Lessons learned from Primary Atopic Disorders (PADs): IEIs presenting with allergic disease

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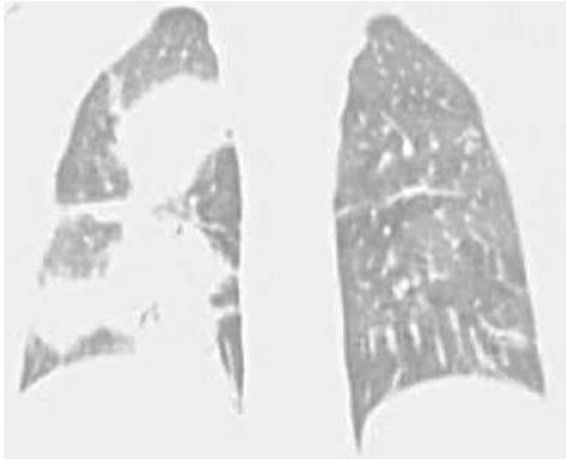
SCHOOL OF MEDICINE

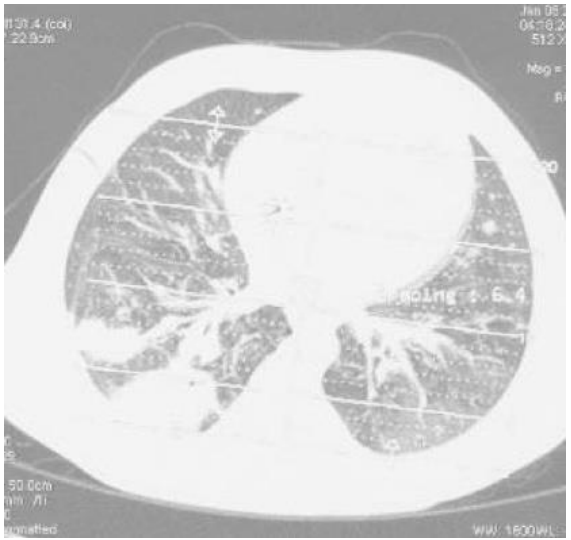
Learning Objectives

- Describe genetic defects and key pathways that contribute to allergic disease
- Understand how specific abnormalities present only in leukocytes or skin can cause the same atopic condition
- Identify clinical findings suggestive of primary atopic disorders

A young boy with ‘hyper-IgE’ syndrome

- 12 year old Egyptian male
  - Elevated IgE and atopy
    - atopic dermatitis, food allergy, asthma, allergic rhinitis
  - Recurrent bacterial infections
    - recurrent staphylococcal skin infections/abscesses
    - recurrent pneumonia
    - chronic otitis externa
  - Leukopenia



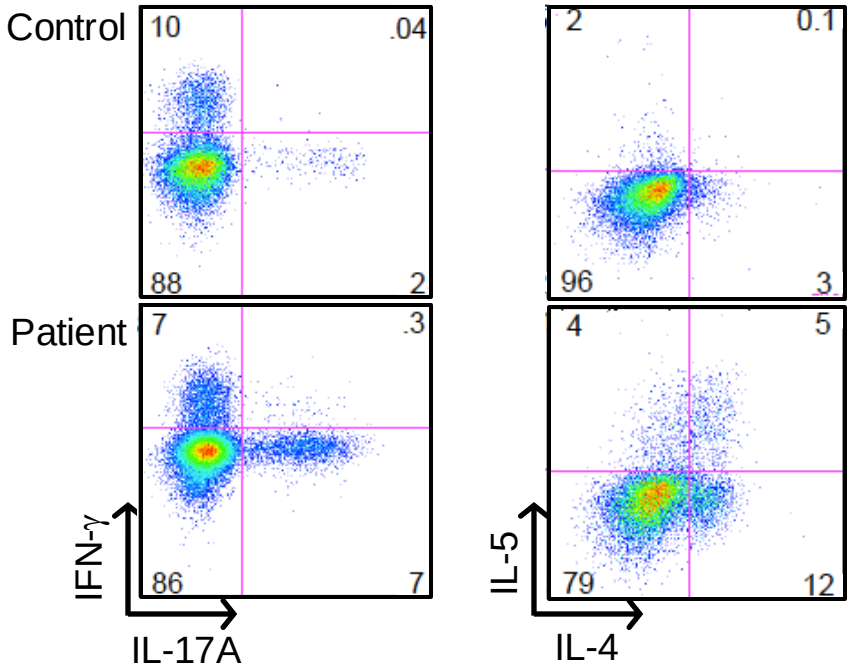


Pertinent Physical Exam

- Dysmorphic
- EACs with erythema, crusting and purulent drainage
- Mucopurulent nasal secretions
- High arched palate
- Multiple axillary abscesses with associated LAD
- Eczematous skin with excoriation; silvery plaque over extensor elbow
- Ataxic, with impaired coordination, pressured/dyspraxic speech; 1+ DTRs

Laboratory Abnormalities

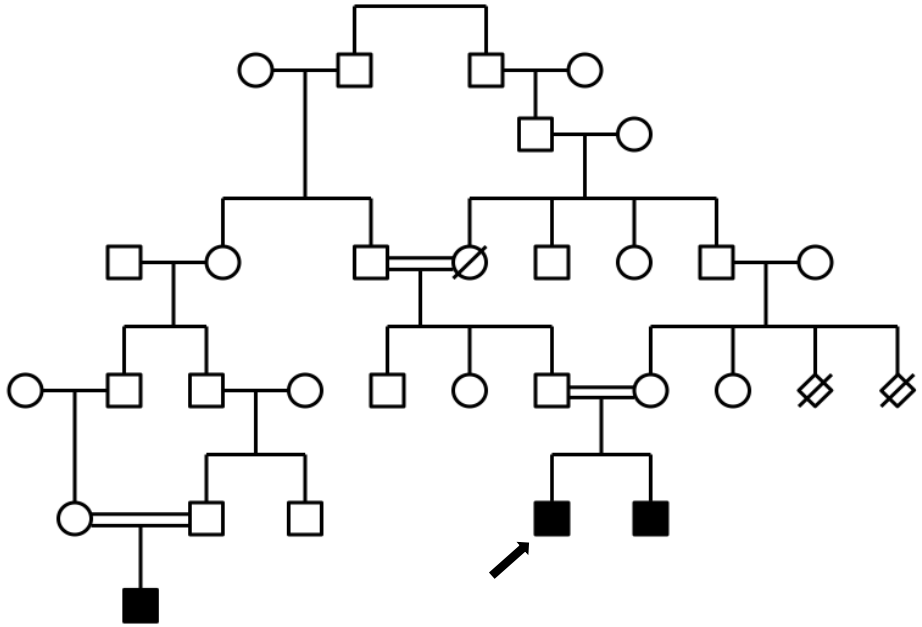
- ESR 16, CRP 0.4
- WBC 2.4
  - ANC 329, ALC 987
  - Low naïve CD3+, low CD8+
  - Low CD27+ Bcells
- IgG 1,690, IgA 497, IgM 147, IgE 30,786
  - protective titers
- Bone marrow biopsy
  - Normocellular; trilineage hematopoiesis; abundant maturing myeloid forms
- DHR wnl



Zhang et al. *JACI*. 2014

Family History

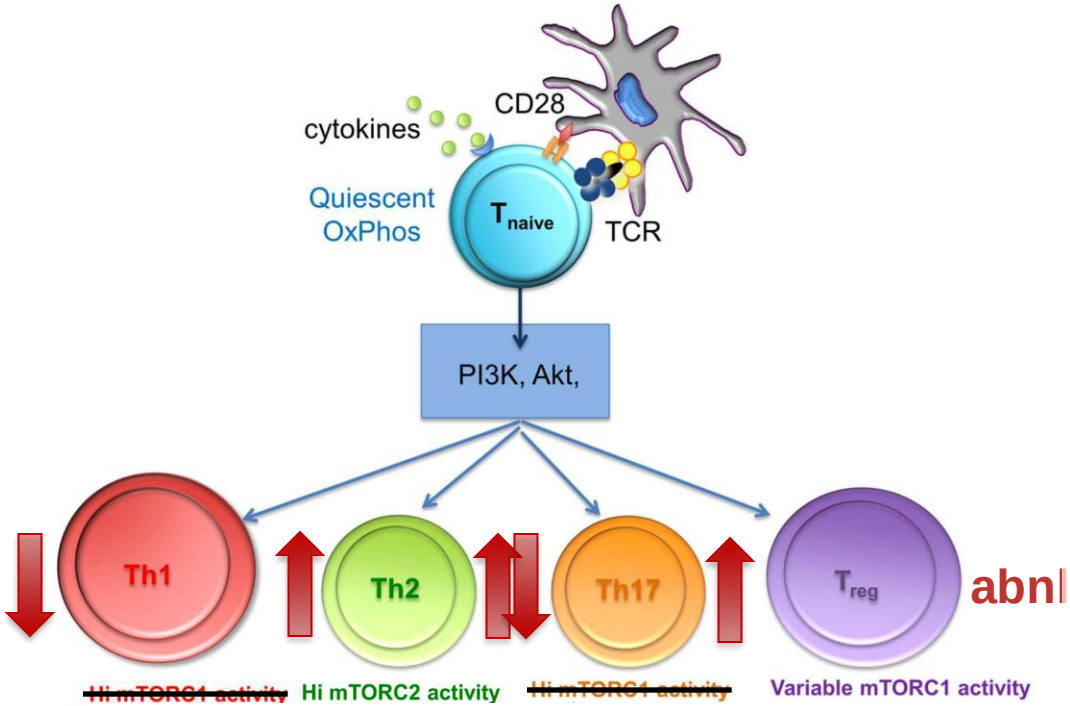
- 10yo brother
  - Atopic dermatitis, staph, neurocognitive impairment, hemolytic anemia
  - IgE 11,405, IgG 2,060, IgA 600
  - ANC 1,000, ALC 1,000, CD4/8 ~3:1
- 9mo M cousin
  - Atopic dermatitis, staph, unable to sit unassisted
  - neutropenia

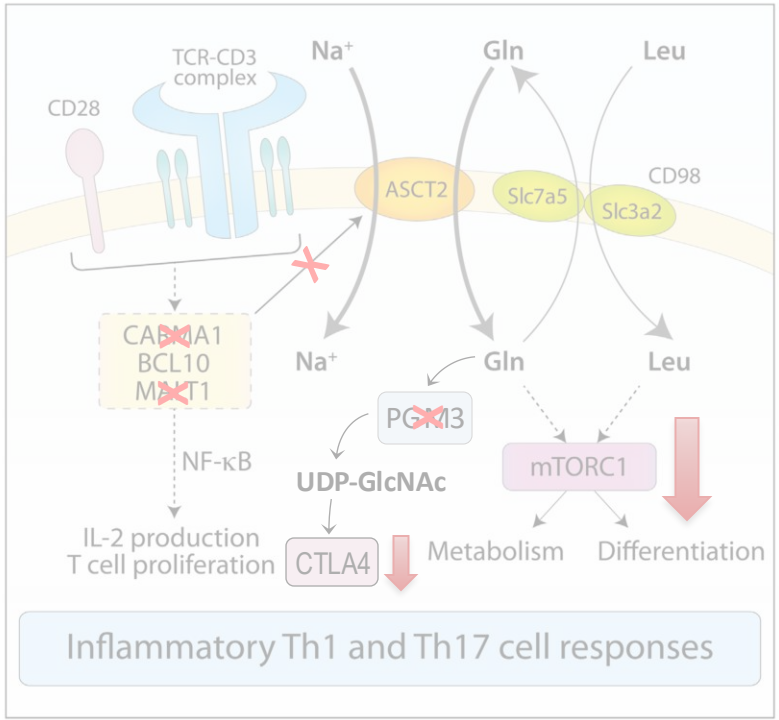


The clinical phenotype

- Allergy
  - high IgE; atopic dermatitis; asthma; food and environmental allergies; IV contrast sensitivity
- Infection
  - chronic otitis externa
  - recurrent staph and URI/pneumonia
  - lung, cutaneous, parotid, periodontal abscesses
- Autoimmunity
  - increased T_H17; elevated IgG; psoriatic lesions
  - ?hemolytic anemia, ?neutropenia
- Neurocognitive impairment
  - developmental delay, ataxia, discoordination and speech abnormalities/dyspraxia
  - febrile seizures

Lymphocyte metabolism and allergic disease

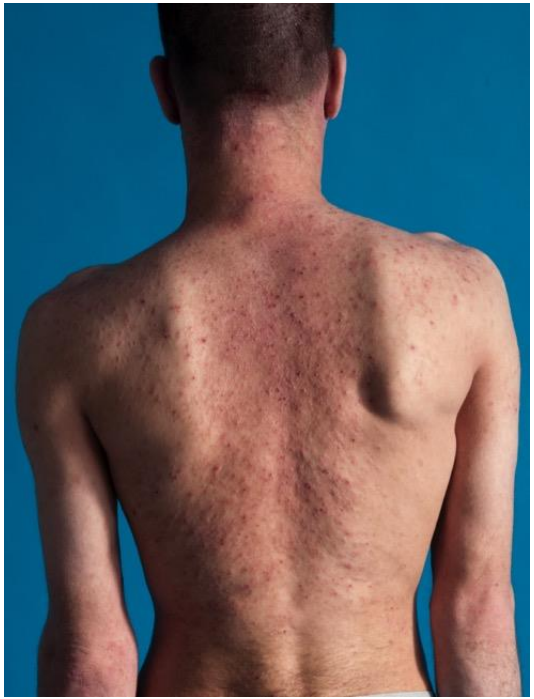


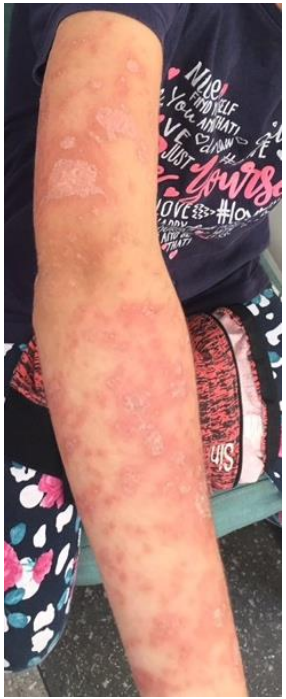


Coe et al. *Front Immunol.* 2014

Adapted from: Nakaya et al. *Immunity.* 2014

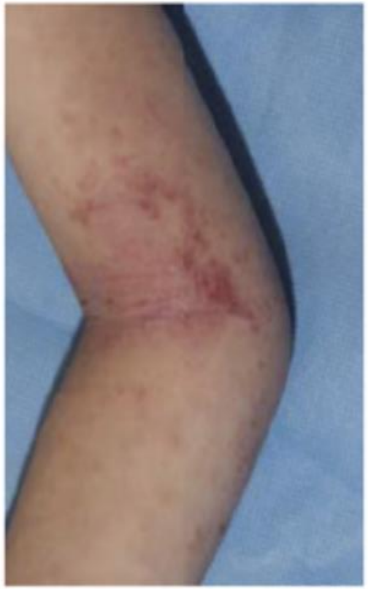
PGM3 deficiency

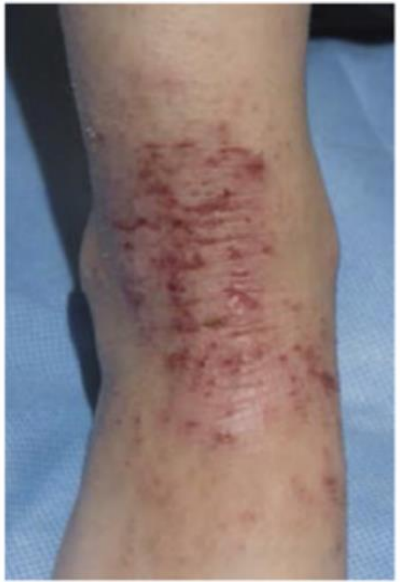




Zhang et al. *JACI*. 2014

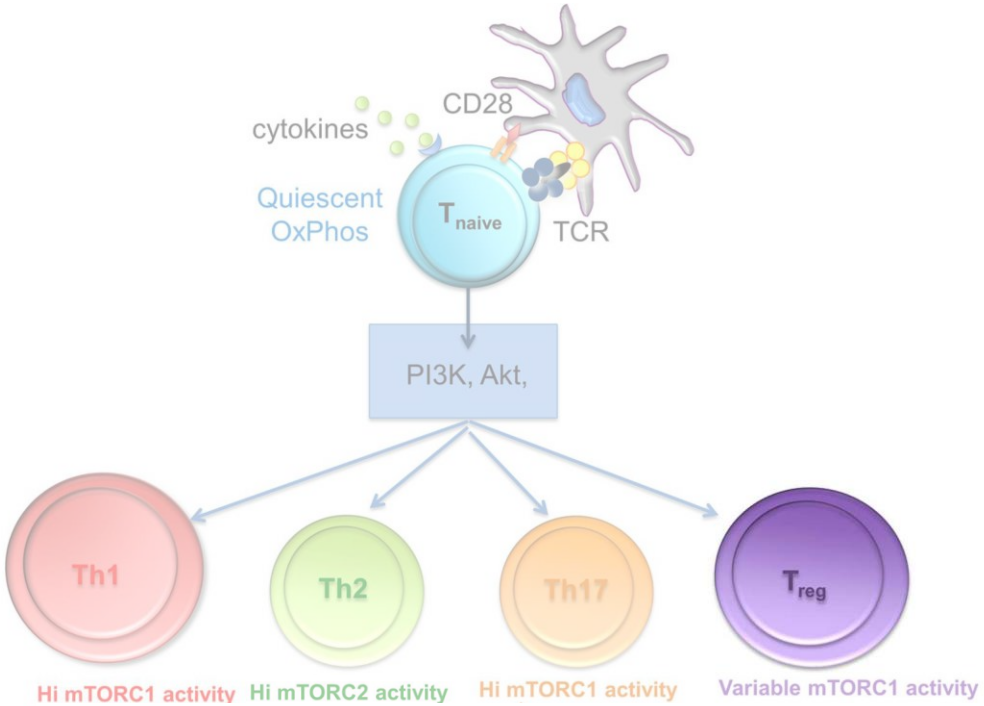
CARD11 haplo/DN

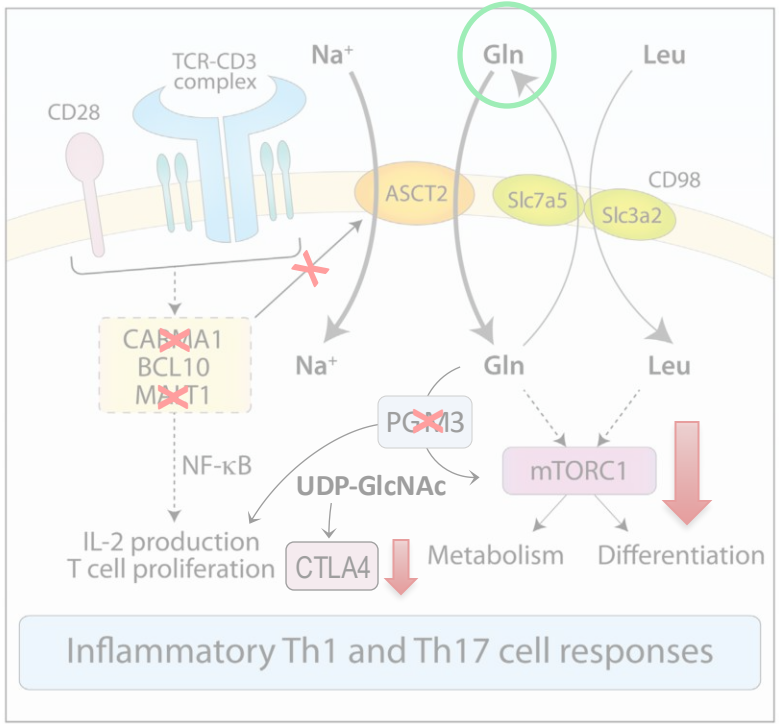




Ma et al. *Nat Genet*. 2017

Lymphocyte metabolism and allergic disease

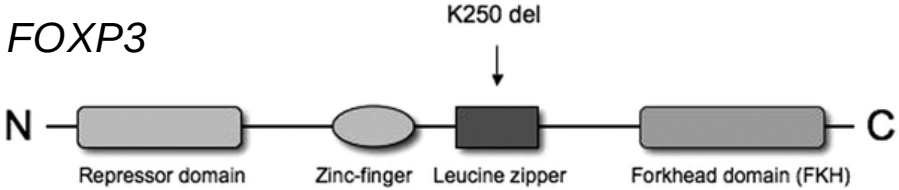




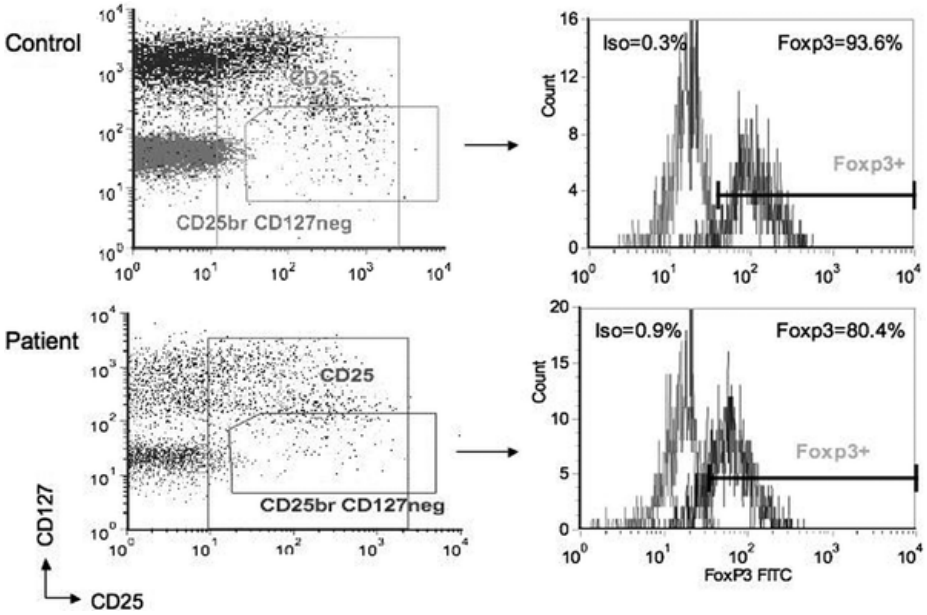
Coe et al. *Front Immunol.* 2014

Adapted from: Nakaya et al. *Immunity.* 2014

21-year-old male with a history of atopic dermatitis, autoimmune nephritis, peripheral eosinophilia, eosinophilic esophagitis, enteropathy, and dilated cardiomyopathy

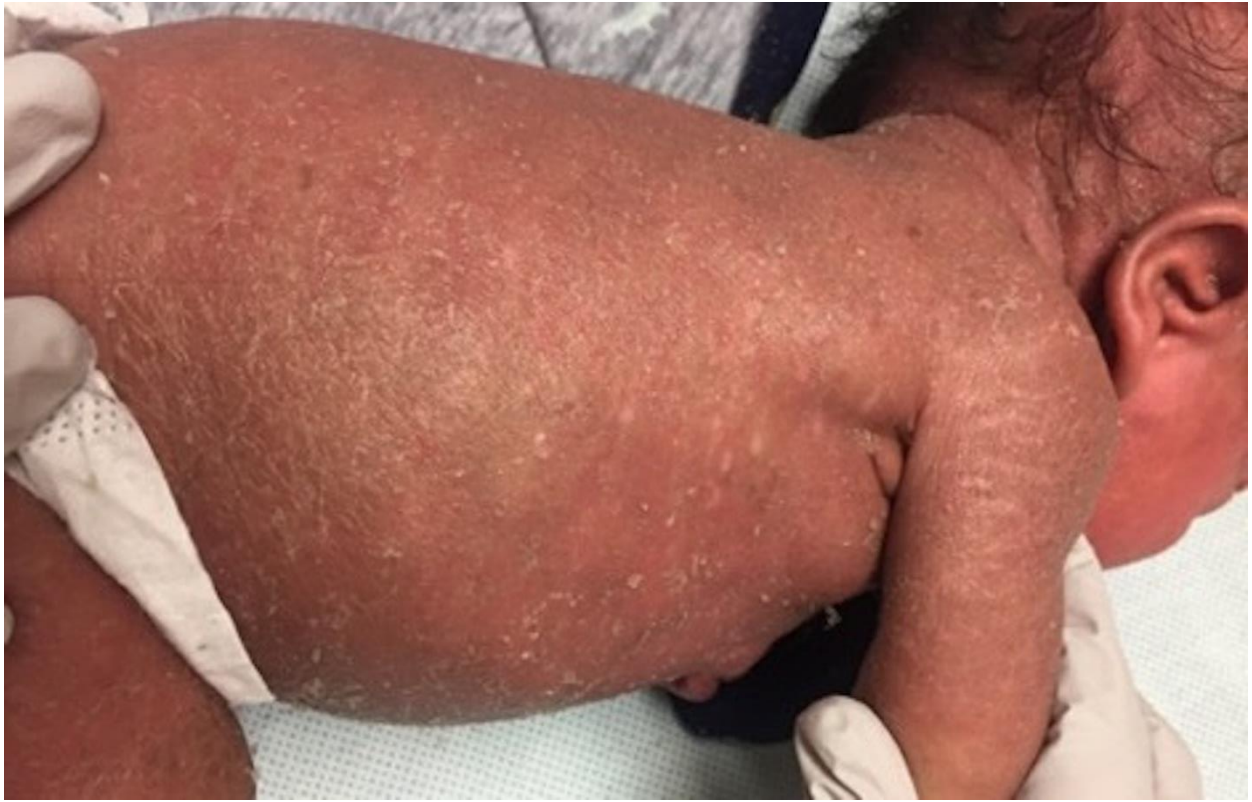


Immune dysregulation, **p**olyendocrinopathy, **e**nteropathy, **X**-linked syndrome (IPEX)



Tourangeau et al. *Allergy Asthma Proc.* 2011

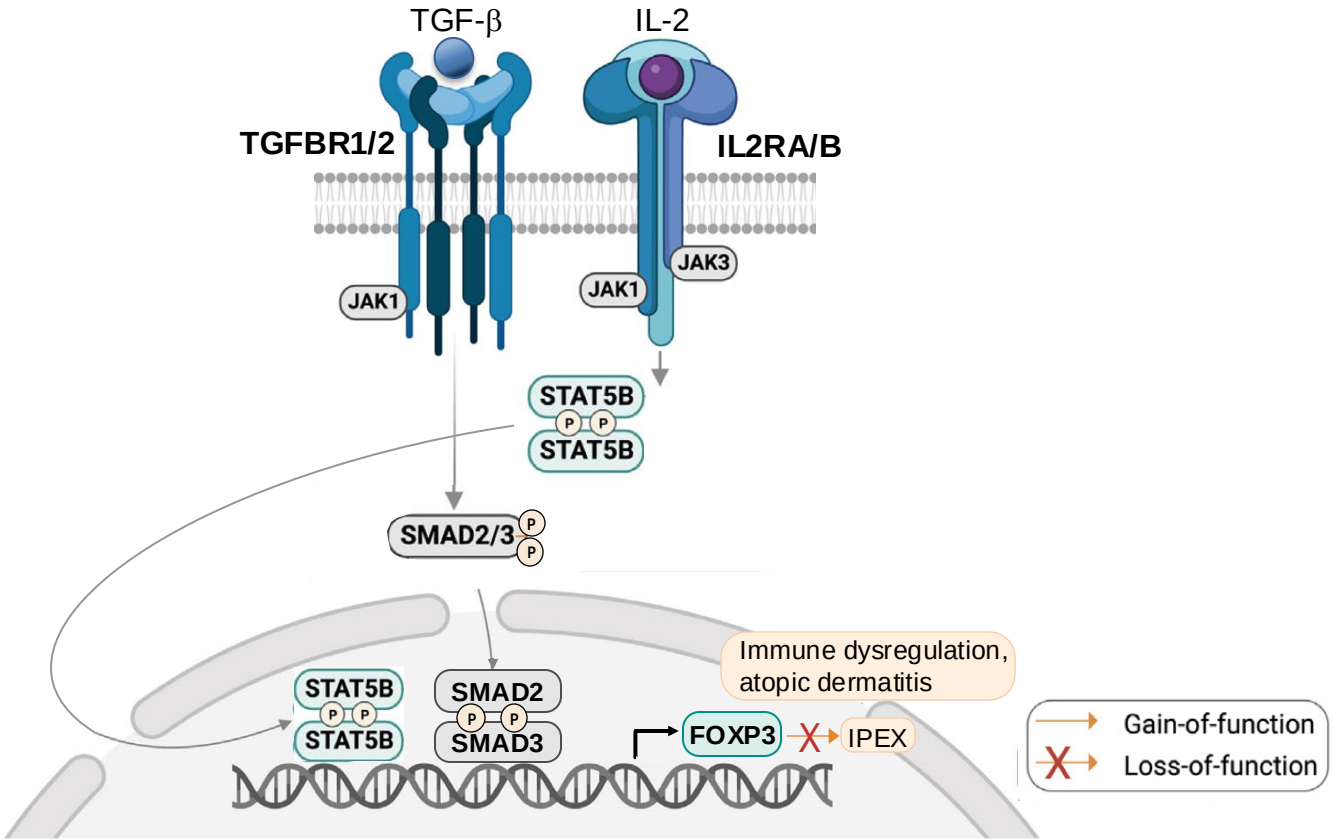
IPEX in an infant



2-month-old boy with failure to thrive, diarrhea, diffuse atopic dermatitis, vitiligo, hypothyroidism, pulmonic stenosis, and food allergy

Maher et al. *Pediatr Dermatol.* 2021

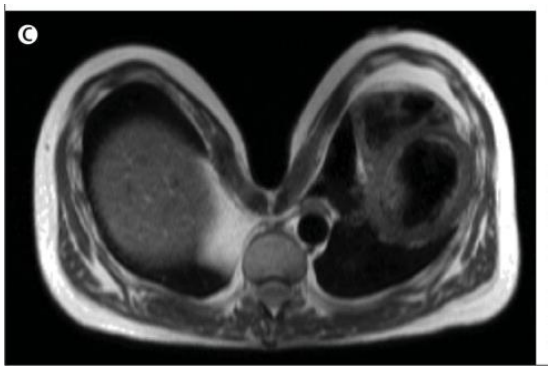
Pathways critical to regulatory T-cells (Tregs) are associated with immune dysregulation and allergy

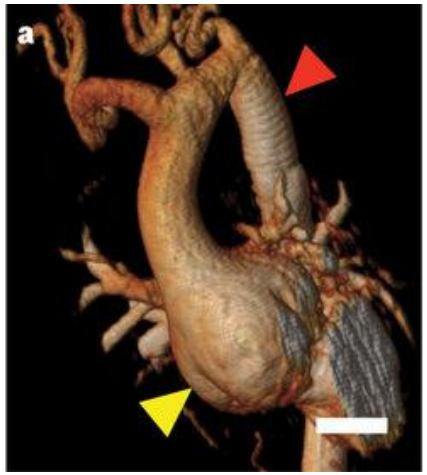


Adapted from: STAT6 GOF Consortium. *Trends Immunol.* 2024

Connective tissue abnormalities are common in PADs

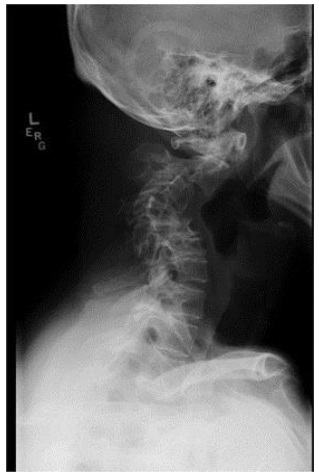
Loeys-Dietz

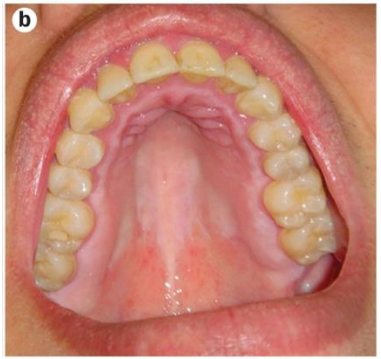




Jabbour et al. *Lancet*. 2012
Grahame at al. *Nat. Rev. Rheumatol.* 2013

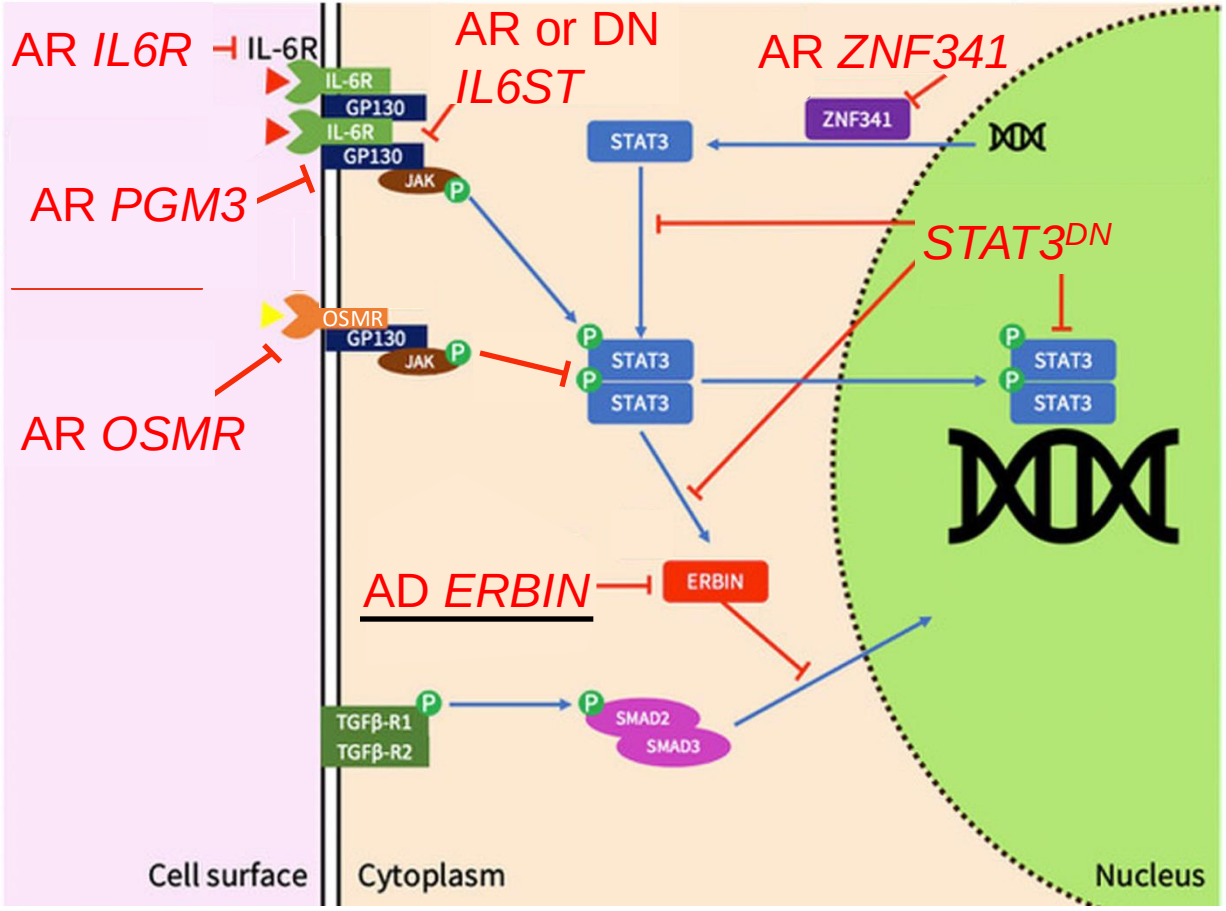
STAT3^{mut}





Freeman et al. *Ped Res*. 2009
Lindsay et al. *Nature.* 2011

Multiple PADs are linked to impaired STAT3 signaling



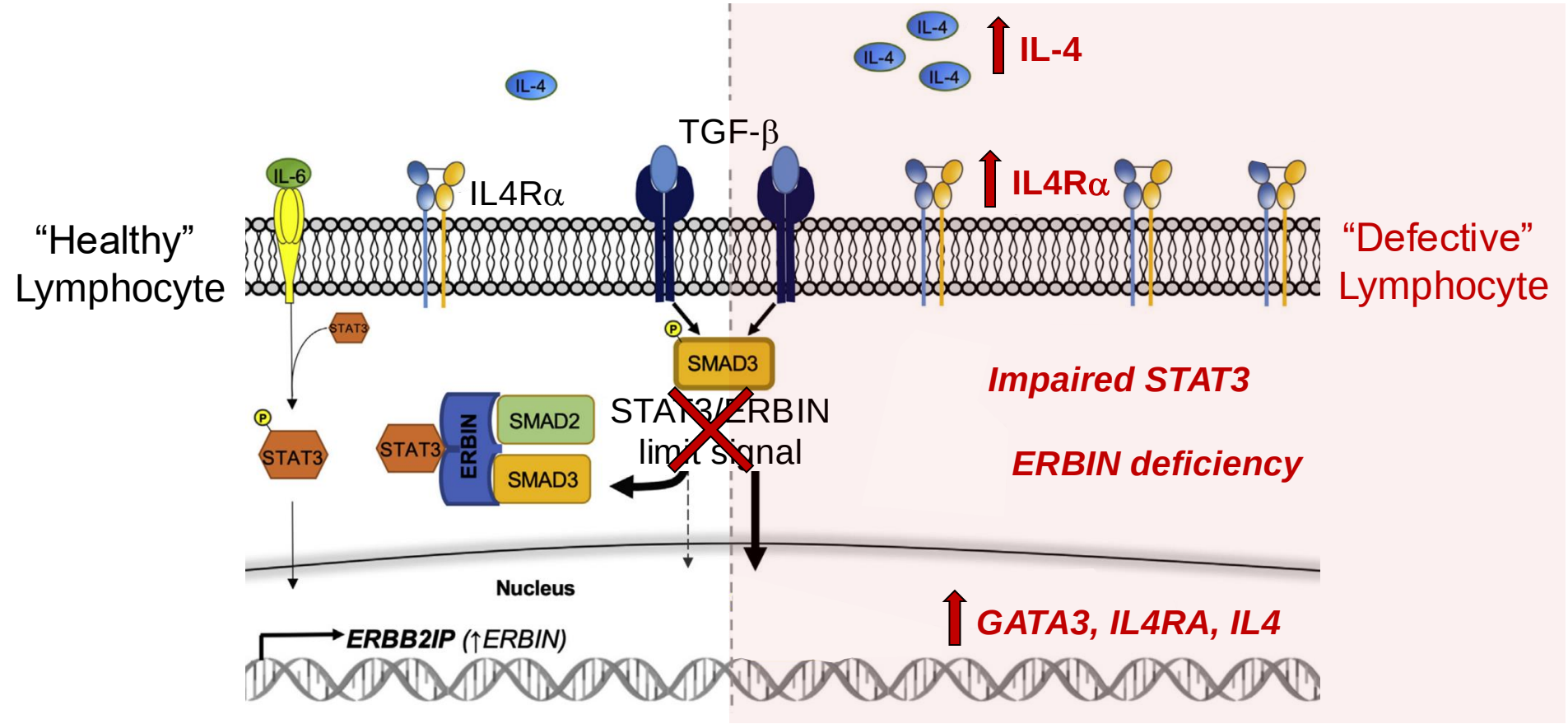
Tsilifis et al. *JoCI.* 2021

ERBIN haploinsufficiency

- EoE
- Dilated aortic root
- Elevated IgE and peripheral Eos
- Scoliosis and hyperextensibility (Beighton>5)
- Atopic dermatitis
- *S. aureus* susceptibility
- Allergic asthma
- CRS with NP

Disease refractory to topical corticosteroids and IL-5 blockade

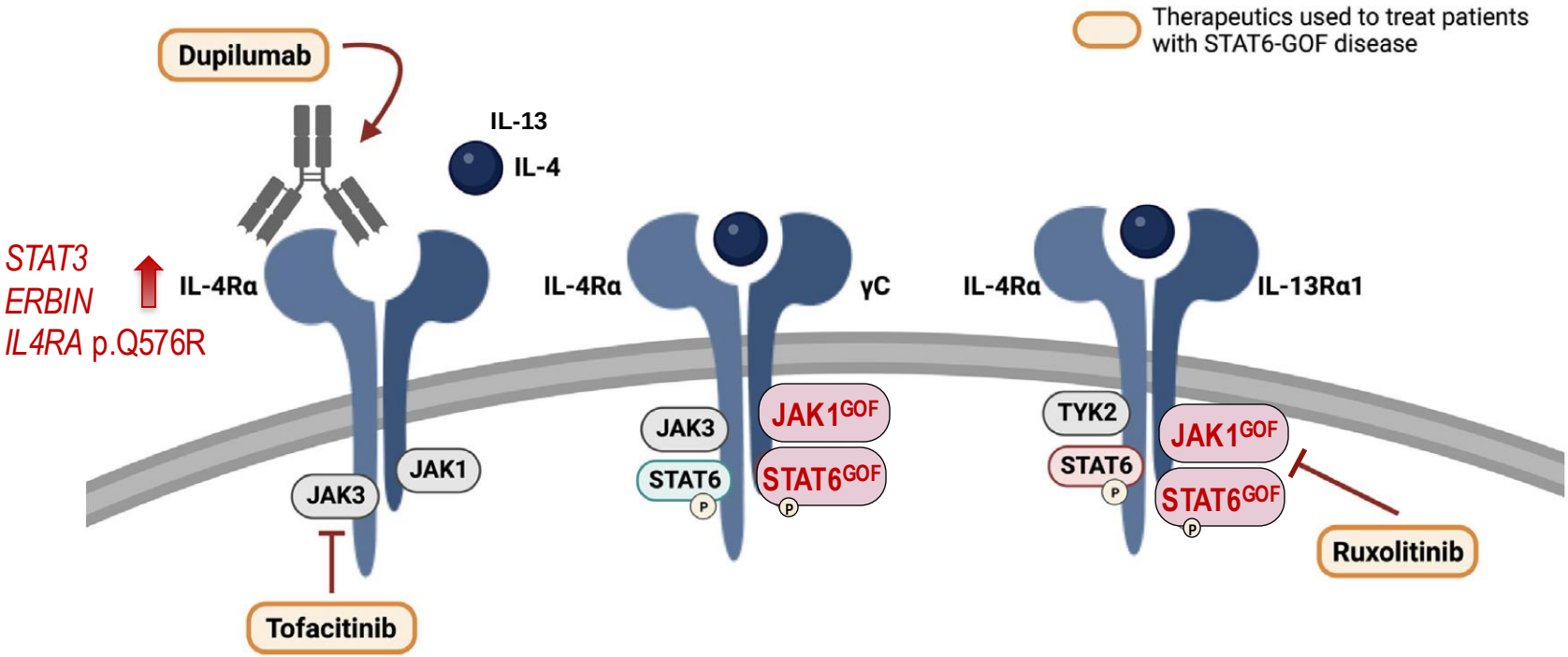
STAT3 and TGF-β defects enhance IL-4 signaling



Lyons et al. *JEM*. 2017

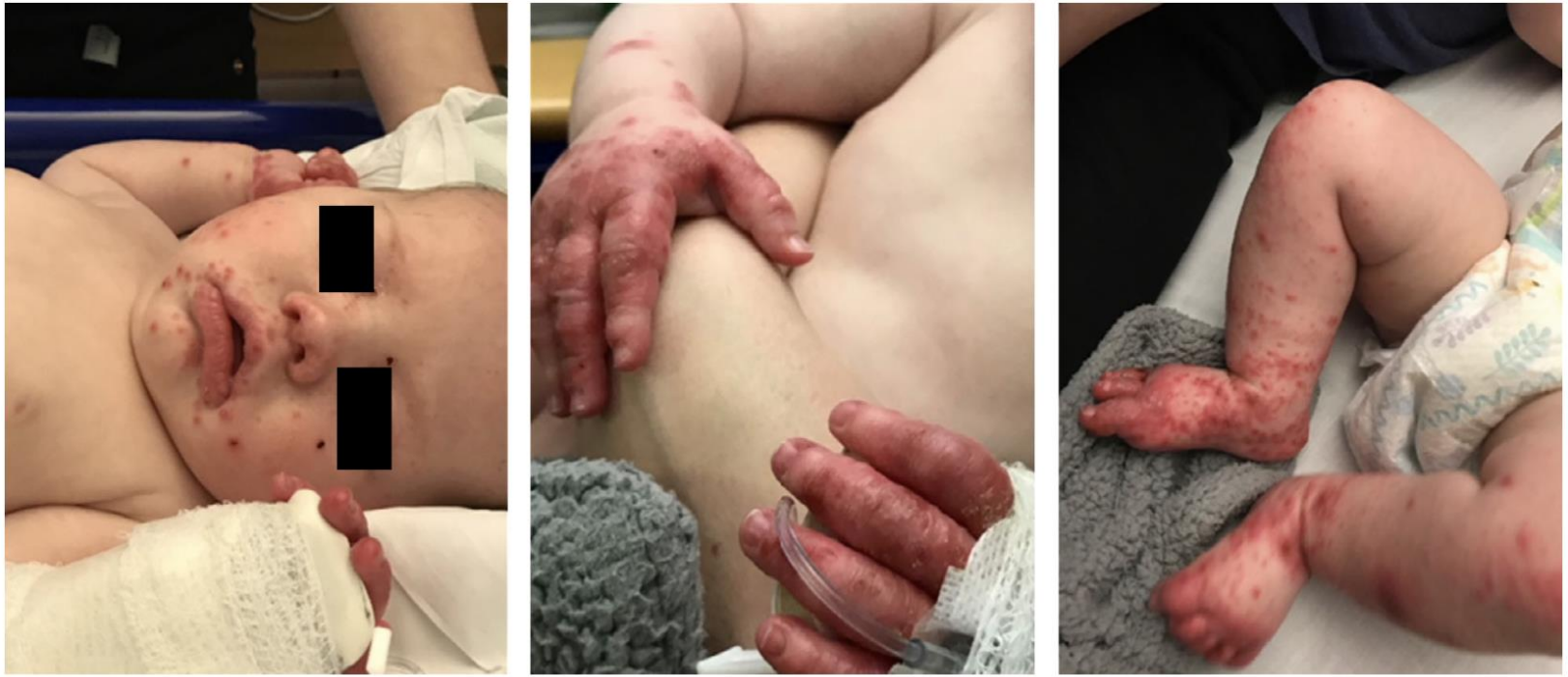
Adapted from: Droghini et al. *JACI Pract*. 2022

Multiple PADs converge on IL-4R/STAT6 signaling



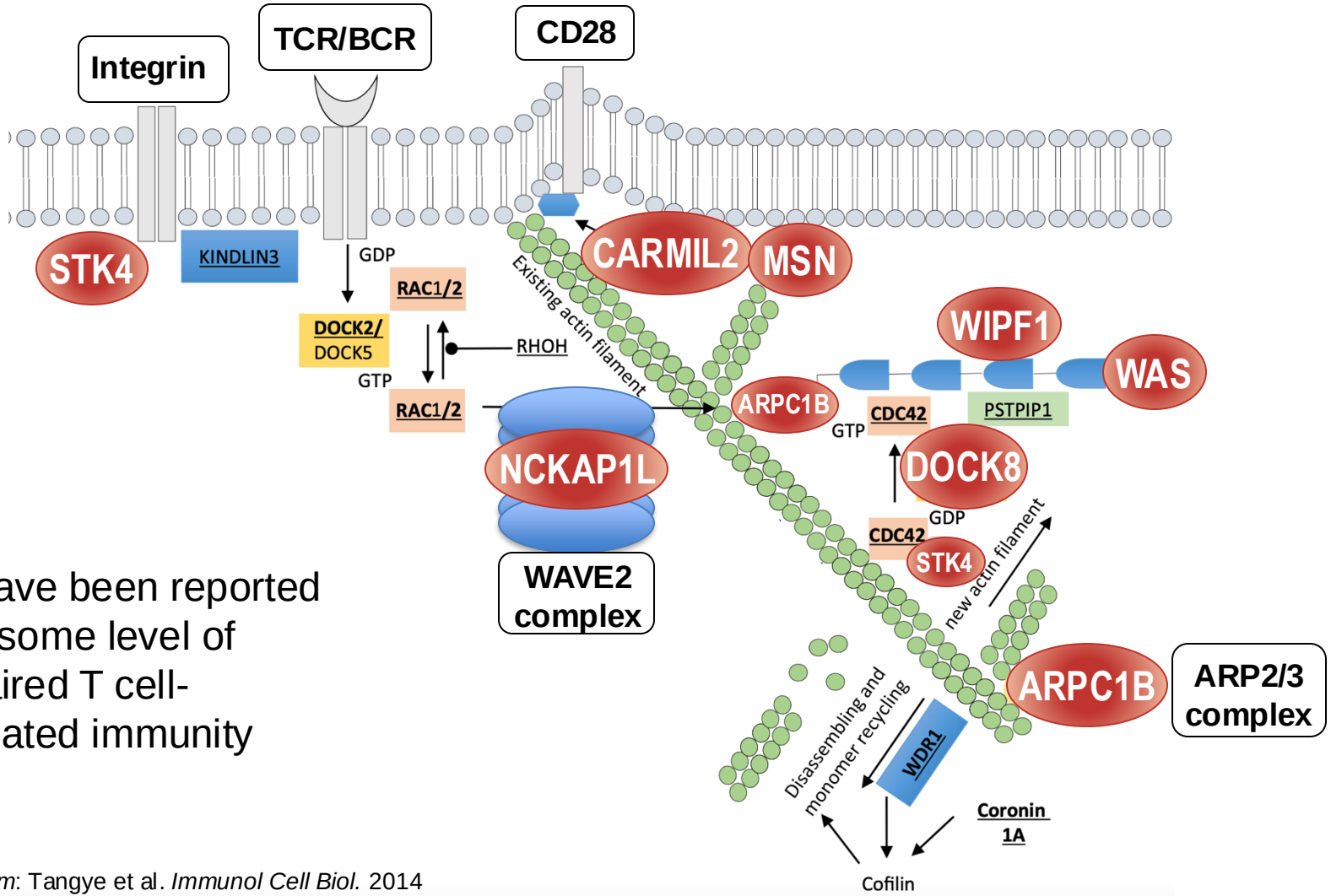
Adapted from: STAT6 GOF Consortium. *Trends Immunol.* 2024

Wiskott-Aldrich syndrome: the archetype for cytoskeletal defects in AD



Severe atopic dermatitis since birth, food allergy, thrombocytopenia and hemolytic anemia. Low CD8+ Tcells but otherwise normal lymphocyte numbers; normal proliferation to PHA and tetanus.

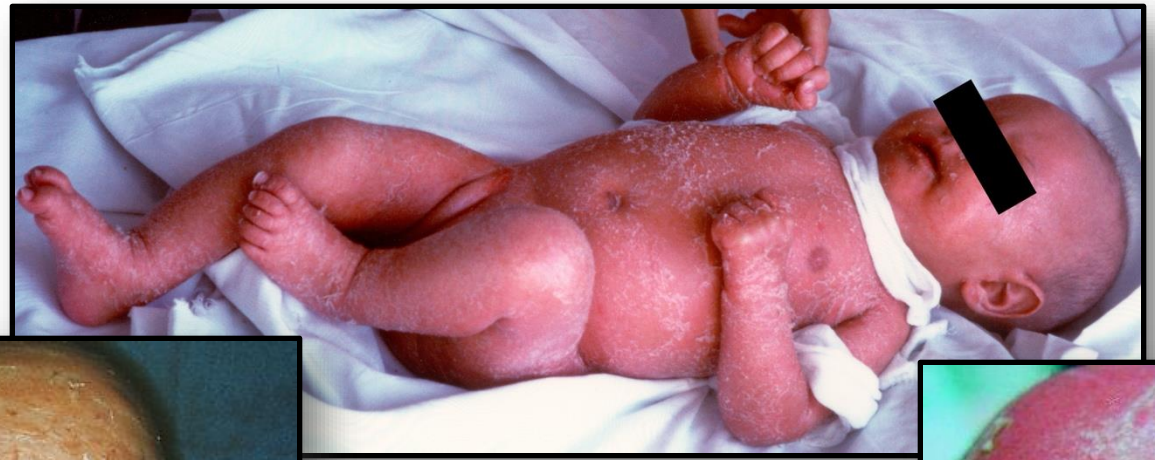
Rivers et al. *Br J Haematol.* 2019

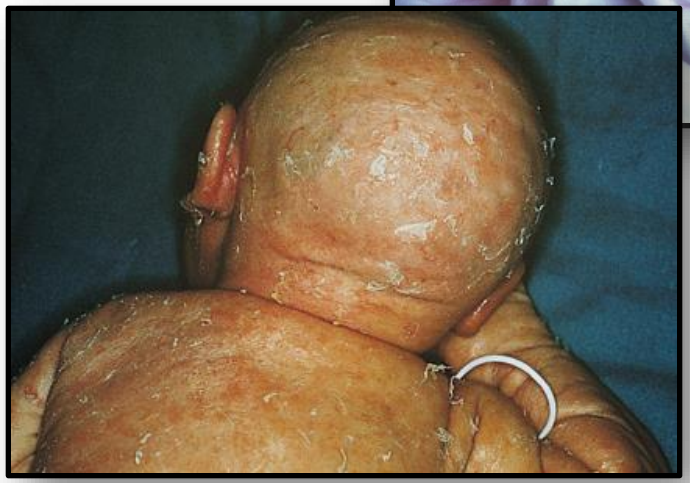


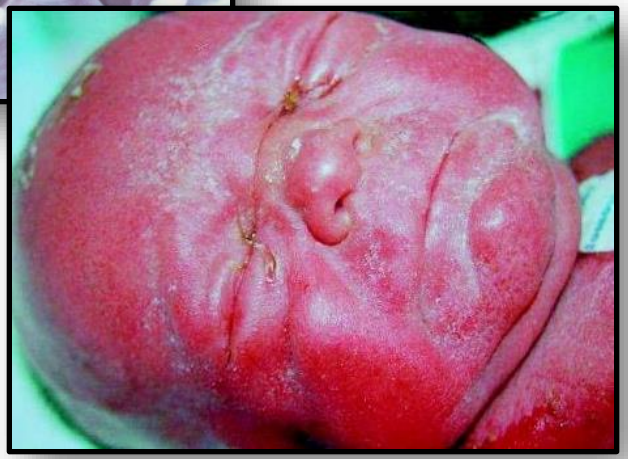
All have been reported with some level of impaired T cell-mediated immunity

Adapted from: Tangye et al. *Immunol Cell Biol.* 2014

“Leaky SCID” results in Omenn syndrome: oligoclonal T-cell expansion with severe Th2 inflammation

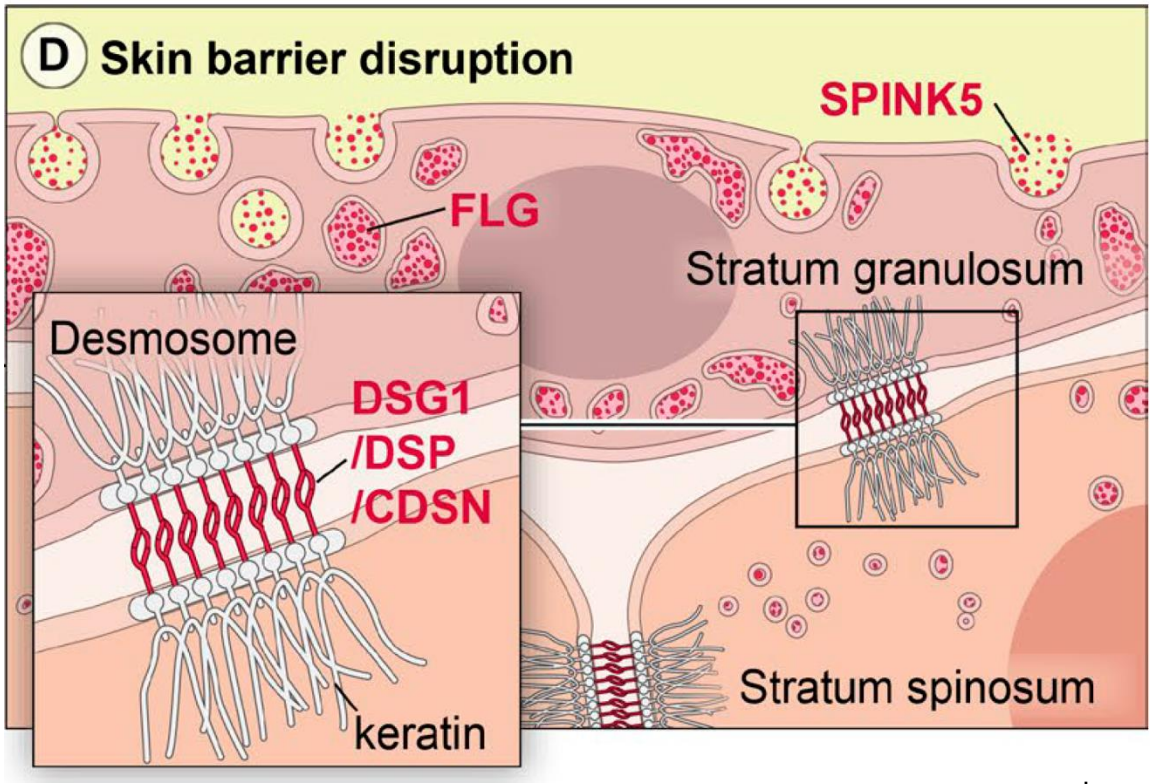




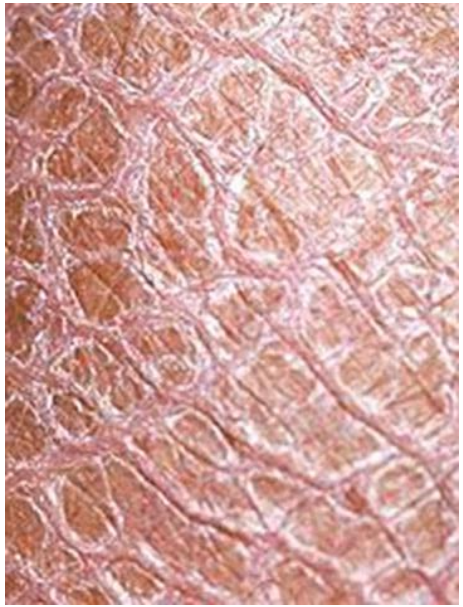
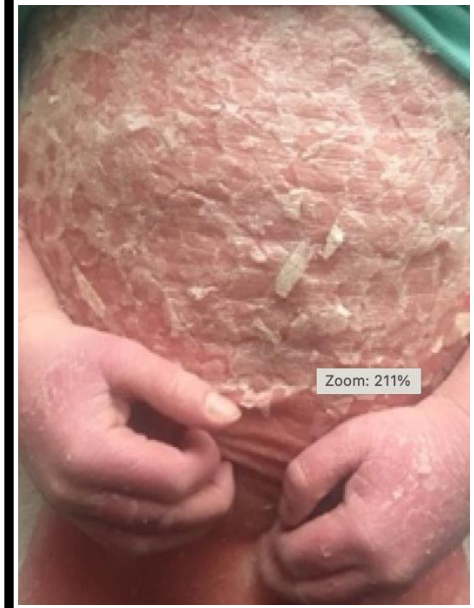
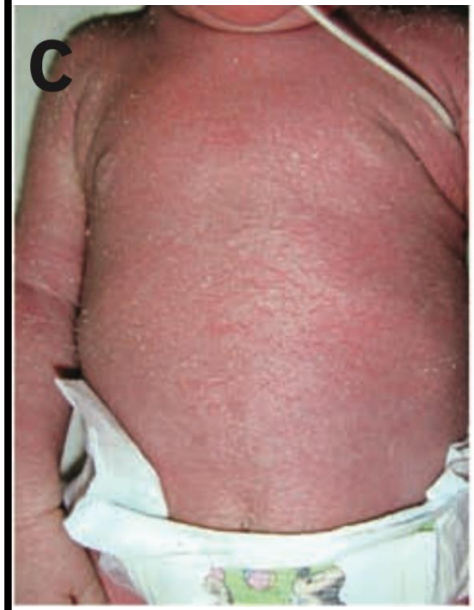
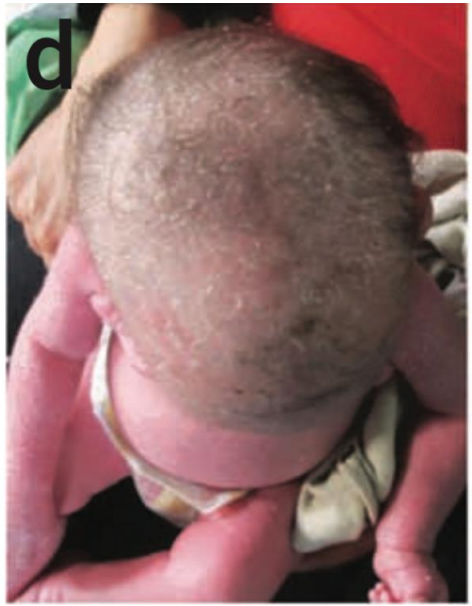


Cossu. *Ital J Pediatr*. 2010

Inborn errors emphasize the importance of skin barrier dysfunction in allergic disease



Lyons and Milner. *J Exp Med.* 2018

Ichthyosis vulgaris	Comel-Netherton syndrome	Severe dermatitis, multiple allergies and metabolic wasting (SAM) syndrome
		 
FLG	*SPINK5*	*CDSN, DSG1, DSP*

Jaffar et al. *Skin Health Dis*. 2022 Kostova et al. Clin Case Rep. 2024 Samuelov *Nat Genet*. 2013

When to suspect an IEI in your allergic patient?

- Early onset (< 2mo of life)
- Pervasive / invasive infections
- Chronic diarrhea / enteritis / failure to thrive
- Endocrinopathies
- Easy bleeding / bruising
- Autoinflammation / autoimmunity
- Immune dysregulation / lymphoproliferation
- Significant connective tissue abnormalities

Conclusions

- Rare disorders in aggregate are common (WHO 1:100 live births)
- Primary atopic disorders provide insights into the pathogenesis of allergic diseases and new strategies for treating our patients
- Alterations in metabolic programs in $CD4^+$ T lymphocytes and impaired activation promote allergy
- Disruption of normal Treg generation and function leads to allergic disease with immune dysregulation
- Connective tissue abnormalities are common in PADs and are associated with alterations in TGF-β signaling
- Defective STAT3 signaling is linked to increased TGF-β signaling and enhance IL-4 signaling
- This can be targeted via IL-4 pathway inhibition successfully in these patients
- Defects limited only to T cells (e.g., *DOCK8*) or skin (e.g., *FLG*) can both lead to similar allergic disease