Ph.D., Joris A. Veltman, Ph.D., and Mihai G. Netea, M.D., Ph.D.









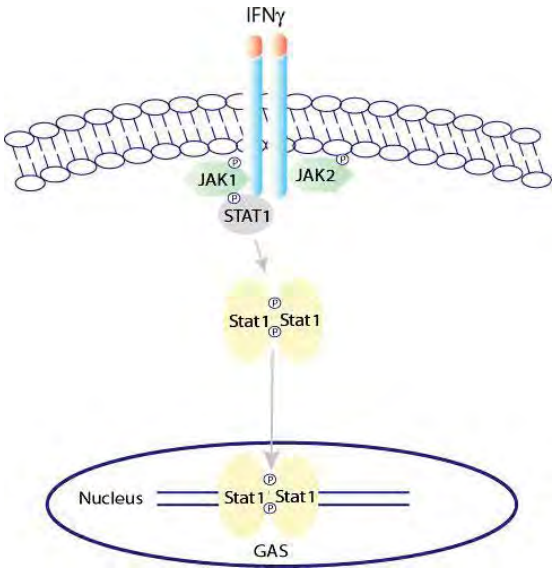


JEM 2011 Article

Gain-of-function human *STAT1* mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis

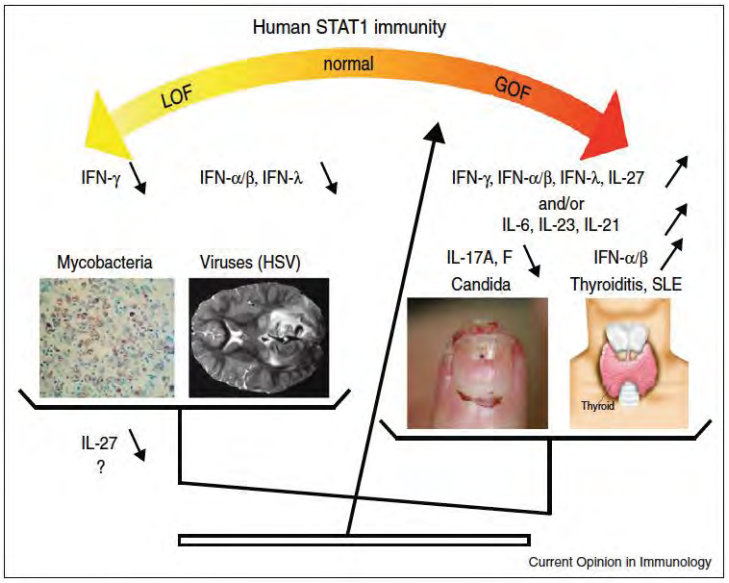
Luyan Liu,[1] Satoshi Okada,[2] Xiao-Fei Kong,[2] Alexandra Y. Kreins,[2] Sophie Cypowyj,[2] Avinash Abhyankar,[2] Julie Toubiana,[3] Yuval Itan,[2] Magali Audry,[2] Patrick Nitschke,[4] Cécile Masson,[4] Beata Toth,[9] Jérome Flatot,[9] Mélanie Migaud,[1] Maya Chrabieh,[1] Tatiana Kochetkov,[2] Alexandre Bolze,[1,2] Alessandro Borghesi,[1] Antoine Toulon,[5] Julia Hiller,[10] Stefanie Eyerich,[10] Kilian Eyerich,[10,11] Vera Gulácsy,[9] Ludmyla Chernyshova,[12] Viktor Chernyshov,[13] Anastasia Bondarenko,[12] Rosa Maria Cortés Grimaldo,[14] Lizbeth Blancas-Galicia,[15] Ileana Maria Madrigal Beas,[14] Joachim Roesler,[16] Klaus Magdorf,[17] Dan Engelhard,[18] Caroline Thumerelle,[19] Pierre-Régis Burgel,[20] Miriam Hoernes,[21] Barbara Drexel,[21] Reinhard Seger,[21] Theresia Kusuma,[22] Annette E Jansson,[22] Julie Sawalle-Belohradsky,[22] Bernd Belohradsky,[22] Emmanuelle Jouanguy,[1,2] Jacinta Bustamante,[1] Mélanie Bué,[23] Nathan Karin,[24] Gizi Wildbaum,[24] Christine Bodemer,[5] Olivier Lortholary,[6] Alain Fischer,[7] Stéphane Blanche,[7] Saleh Al-Muhsen,[24] Janine Reichenbach,[21] Masao Kobayashi,[26] Francisco Espinosa Rosales,[15] Carlos Torres Lozano,[14] Sara Sebnem Kilic,[27] Matias Oleastro,[28] Amos Etzioni,[24] Claudia Traidl-Hoffmann,[10,11] Ellen D. Renner,[22] Laurent Abel,[1,2] Capucine Picard,[1,6,8] László Maródi,[9] Stéphanie Boisson-Dupuis,[1,2] Anne Puel,[1] and Jean-Laurent Casanova[1,2,7,25]

STAT1 mutations



- Amorphic
  - Autosomal recessive
  - Severe viral and bacterial infections
  - Typically fatal
- Hypomorphic
  - Autosomal recessive
  - Non tuberculous mycobacteria
- Hypermorphic
  - Autosoma Dominant
  - CMC
  - Coccidoides
  - Histoplasma

Clinical Presentation
STAT1 GOF



Expanded GOF Phenotype

❖ **IPEX-like phenotype**
Autoimmunity
Enteropathy

❖ **Combined Immunodeficiency**
Antibody Deficiency
T cell defects

❖ **Broader infection susceptibility**
Histoplasmosis
Cryptococcus
Coccidioidomycosis
HSV
VZV
EBV

Boisson-Dupuis S. Current Opinion in Immunology, 2012
Liu L, JEM; 2011
Van de Veerdonk FL, NEJM, 2011.
Sampaio EP. J Allergy Clinical Immunology, 2013.
Uzel G. J Allergy Clinical Immunology, 2013.
Toth B. The Lancet, 2012.

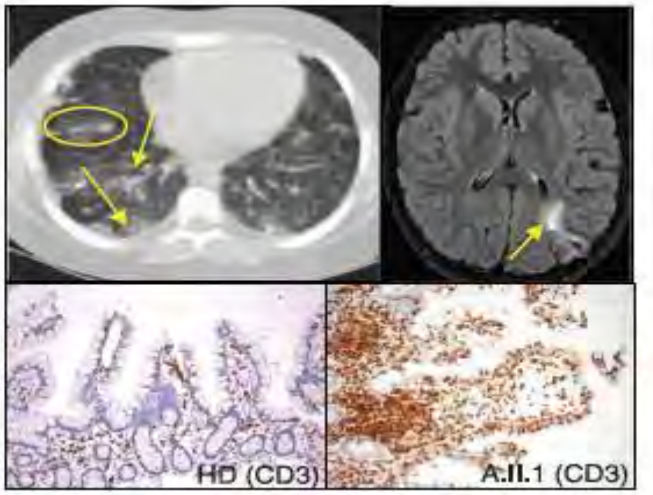
Lisa Forbes

Hematologic Cytopenias and Lymphoproliferative Disease
Case 6

- 5yo male with 1 year history of profound thrombocytopenia
- + anti-platelet antibodies
- + Coomb's
- +anti-granulocyte antibody
- Splenomegaly
- Enlarged axillary and cervical lymphadenopathy
- Mild lymphopenia
- Mild hypogammaglobulinemia (IgG 500)

CTLA-4 deficiency (Cytotoxic T Lymphocyte Associated Protein 4)

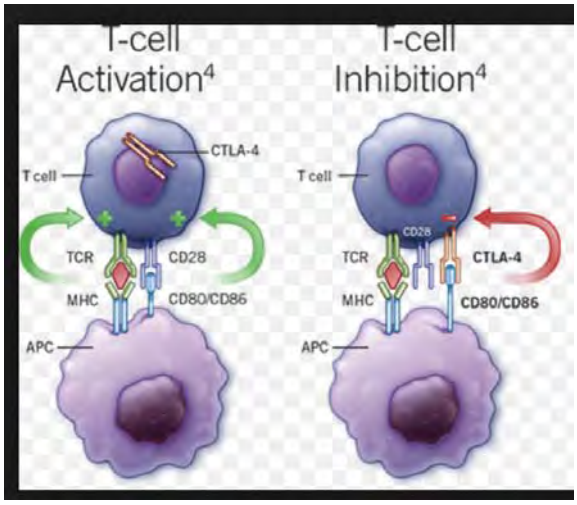
- Brain, GI, lung, lymphocytic infiltrates.
- Autoimmune thrombocytopenia and other cytopenias,
- Hypogammaglobulinemia
- Clonally expanded gd-CD8+ T cells
- CD4 T cell lymphopenia.
- Low circulating mature B cells
- Reduced expression of FOXP3 Treg cells



Kuehn HS et al. *Science*. 2015.

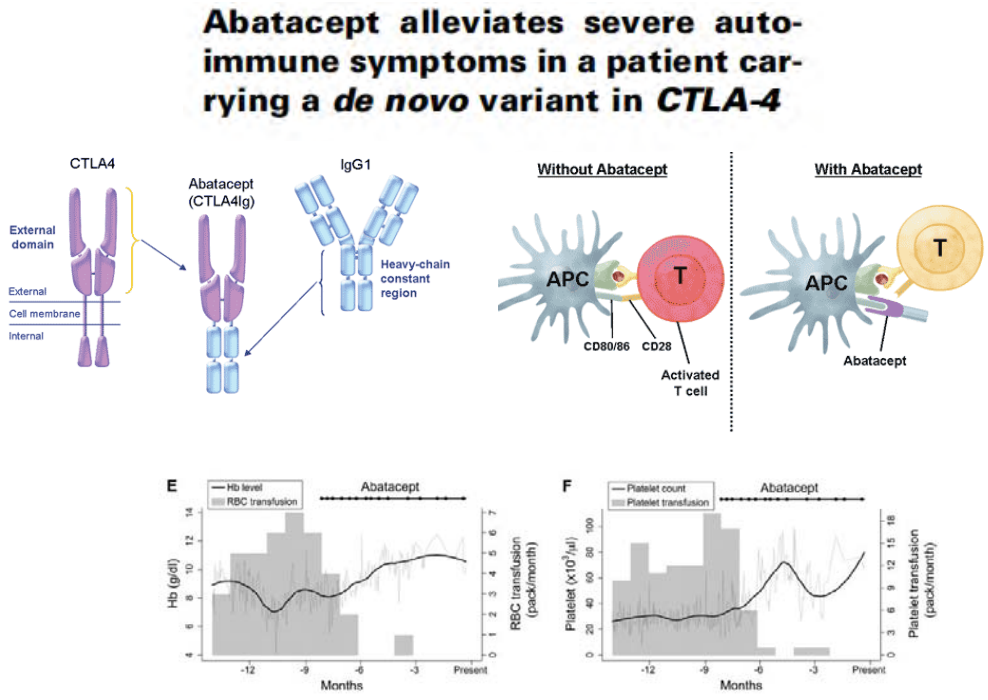
CTLA-4

- Inhibitory receptor expressed on activated T cells



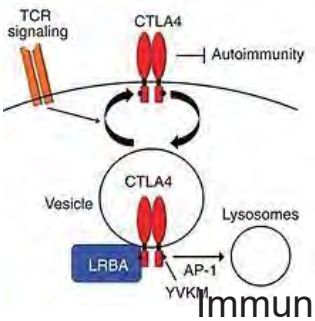
Treatment of this patient

- Steroids
- Rituximab



Lee et al. *JACI*. 2016

LPS-responsive beige-like anchor protein(LRBA) deficiency



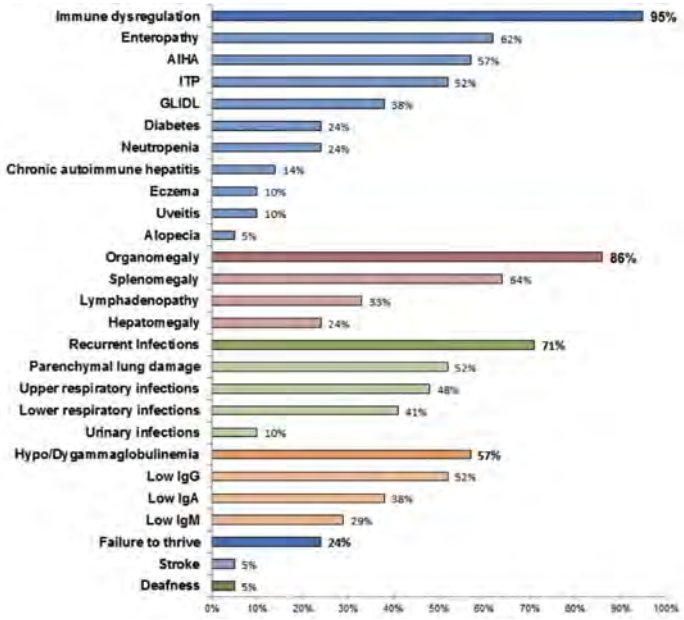
- Chronic Diarrhea
- Autoimmunity – Cytopenias, arthritis
- Organomegaly
- Respiratory Infections – frequent bronchiectasis
- Hypogammaglobulinemia
- Growth Retardation
- Neurologic Disease – cerebral lesions

Immune Phenotype

Very low number of peripheral Treg cells
Decreased immunoglobulins
Decreased B cells
Absent class switched B cells
ALPS like phenotype

Charbonnier et al. *JACI* 2015.
Alkhairy et al. *JoCI*. 2016.
Gamez-Diaz L. JACI. 2016.

Extended Spectrum



Gamez-Diaz et al. *JACI*. 2016

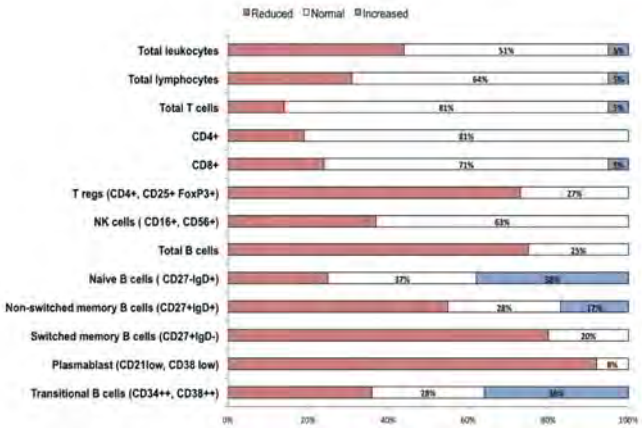


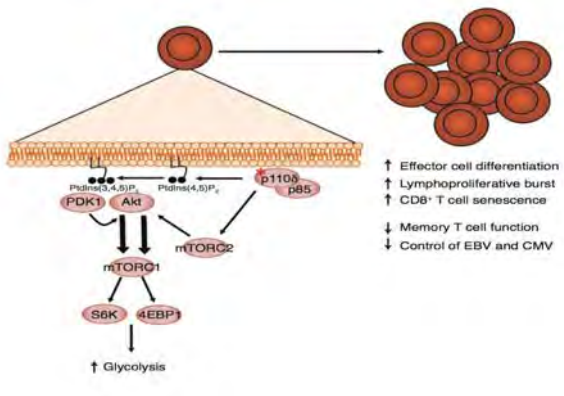
TABLE III. Current treatment of living and symptomatic patients with the diagnosis of definitive LRBA deficiency

Current treatment	Frequency, no. (%)
Systemic corticosteroids	7 (39)
Immunoglobulin replacement	7 (39)
Mycophenolate mofetil	4 (22)
Abatacept	3 (15)
HSCT	2 (11)
Tacrolimus + sirolimus	2 (11)
Budesonide	2 (11)
Cyclosporine	1 (5)
Azathioprine	1 (5)
Rapamycin	1 (5)
Rituximab	1 (5)
Infliximab	1 (5)
Hydroxychloroquine	1 (5)
Romiplostim	1 (5)
Total parenteral nutrition	1 (5)

12yo male with lymphdenopathy and bronchiectasis

- Recurrent pneumonia
- Recurrent sinusitis and otitis media
- Lymphopenia
- Cervical and occipital lymphadenopathy – benign hyperplasia
- Cobblestoning of the mucosal layer of the respiratory and gastrointestinal tract.

Gain of Function PI3 Kinase



T cell development markers
Naïve: CD45RA+ CD62L+ CCR7+
Central Memory: CD45RA-CD62L-CCR7+
Effector Memory: CD45RA-CD62L-CCR7-
TEMRA: CD45RA+ CD62L- CCR7-

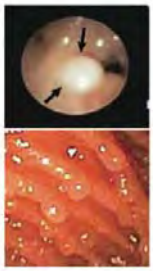
B cell development markers
Naïve: CD27- CD10-
Transitional: CD27 – CD10+
Memory: CD27+ CD10-

Lucas CL et al. *Nature Immunology*. 2015.

Table 1 Patient characteristics

	Kinase domain			Helical domain					C2 domain
	A.1	**B.III.1**	**C.1**	**D.I.1**	**D.II.1**	**D.II.2**	**E.1**	**F.II.1**	**G.1**
Age, sex	12, M	14, F	15 (†), F	40, M	15, M	12, F	7, F	17, F	12, F
EBV viremia	✓	✓	✓	✓	✓	✓	✓	✓	✓
CMV	✓	Naive	ND	✓	✓	✓	✓	Naive	Naive
Sinopulmonary bacterial infections	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lymphoma diagnosis	No	No*	EBV⁺ diffuse B cell lymphoma	No		No	No	EBV⁺ nodular sclerosis Hodgkin	No
Lymphadenopathy	✓	✓	✓	No		No	✓	✓	✓
Mucosal lymphoid aggregates	✓	ND	ND	✓		✓	✓	ND	✓
T & B lymphocyte subsets	CD4⁺ ↓	CD4⁺ ↓	CD4⁺ ↓	CD4⁺		CD4⁺ ↓	CD4⁺ ↓	CD4⁺ nl	CD4⁺ ↓
	CD4⁺ naive ↓	CD4⁺ naive ↓	CD4⁺ naive ↓	CD4⁺		CD4⁺ naive ↓	CD4⁺ naive ↓	CD4⁺ naive nl	CD4⁺ naive ↓
	CD8⁺ CM, EM ↑	CD8⁺ effector ↑	CD8⁺ effector ↑	CD8⁺		CD8⁺ CM & EM nl	CD8⁺ EM ↑	CD8⁺ CM, EM ↑	CD8⁺ EM ↑
	CD5⁺CD20⁺ ↑	CD5⁺CD20⁺ ↑	CD5⁺CD20⁺ ↑	CD5⁺(		CD5⁺CD20⁺ ↑	CD5⁺CD20⁺ ↑	CD5⁺CD20⁺ ↑	CD5⁺CD20⁺ ↑
	Bmem switch ↓	Bmem switch ↓	ND	Bmen		Bmem switch nl	Bmem switch ↓	Bmem switch ↓	Bmem switch ↓
T_{reg} cells**	nl	nl	nl	ND		ND	↑	nl	↓
CD3⁺CD8⁺CD57⁺ cells	44%	ND	42%	ND	35%	ND	ND	ND	41%
NK cells	NK nl	NK nl	NK nl	NK ↓	NK ↓	NK nl	NK ↑	NK nl	NK nl
	NKT nl	NKT nl	NKT nl	NKT ↑	NKT ↓	NKT nl	NKT ↑	NKT nl	NKT nl
Immunoglobulins	IgG↓, IgA↓	IgG nl, IgA nl	IgG↓, IgA↓	IgG↑, IgA nl	IgG↓, IgA↓	IgG↑, IgA↓	nl	IgG nl IgA↓	IgG↓, IgA↓
	IgM↑	IgM↑	IgM↓	IgM nl	IgM nl	IgM nl		IgM nl	IgM↑

a



Lucas CL et al. *Nature Immunology*. 2015.

Gain of Function PI3 Kinase

<u>Phenotype</u>

Sinopulmonary Infections
Lymphoproliferation
Chronic EBV or CMV
Nodular lymphoid hyperplasia
Autoimmune cytopenias

<u>Immunology</u>

Low IgG, high IgM, low IgA
Low memory B cells
High/normal CD8 T cells
Low CD4 T cells
Low naïve T cells
CD45RA+CD62L+
High effector memory and TEMRA T cells
CD45RA-CD62L-
CD45RA+CD62L-

Lucas CL et al. *Nature Immunology*. 2015.

Summary

- Immune dysregulatory diseases are newly recognized and an expanding field.
- Infections still are key, but PIDD patients present and develop a a variety of other symptoms.