

When and How to Address Significantly Elevated IgE Levels in Food Allergy

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Learning Objectives

Upon completion of this learning activity, participants should be able to...

- Differentiate features of food allergy and elevated IgE which may be inborn errors of immunity/ primary atopic disorder from more routine atopy
- Plan an evaluation for children with food allergy and elevated IgE
- Describe how elevated specific IgE affects the diagnosis and prognosis and management of food allergy

PBL: Noah, A 7-year-old with food allergies and comorbid asthma

Food Allergy History

- **Peanut** allergy since infancy (hives on first exposure; IgE positive)
- Strict avoidance of peanut; tolerates tree nuts
- Severe reaction to **sesame/tahini** 4 months ago → ED care with IM epinephrine, O₂, albuterol

Asthma History

- Onset age 4; **suboptimal control**
- ACT = **17**; albuterol ~3×/week
- 2 prednisone bursts/year
- On budesonide/formoterol 80/4.5, 2 puffs BID

Atopic Comorbidities

- Chronic itchy/runny nose; partial control on loratadine + fluticasone
- Infantile eczema, mild recurrence

PBL: Noah, A 7-year-old with food allergies and comorbid asthma

Old Allergy Records (3 months ago)

- Total IgE: **1,000 IU/mL**
- Skin tests: >10 mm to **peanut, sesame**, HDM, cat, dog; negative to tree nuts
- Serum IgE: peanut **30 IU/mL**, sesame **20 IU/mL**
- Spirometry: normal
- FeNO: **45 ppb**
- Blood eosinophils: **600**
- C-ACT: **17**

Environment

- Lives with parents; dog + cat in home
- Bedroom HDM control; HEPA filter; pet restriction

PBL: Noah, A 7-year-old with food allergies and comorbid asthma

Medications

- Epinephrine autoinjector 0.15 mg
- Budesonide/formoterol BID
- Albuterol PRN
- Loratadine; fluticasone nasal spray

Exam

- Vitals normal; clear rhinorrhea; Dennie–Morgan lines; Flexural erythema; lungs clear
- Weight 25kg

Testing Today

- Spirometry: normal
- FeNO: **45 ppb**
- ACT: **17**

Differential Diagnosis of Elevated IgE

- Allergic, infectious, inflammatory, immunodeficiency causes

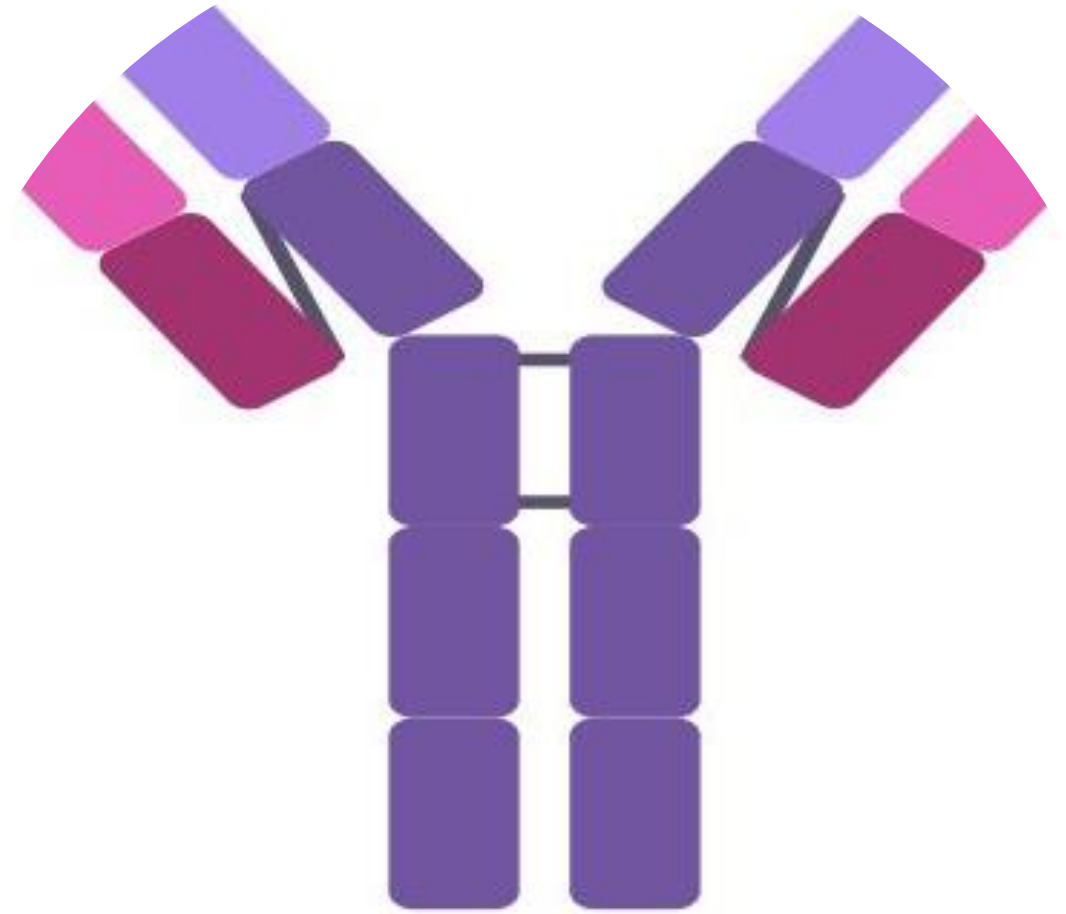
Differential Diagnosis of Elevated IgE

- Allergic, **infectious**, inflammatory, immunodeficiency causes

Elevated Total IgE – What Does It Mean for Diagnosis?

Rare but critical
immunodeficiency/inflammatory or primary
atopy syndromes

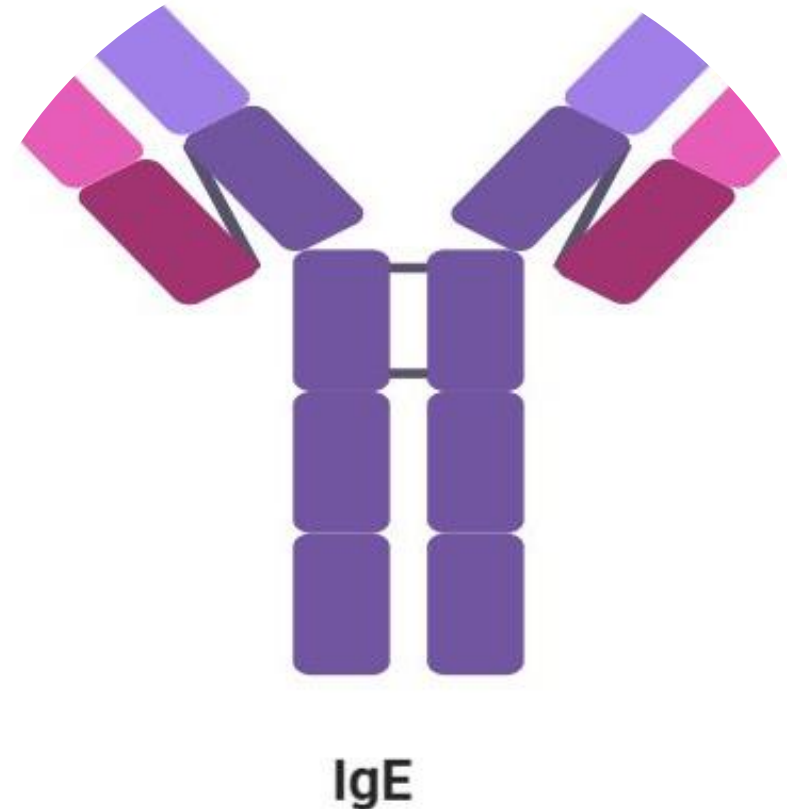
Common
allergic
disorders



IgE

Elevated Total IgE what is elevated?

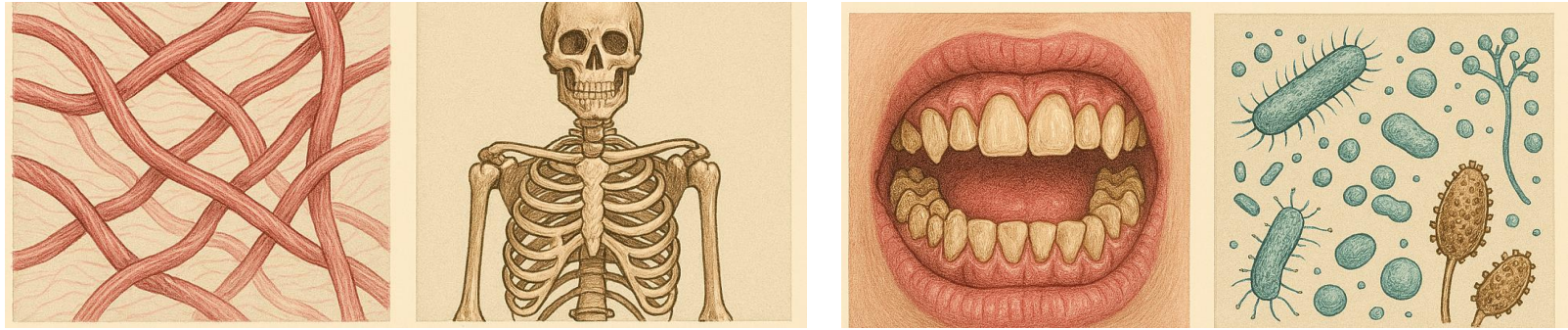
- Upper limit of normal for age values >100–200 IU/mL are typically considered elevated in children, and levels >1000 IU/mL are regarded as significantly elevated in both adults and children
- Reference ranges vary by age, sex, population and laboratory



Inborn Errors of Immunity

- Cytokine signalling
- Cytoskeleton
- T- cell defects
- Barrier

Cytokine Signaling Defects (JAK-STAT Pathway)



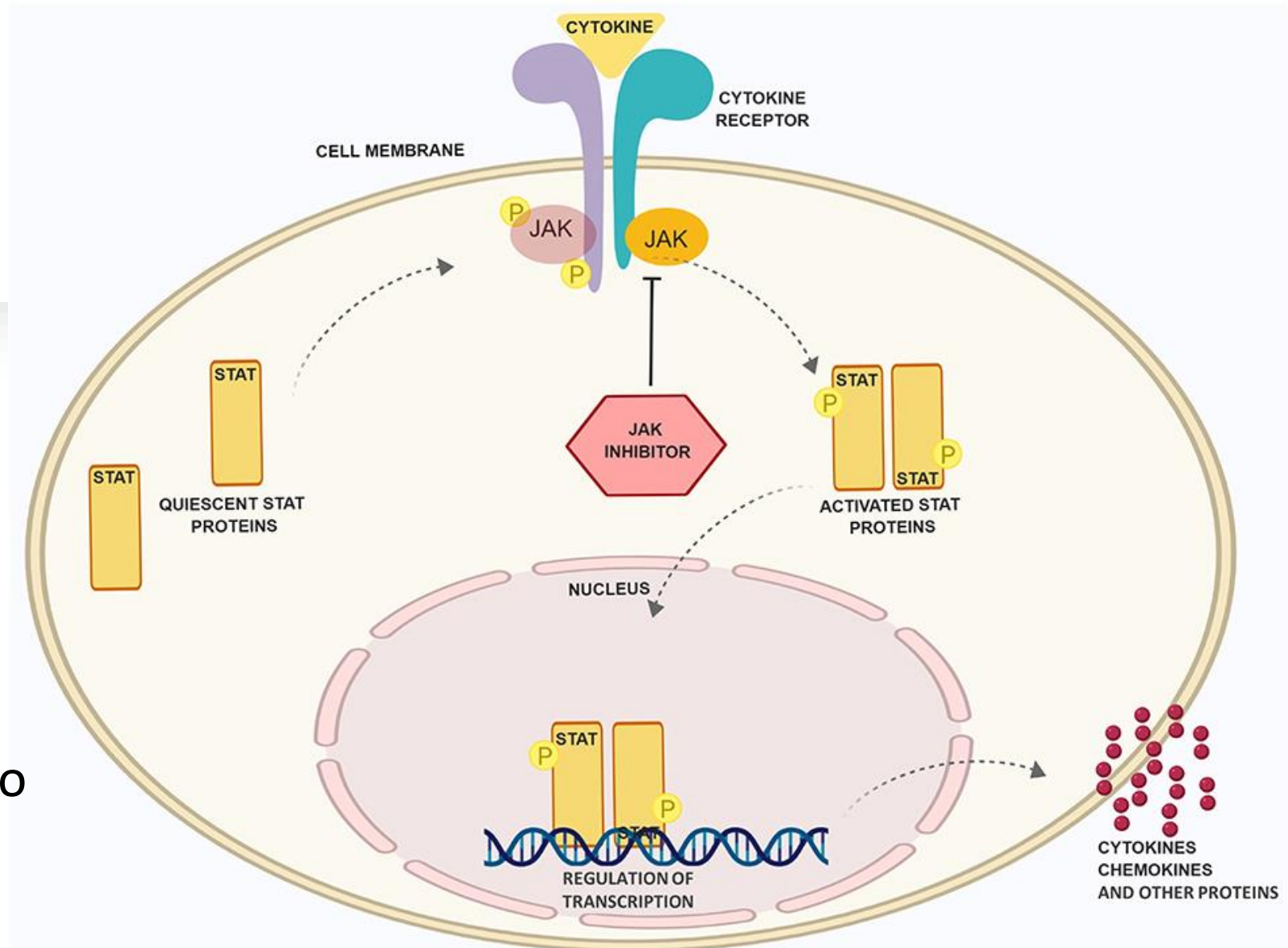
Critical for cytokine-mediated immune responses and Th17 differentiation:

- **STAT3 deficiency** (AD-HIES): Prototype hyper-IgE syndrome with impaired IL-6, IL-10, IL-21, and IL-23 signaling, leading to defective Th17 immunity and susceptibility to *Staphylococcus aureus* and *Candida* infections
- **ZNF341 deficiency**: Phenotypically similar to STAT3 deficiency, as ZNF341 regulates STAT3 expression
- **PGM3 deficiency** (AR-HIES): Affects N-glycosylation pathways, impairing cytokine receptor function and multiple signaling cascades

Cytokine Signaling Defects (JAK-STAT Pathway)

Critical for cytokine-mediated immune responses and Th17 differentiation:

- STAT3 deficiency (AD-HIES)
- ZNF341 deficiency: Phenotypically similar to STAT3
- PGM3 deficiency (AR-HIES)



STAT6 GOF

- Interleukin (IL)-4 and IL-13 are known to activate the STAT6 signaling pathway
- STAT6 GOF puts the TH2 pathway in hyperdrive





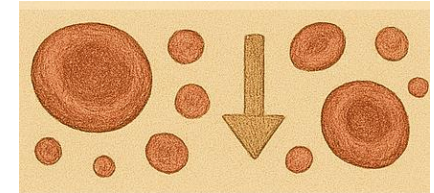
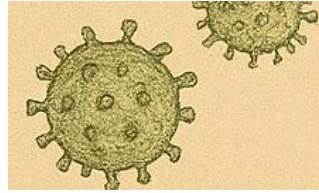
STAT6 GOF

- Treatment-resistant dermatitis
- Food allergies
- Asthma
- Eosinophilic gastrointestinal disease
- Severe episodes of anaphylaxis including fatality

Non atopic features

- Recurrent skin, respiratory, and viral infections, although none had history of fatal infections
- Like HIES, short stature, skeletal issues such as pathologic fractures, and generalized hypermobility
- B cell lymphoma
- Fatality due to a cerebral aneurysm also occurred
- T, B, and natural killer cell numbers all typically in the normal range although clinical evidence of chronic systemic inflammation was documented (i.e., elevations in white blood cell counts, platelets, and serum immunoglobulin levels).

Cytoskeletal/Actin Regulation Defects



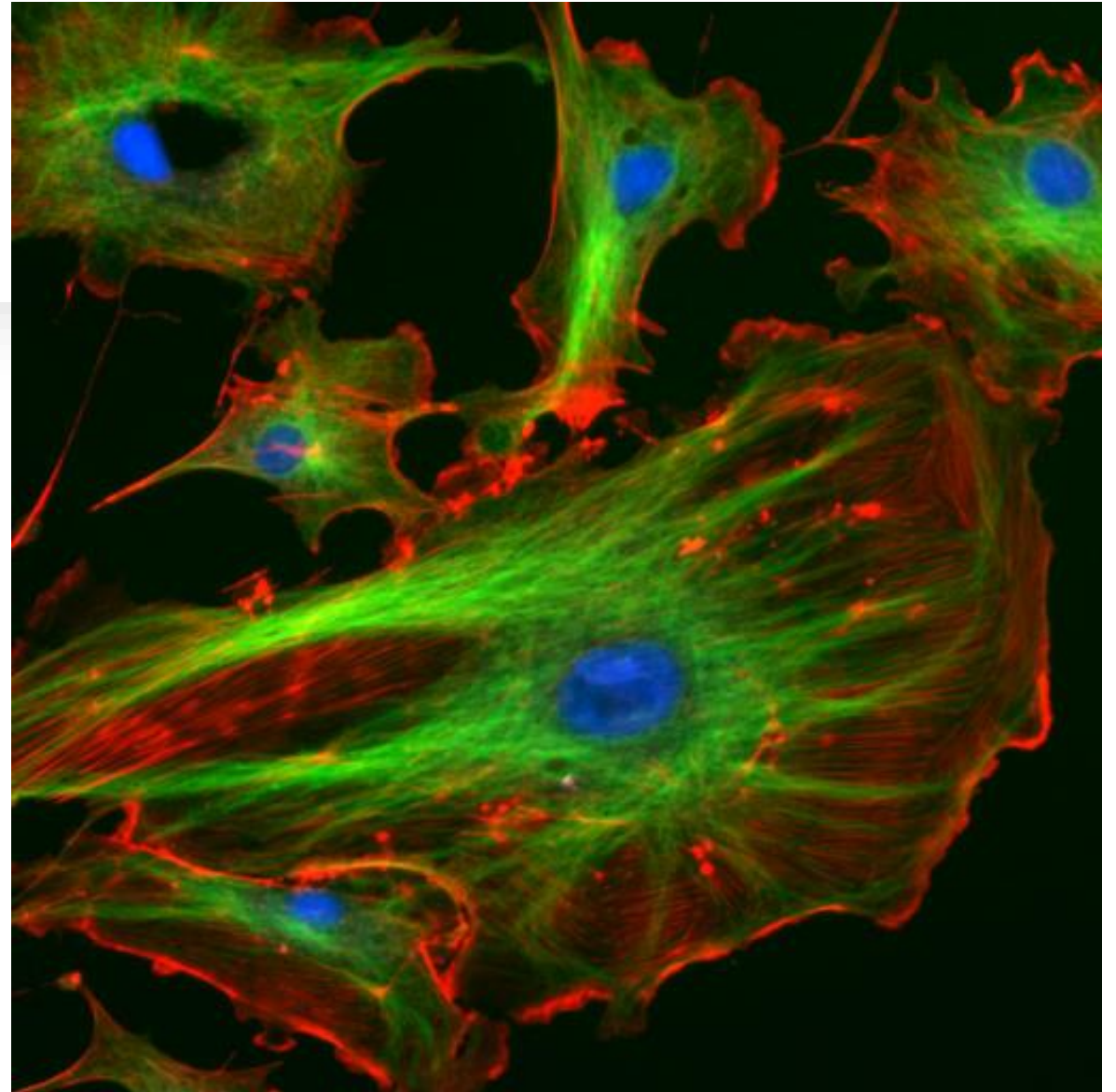
Severe viral infections, eczema, food allergies, autoimmunity, increased malignancy risk, and often thrombocytopenia

- **DOCK8 deficiency:** Impairs actin cytoskeleton reorganization in lymphocytes, leading to defective cell migration and immune synapse formation.
- **Wiskott-Aldrich syndrome** (WASp deficiency): Disrupts actin nucleation downstream of the ARP2/3 complex
- **ARPC1B deficiency** (ARP2/3 complex): Directly affects the actin-nucleating ARP2/3 complex

Cytoskeletal/Actin Regulation Defects

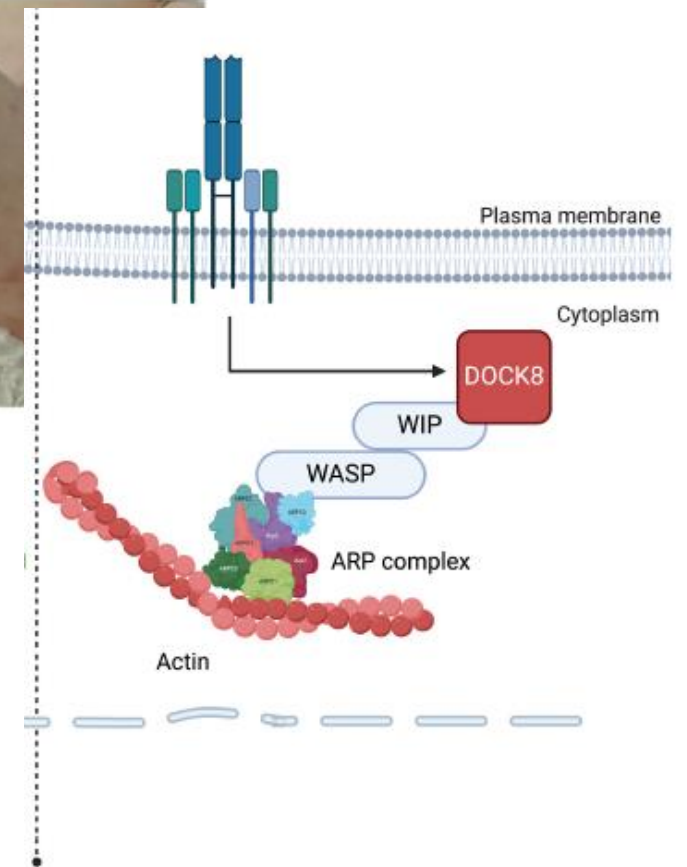
Defects in actin polymerization and cytoskeletal remodeling, critical for immune cell migration, synapse formation, and platelet function:

- **DOCK8 deficiency**
- **Wiskott-Aldrich syndrome**
- **ARPC1B deficiency (ARP2/3 complex)**



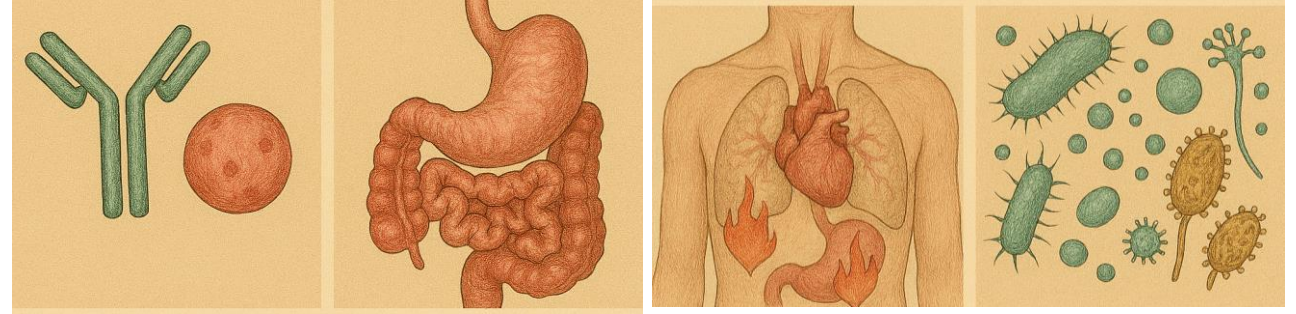
Arp 2/3

- Similar to Wiskott Aldrich because is downstream of the WAS protein
- Autoimmunity
- Atopy
- High IgE, eosinophilia, Platelet counts normal



Kahr WH, Pluthero FG, Elkadri A, Warner N, Drobac M, Chen CH, Lo RW, Li L, Li R, Li Q, Thoeni C, Pan J, Leung G, Lara-Corrales I, Murchie R, Cutz E, Laxer RM, **Upton J**, Roifman CM, Yeung RS, Brumell JH, Muise AM. Loss of the Arp2/3 complex component ARPC1B causes platelet abnormalities and predisposes to inflammatory disease. Nat Commun. 2017 Apr 3;8:14816. doi: 10.1038/ncomms14816. PMID: 28368018; PMCID: PMC5382316.

Immune Dysregulation/ T cell signalling defects



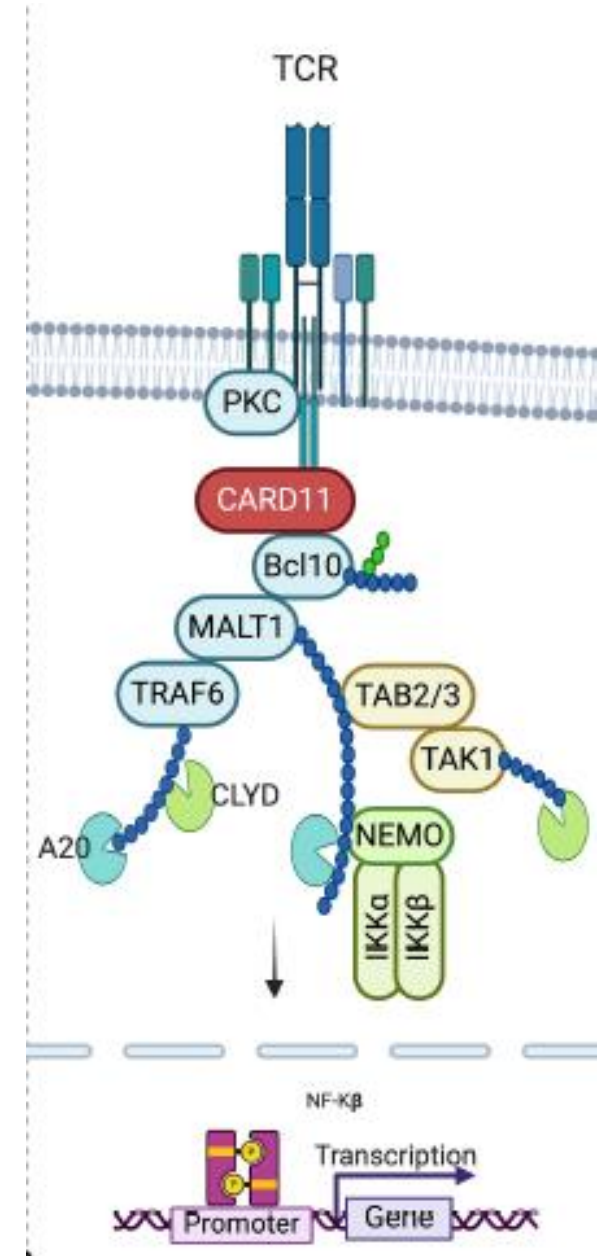
Defective regulatory T cell function or aberrant immune activation, leading to autoimmunity and inflammatory manifestations:

- **IPEX syndrome (FOXP3 deficiency):** Loss of regulatory T cell function causes multi-organ autoimmunity with enteropathy, endocrinopathy, and severe eczema.
- **Omenn syndrome:** Severe combined immunodeficiency (SCID) with oligoclonal T cell expansion, erythroderma, and lymphoproliferation.
- **CARD11 deficiency:** Impairs NF- κ B signaling with variable presentations including atopy and combined immunodeficiency.
- **MALT1 deficiency:** Disrupts the CBM signalosome and NF- κ B activation, causing combined immunodeficiency with Th2 skewing and decreased regulatory T cells
- **Atypical DiGeorge syndrome:** (rare-disease/22q112-deletion-syndrome): Thymic hypoplasia with variable immunodeficiency and occasional IgE elevation

Immune Dysregulation/ T cell signalling defects

Defective regulatory T cell function or aberrant immune activation, leading to autoimmunity and inflammatory manifestations:

- **IPEX syndrome (FOXP3 deficiency)**
- **Omenn syndrome**
- **CARD11 deficiency**
- **MALT1 deficiency**



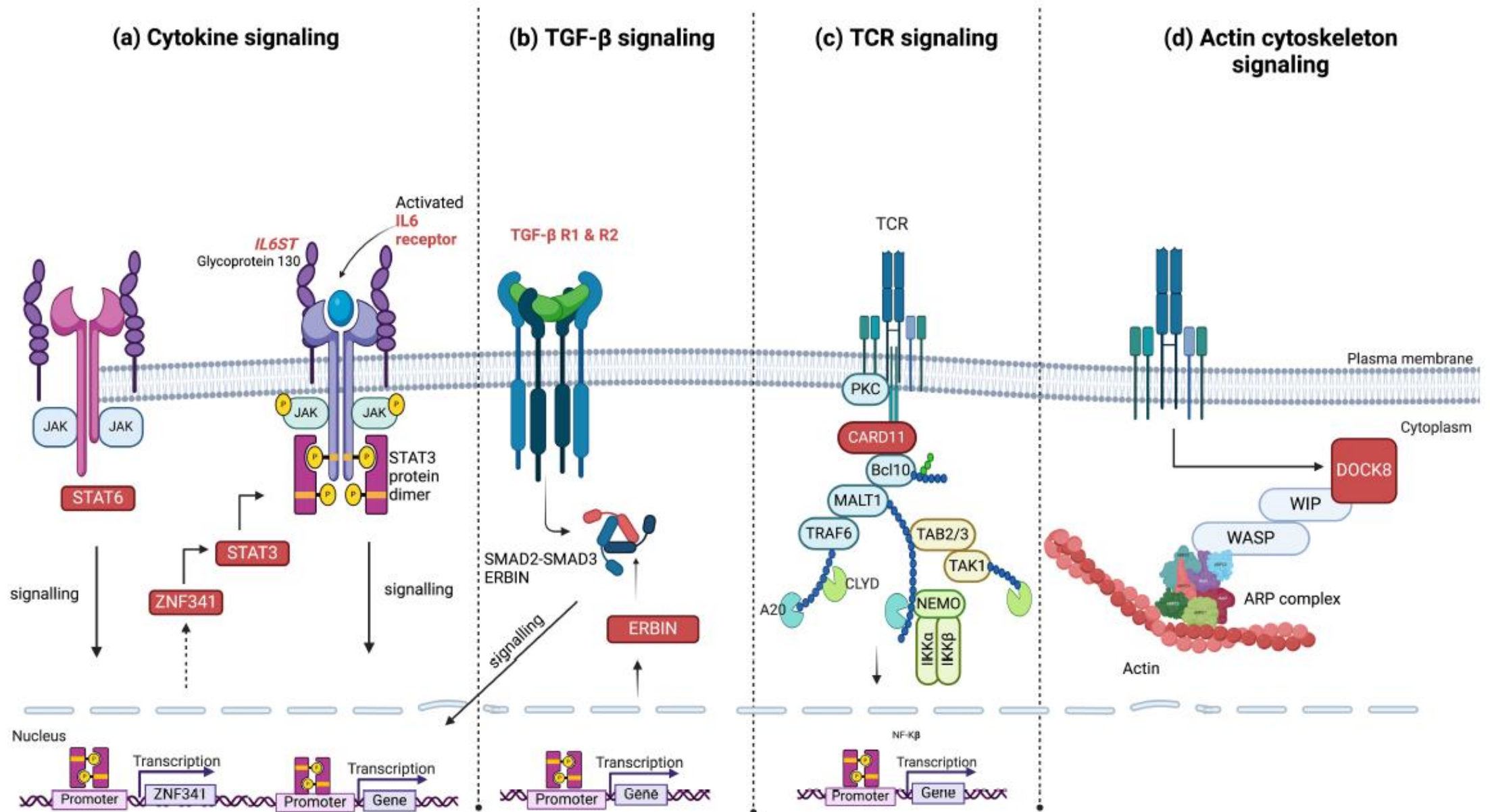
Barrier/Structural/ connective tissue Defects:



Skin barrier defect allows the allergens in

- **SPINK5 deficiency (Netherton syndrome):** Protease inhibitor defect causing severe barrier dysfunction with ichthyosis, hair shaft abnormalities, and atopic manifestations
- **Filaggrin loss of function:** Impaired barrier function
- **Desmoglein 1 deficiency:** Disrupts epithelial cell adhesion, leading to severe dermatitis and allergies
- **Loeys-Dietz syndrome** (rare-disease/loeys-dietz-syndrome) (TGFB1/2 mutations): Connective tissue disorder with vascular abnormalities, skeletal features, and severe allergic manifestations

Niehues T, von Hardenberg S, Velleuer E. Rapid identification of primary atopic disorders (PAD) by a clinical landmark-guided, upfront use of genomic sequencing. Allergol Select. 2024 Oct 2;8:304-323. doi: 10.5414/ALX02520E. PMID: 39381601; PMCID: PMC11460323.



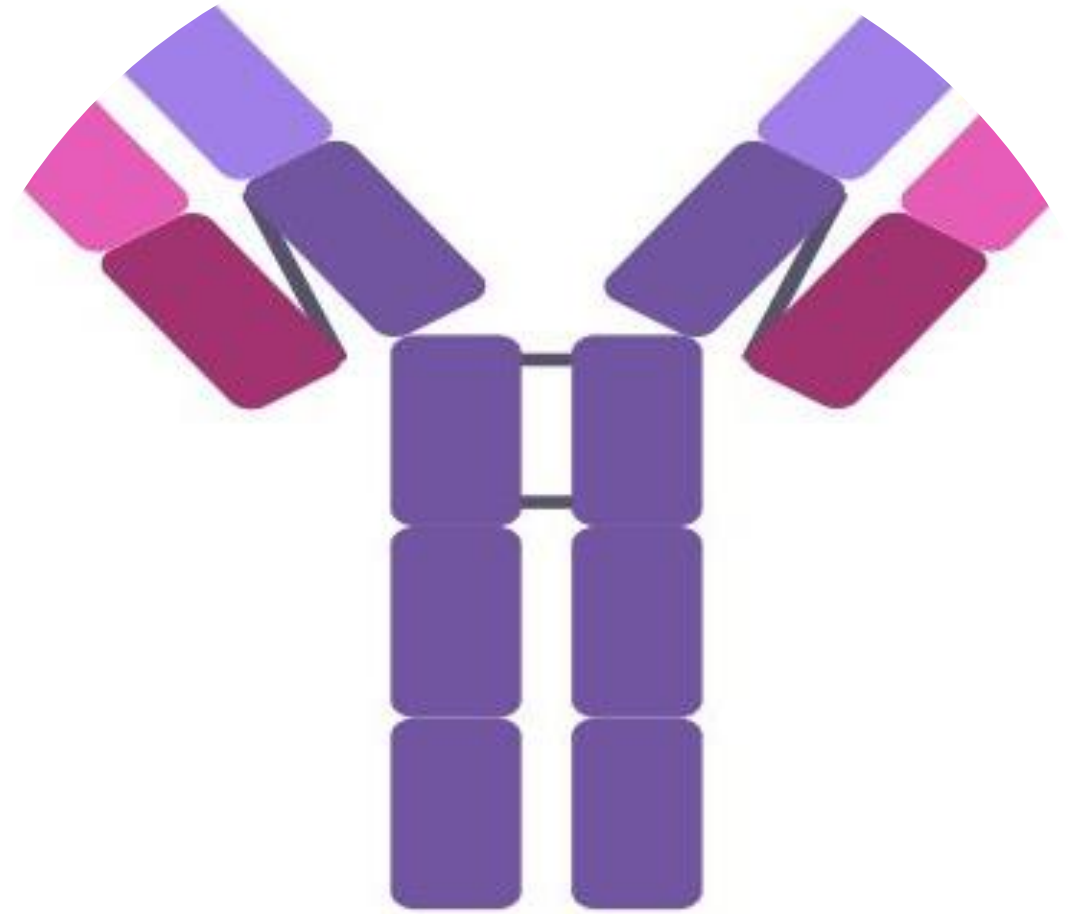
AlYafie R, Velayutham D, van Panhuys N, Jithesh PV. The Genetics of Hyper IgE Syndromes. *Frontiers in Immunology*. 2025;16:1516068.

<https://doi.org/10.3389/fimmu.2025.1516068>

Elevated Total IgE – What Does It Mean for Diagnosis?

Rare but critical
immunodeficiency
or primary atopy
syndromes

**Common allergic
disorders**



IgE

sIgE in Diagnosis of Food Allergy

		Likelihood of allergy from test results		
		Low	Intermediate	High
Likelihood of allergy from clinical history	High	<i>Possible allergy</i>	<i>Probably allergic</i>	<i>Likely to be allergic</i>
	Intermediate	<i>Possible allergy</i>	<i>Possible allergy</i>	<i>Probably allergic</i>
	Low	<i>Unlikely to be allergic</i>	<i>Possible allergy</i>	<i>Possible allergy</i>

Santos AF, Riggioni C, Agache I, et al. EAACI guidelines on the diagnosis of IgE-mediated food allergy. *Allergy*. 2023; 78: 3057-3076. doi:[10.1111/all.15902](https://doi.org/10.1111/all.15902)

High IgE Food Allergy Diagnostic Considerations

- Total IgE is not a significant predictor of food allergy or food allergy severity prediction
- Specific IgE has a known association with statistical chance of food allergy
- Specific IgE does not have a clear relationship to food allergy severity

Evaluation: history

- Detailed food exposure history: Timing of symptom onset after ingestion, specific foods implicated, reproducibility with re-exposure, and severity of reactions
- Atopic history: Personal and family history of eczema, asthma, allergic rhinitis, other food allergies
- Infection history: Recurrent bacterial infections (especially skin/lung abscesses), fungal infections, or unusual pathogens suggesting immunodeficiency

Evaluation: physical exam and labs

- Quantitative IgE level: Extreme elevation (>2000 IU/mL) raises concern for hyper-IgE syndrome but can be seen in eczema
- Consider if need immune evaluation, viral testing
- Genetics
- Food-specific IgE testing or skin prick testing: Only if clinical history suggests high pretest probability
- Oral food challenge: Gold standard for confirming or excluding IgE-mediated food allergy when diagnosis is uncertain

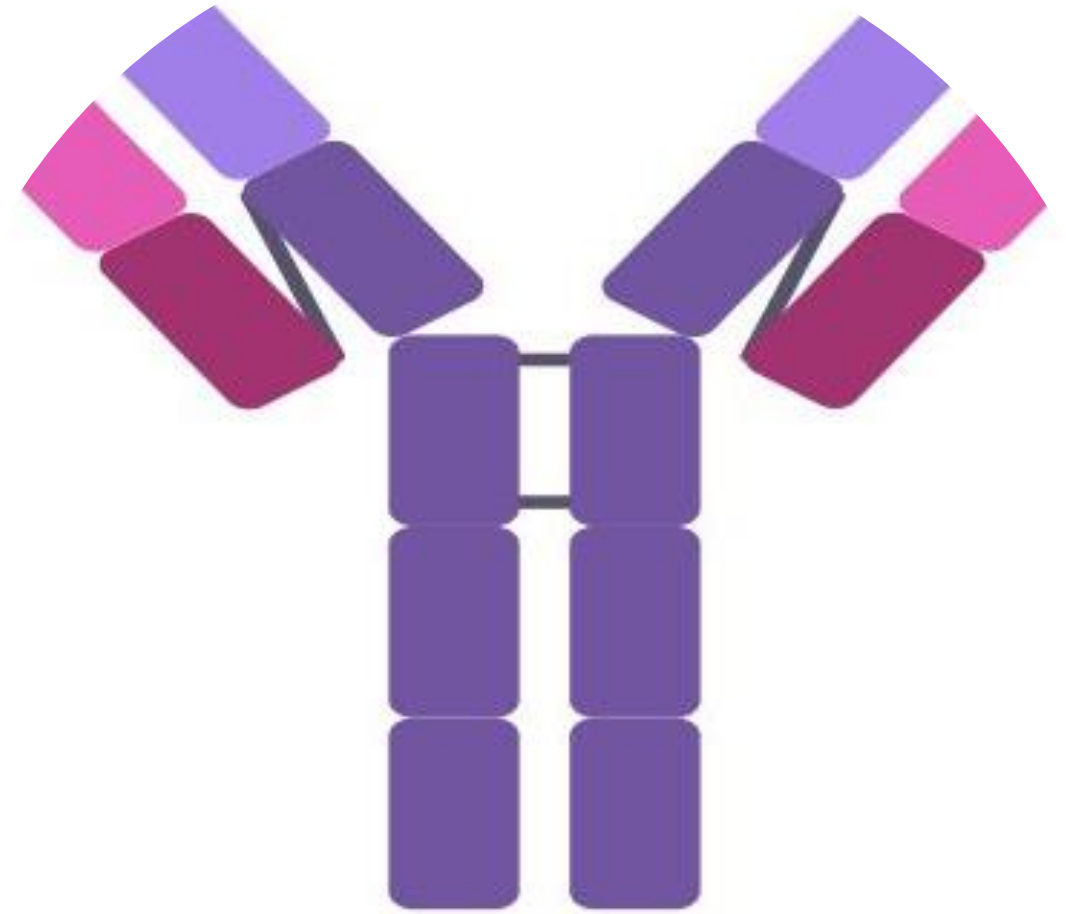
Evaluation: physical exam and labs

- Physical examination: Assess for growth, eczema distribution/severity, dysmorphic features, dental abnormalities, skeletal findings

Elevated Total IgE – What does it mean for management?

Severity
prediction?

Management



IgE

Are all the children with IEI “Treatment refractory?”

New Medications can work very well in the IEI

- Dupilumab
- Jak inhibitors

Some need a transplant so need to be careful

High IgE Treatment Considerations

- Omalizumab now approved for food allergy in the USA
- Dosing is related to sIgE and can limit its use
- Dupilumab can be used to manage the other atopic conditions as approved and often drops the IgE
- Future studies may change support a weight based dosing approach

Langlois A, Lavergne M-H, Leroux H, ... Upton J... Begin P. Protocol for a double-blind, randomized controlled trial on the dose-related efficacy of omalizumab in multi-food oral immunotherapy. Allergy, Asthma & Clinical Immunology 2020;16(1):25, doi:10.1186/s13223-020-00419-z

Table 4. Subcutaneous XOLAIR Doses Every 2 or 4 Weeks* for Adult and Pediatric Patients 1 Year of Age and Older with IgE-Mediated Food Allergy

Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight (kg)												
		≥10-12	>12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90 - 125	>125 - 150
		Dose (mg)												
≥30 - 100	Every 4 Weeks	75	75	75	75	75	75	150	150	150	150	150	300	300
>100 - 200		75	75	75	150	150	150	300	300	300	300	300	450	600
>200 - 300		75	75	150	150	150	225	300	300	450	450	450	600	375
>300 - 400		150	150	150	225	225	300	450	450	450	600	600	450	525
>400 - 500		150	150	225	225	300	450	450	600	600	375	375	525	600
>500 - 600		150	150	225	300	300	450	600	600	375	450	450	600	
>600 - 700		150	150	225	300	225	450	600	375	450	450	525		
>700 - 800	Every 2 Weeks	150	150	150	225	225	300	375	450	450	525	600		
>800 - 900		150	150	150	225	225	300	375	450	525	600			
>900 - 1000		150	150	225	225	300	375	450	525	600				
>1000 - 1100		150	150	225	225	300	375	450	600					
>1100 - 1200		150	150	225	300	300	450	525	600	Insufficient data to Recommend a Dose				
>1200 - 1300		150	225	225	300	375	450	525						
>1300 - 1500		150	225	300	300	375	525	600						
>1500 - 1850			225	300	375	450	600							

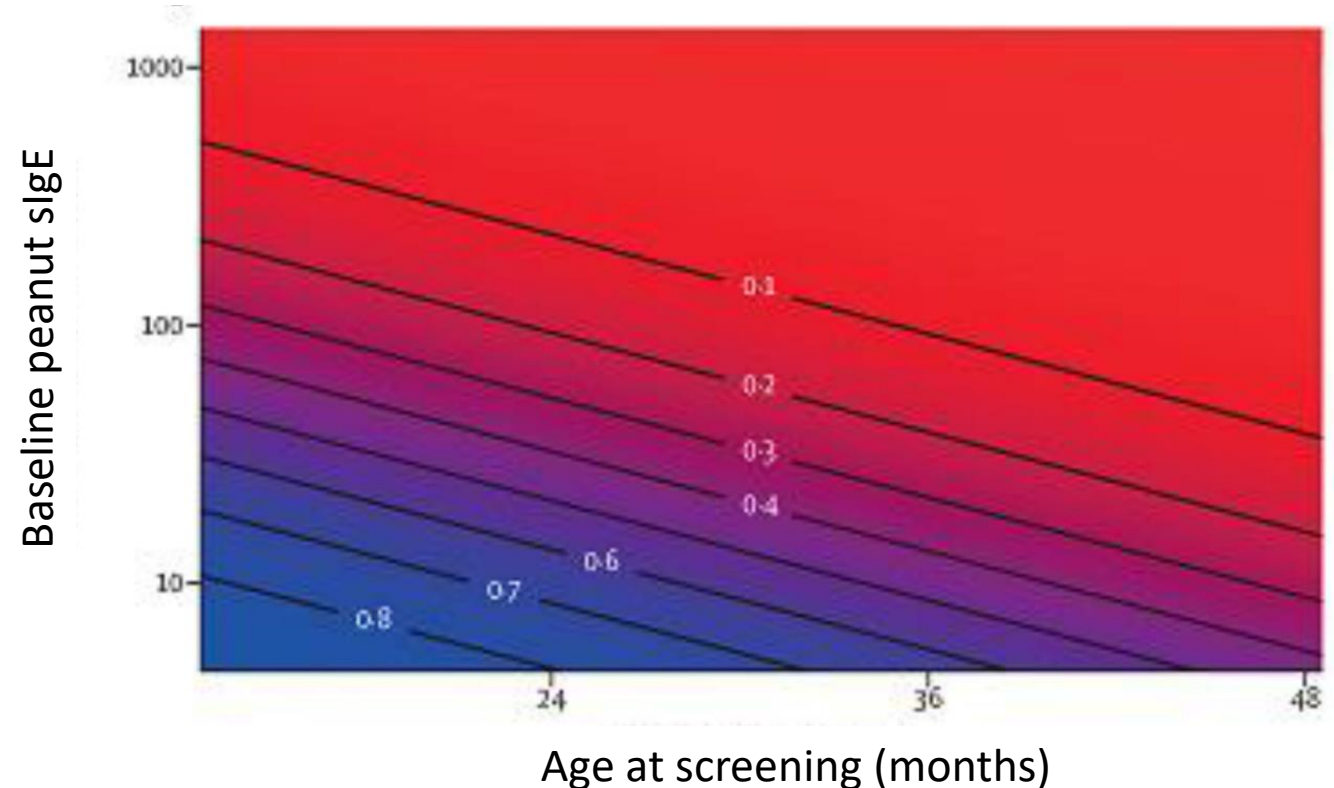
*Dosing frequency:

- ☒ Subcutaneous doses to be administered every 4 weeks
- ☐ Subcutaneous doses to be administered every 2 weeks

High IgE Prognosis Considerations for food allergy

- IMPACT suggested that low sIgE and low age may give the best prognosis for oral immunotherapy to peanut

Jones SM et al. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. *Lancet*. 2022;399(10322):359-371 'doi':10.1016/S0140-6736(21)02390-4.



Values in blue show >50% probability of remission, while values in red show <50% probability of remission.

What do we think of Noah's IgE?

- Asthma (uncontrolled)
- Allergic rhinitis
- Mild eczema
- We don't have other physical exam findings, cell counts, infectious hx, family hx but if negative then I would assume the cause is atopic (eczema especially)
- The significance here is related to **prognosis** and omalizumab dosing (if prescribed)

Conclusions

- Elevated total IgE can be seen in atopy but also in inborn errors of immunity/primary atopy syndromes
- The IEI/PAS are largely related to Cytokine signalling, Cytoskeleton, T- cell defects, Barrier function and clinical features follow (family history, connective tissue, skeleton, growth, infections, autoimmunity)
- High sIgE increases likelihood of food allergy and is likely a prognostic factor for outgrowing and treatment
- High total IgE can limit omalizumab on label use

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