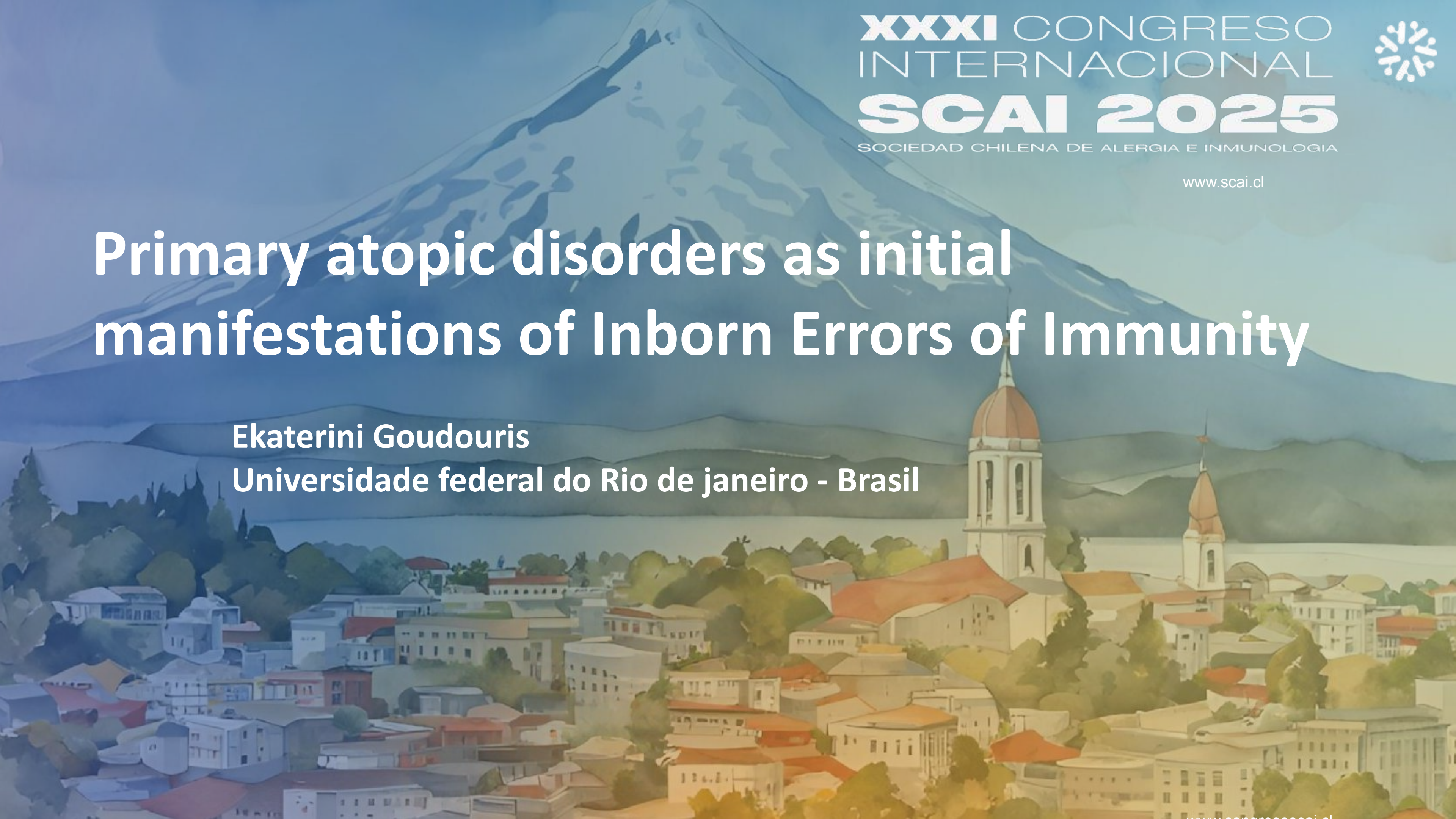




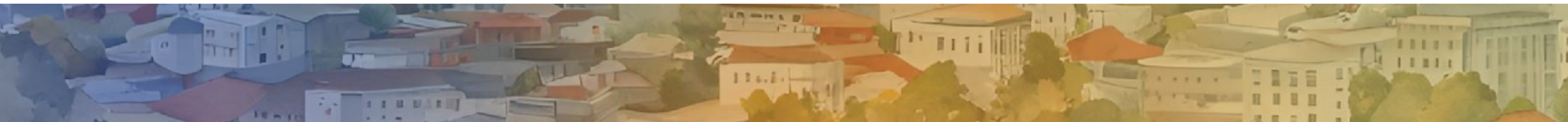
Primary atopic disorders as initial manifestations of Inborn Errors of Immunity

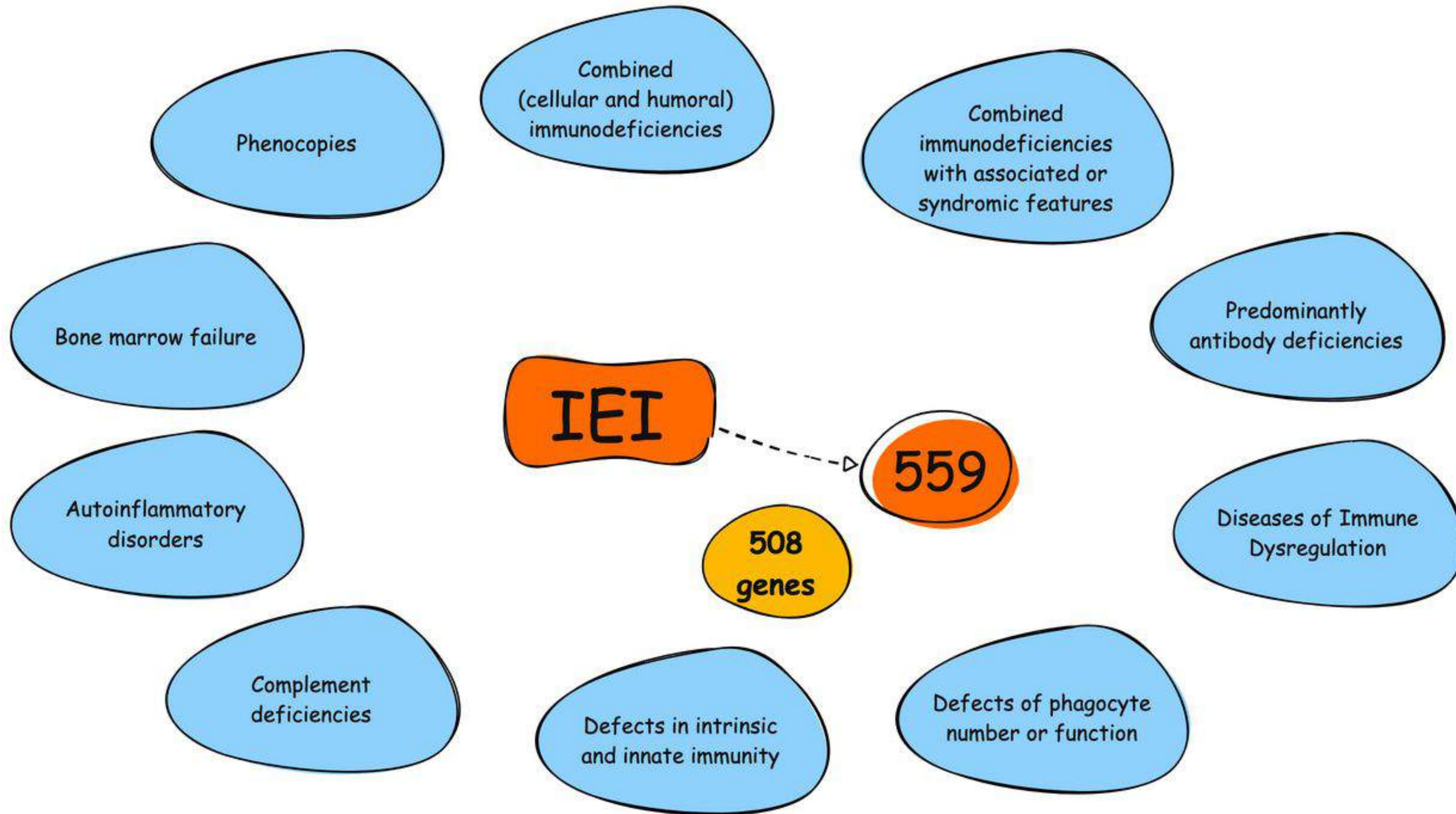
Ekaterini Goudouris

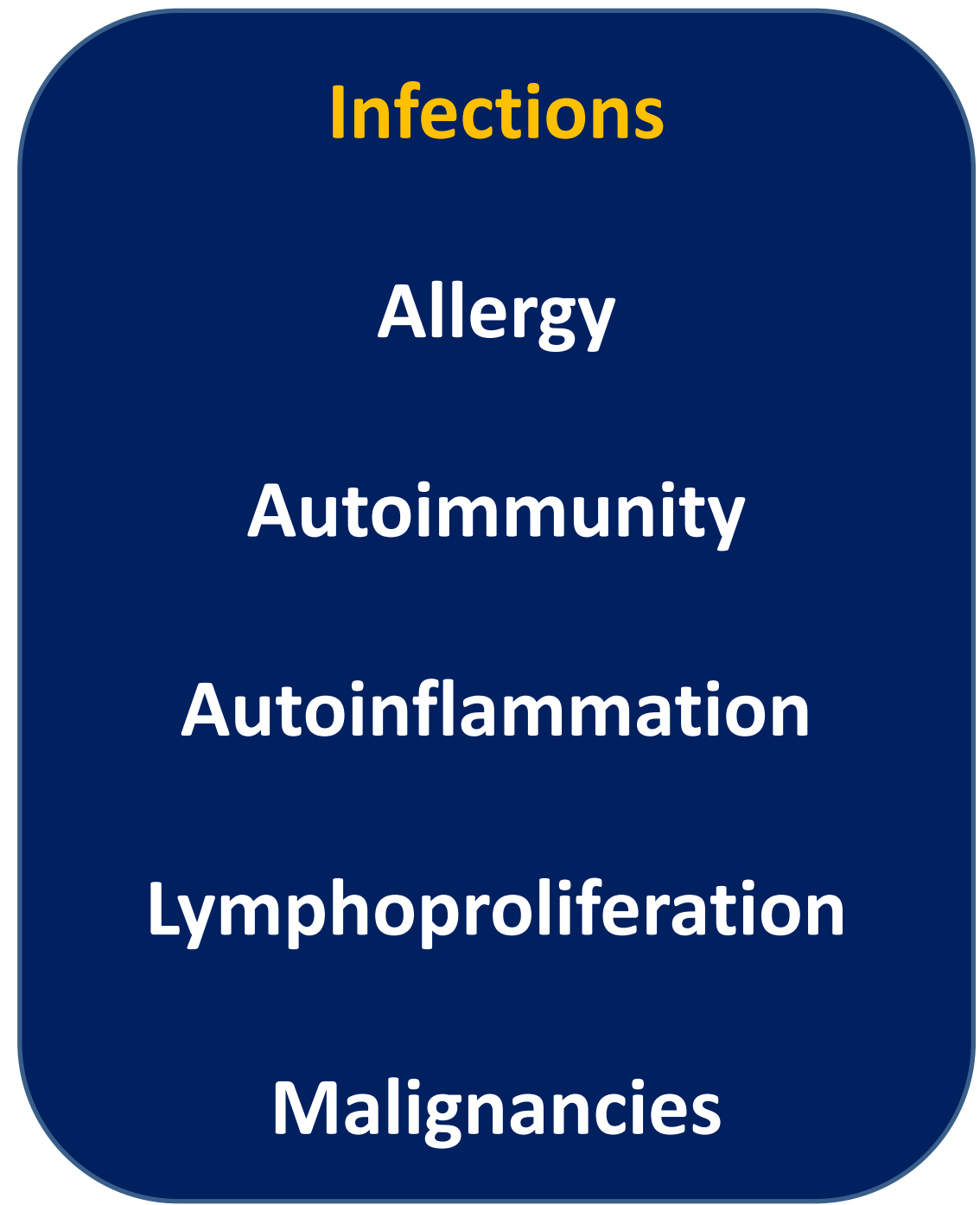
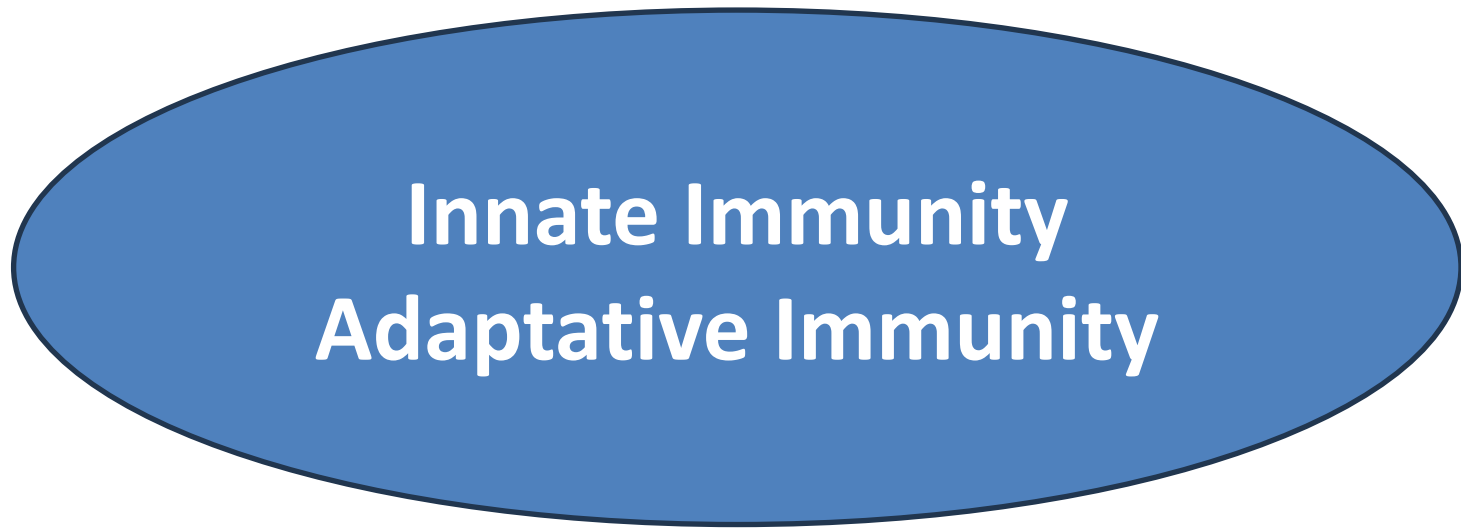
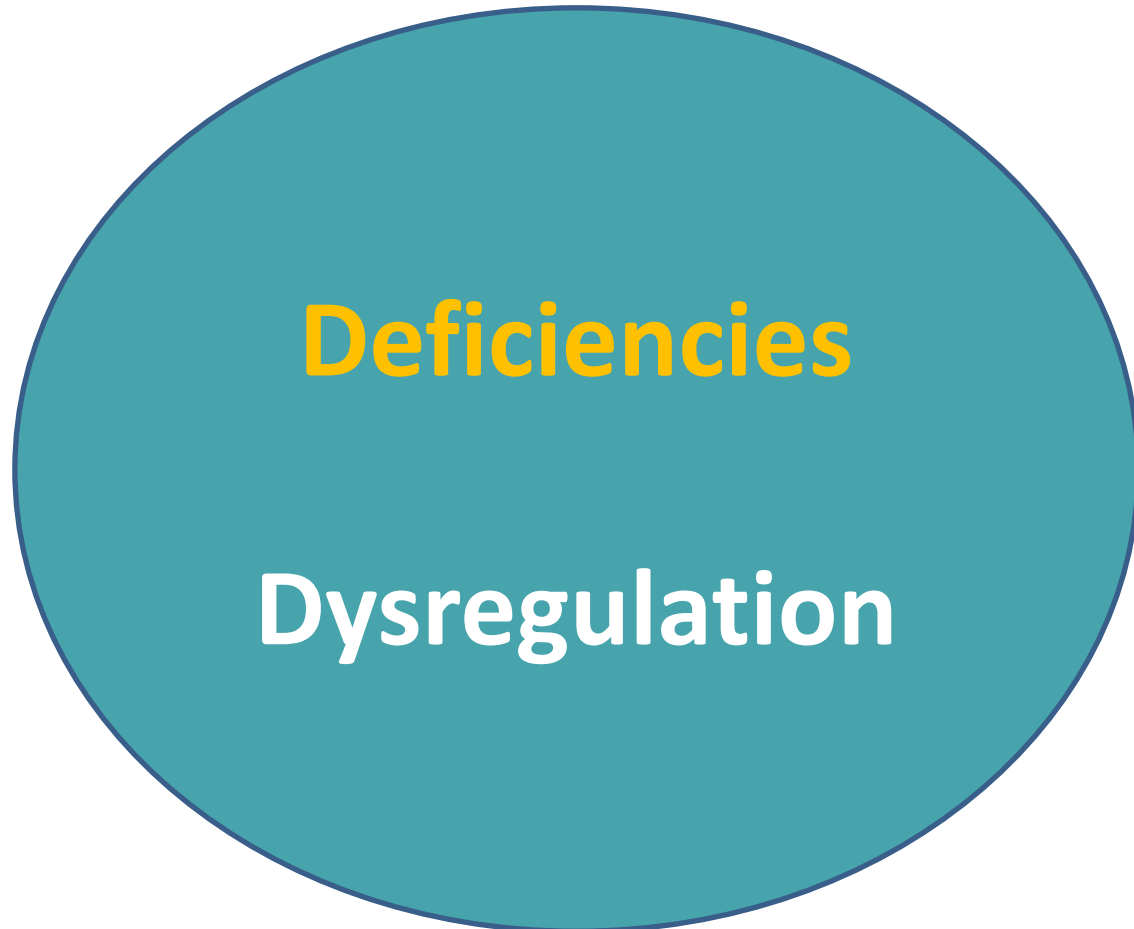
Universidade federal do Rio de Janeiro - Brasil

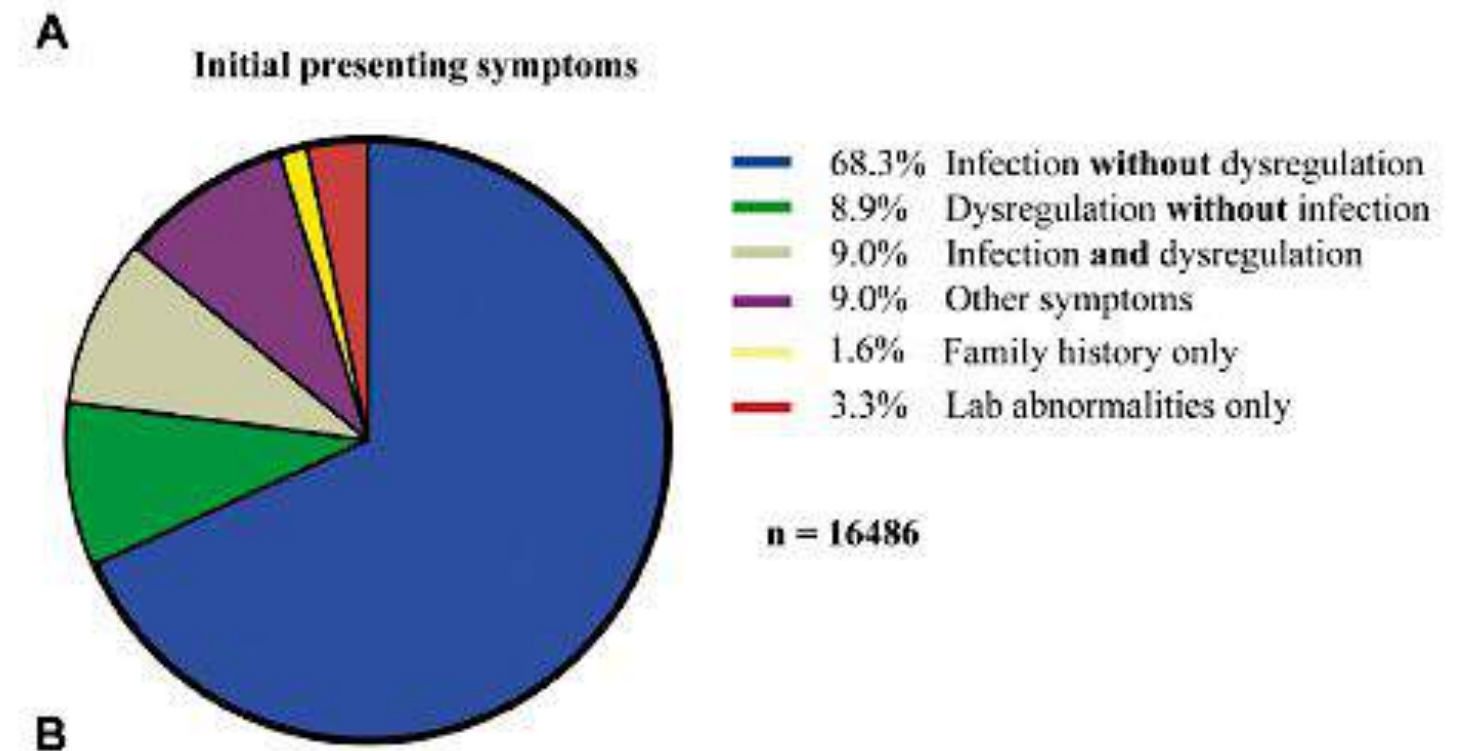
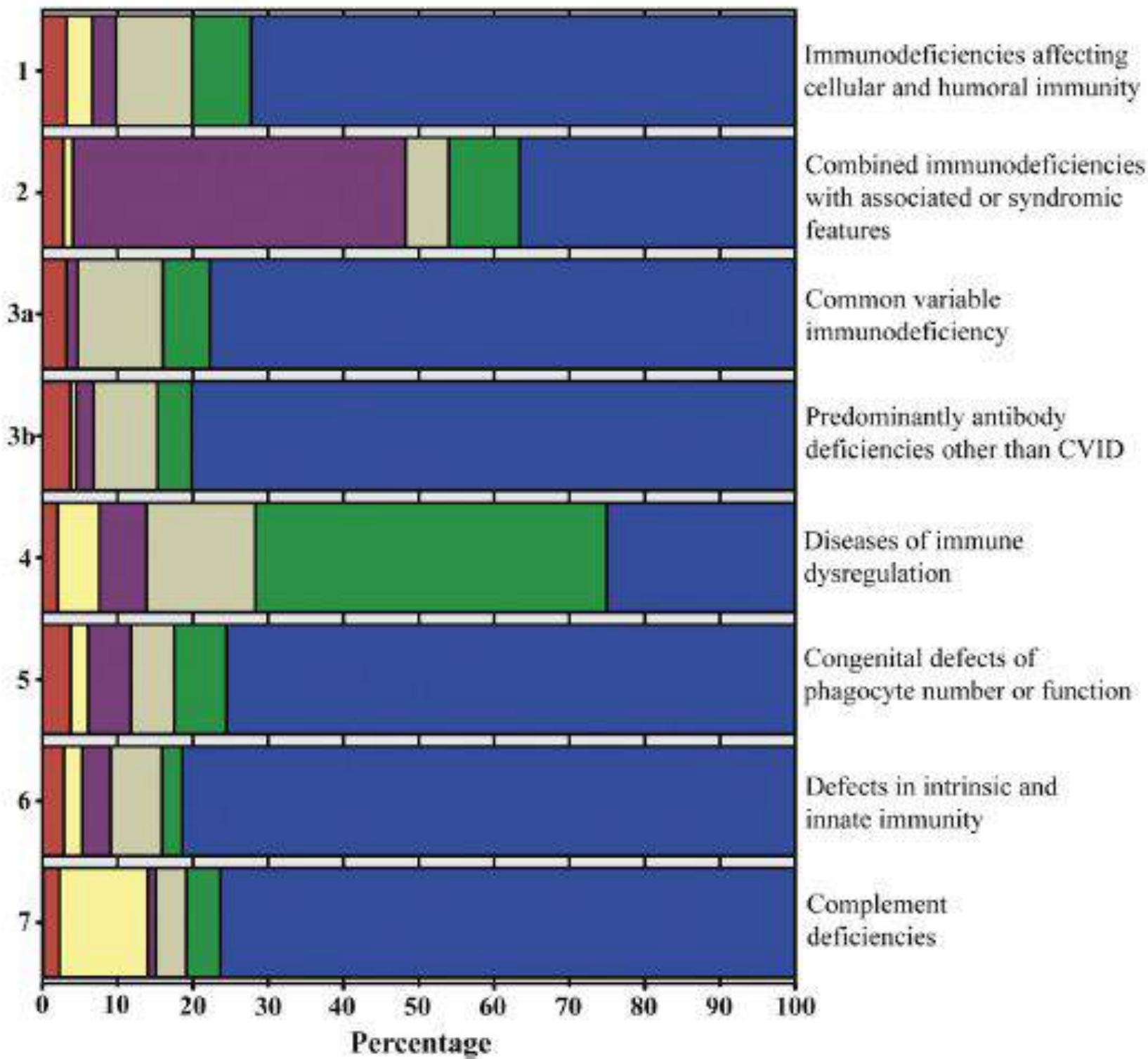


I declare that I have no conflicts of interest in relation to this presentation.



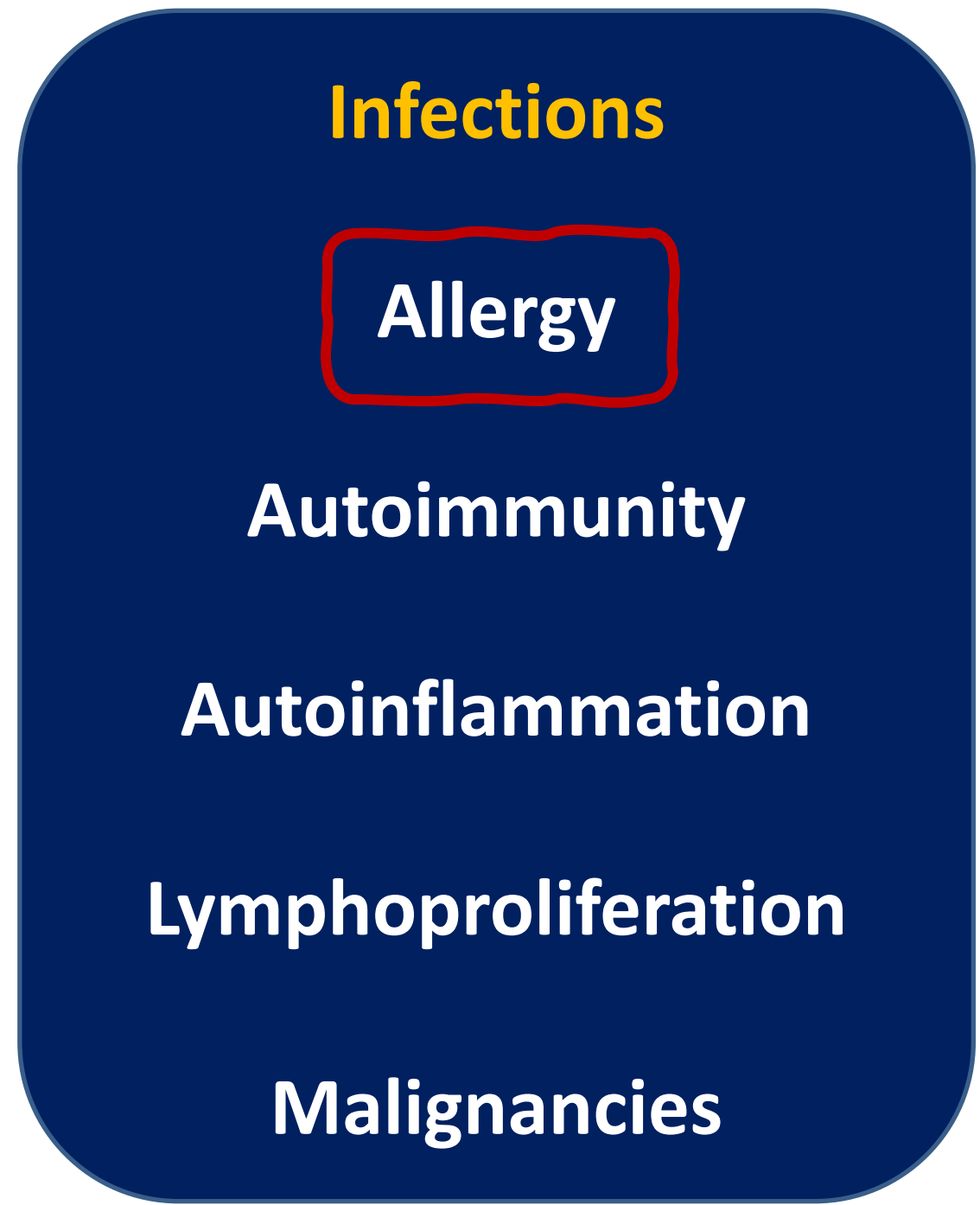
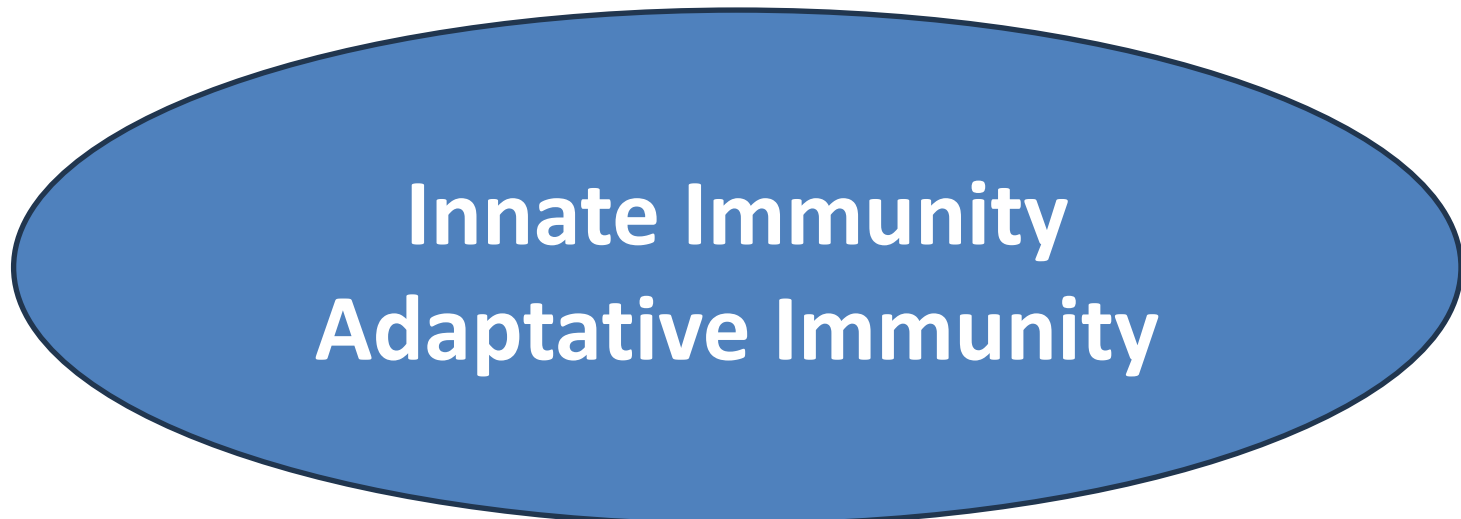
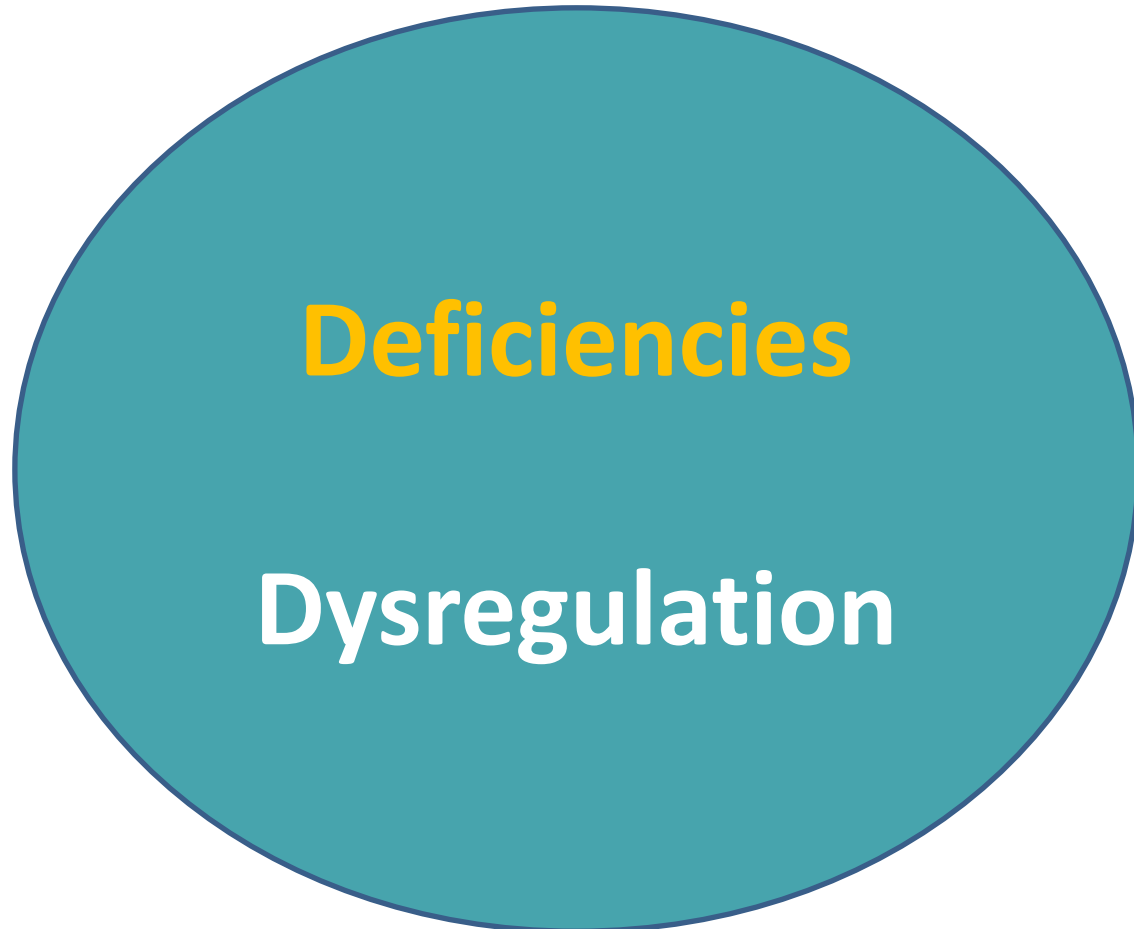






Conclusions: An exclusive focus on infection-centered warning signs would have missed around 25% of patients with IEI who initially present with other manifestations. (J Allergy Clin Immunol 2021;148:1332-41.)

*Talhammer et al.
J Allergy Clin Immunol 2021;148:1332-41.*

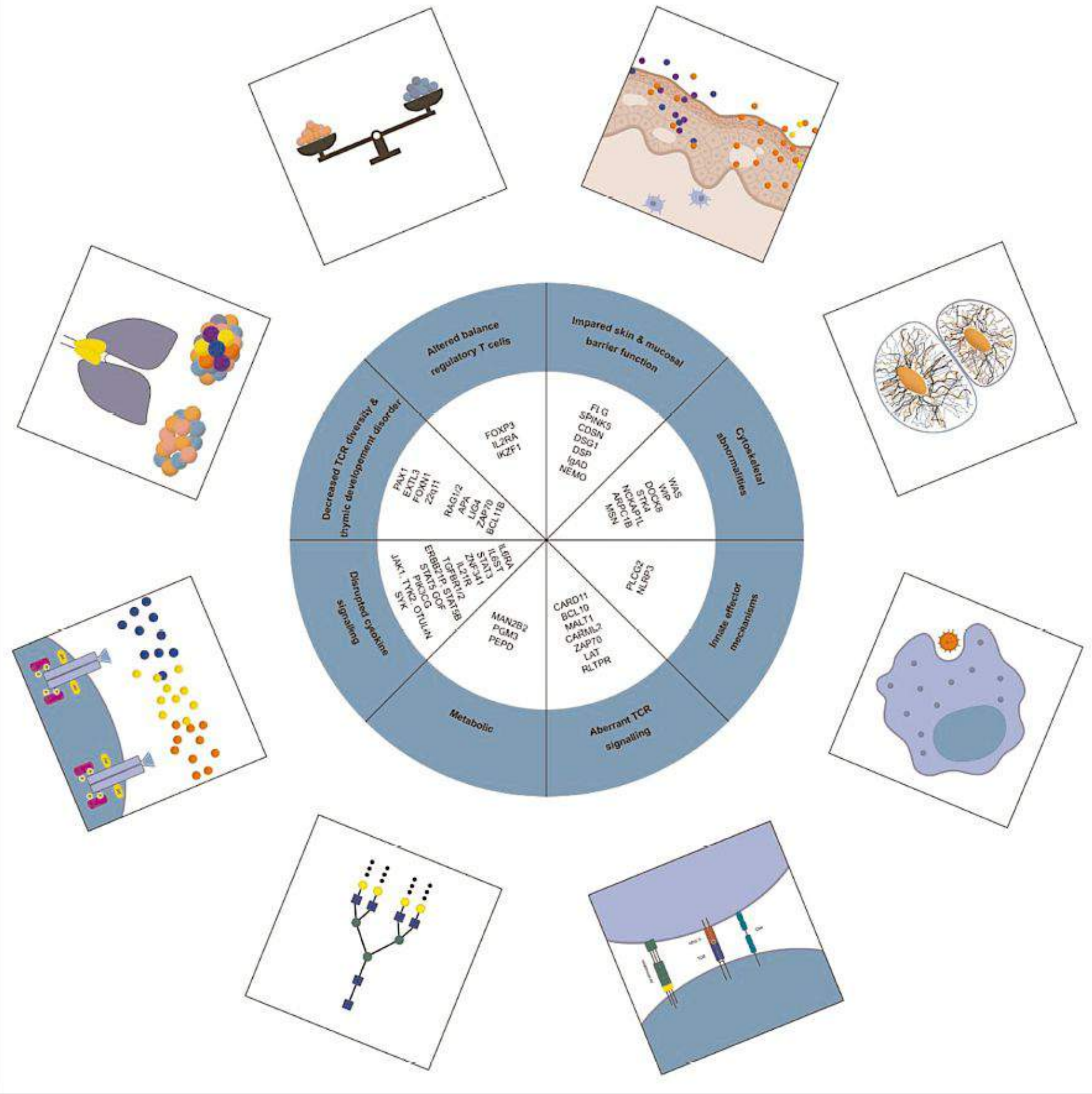


A total of 738 articles (reporting on **3050 individual patients**) were included.

226 (7.4%) of the patients were reported to have an allergy.

Food allergy was most frequently reported (n=172, 76.1%), followed by allergic rhinitis (n=56, 24.8%).

Immunopathogenic Mechanisms





Allergy and Immune Deficiencies

WAS

AD HyperIgE

Omenn Syndrome

IPEX

Comèl-Netherton Syndrome

Particularly Eczema ...



Primary Atopic Disorders (2018)

*“..we would propose the term
“primary atopic disorders”
to classify heritable genetic disorders
which present with deregulated
pathogenic allergic effector responses
irrespective of sensitization.”*



Primary Atopic Disorders

Phenotypes:

*hives and other consequences of **abnormal mast cell degranulation**,
chronic type 2 Thelper (Th2)- and eosinophil-mediated allergic inflammation,
and **exuberant IgE production**.*

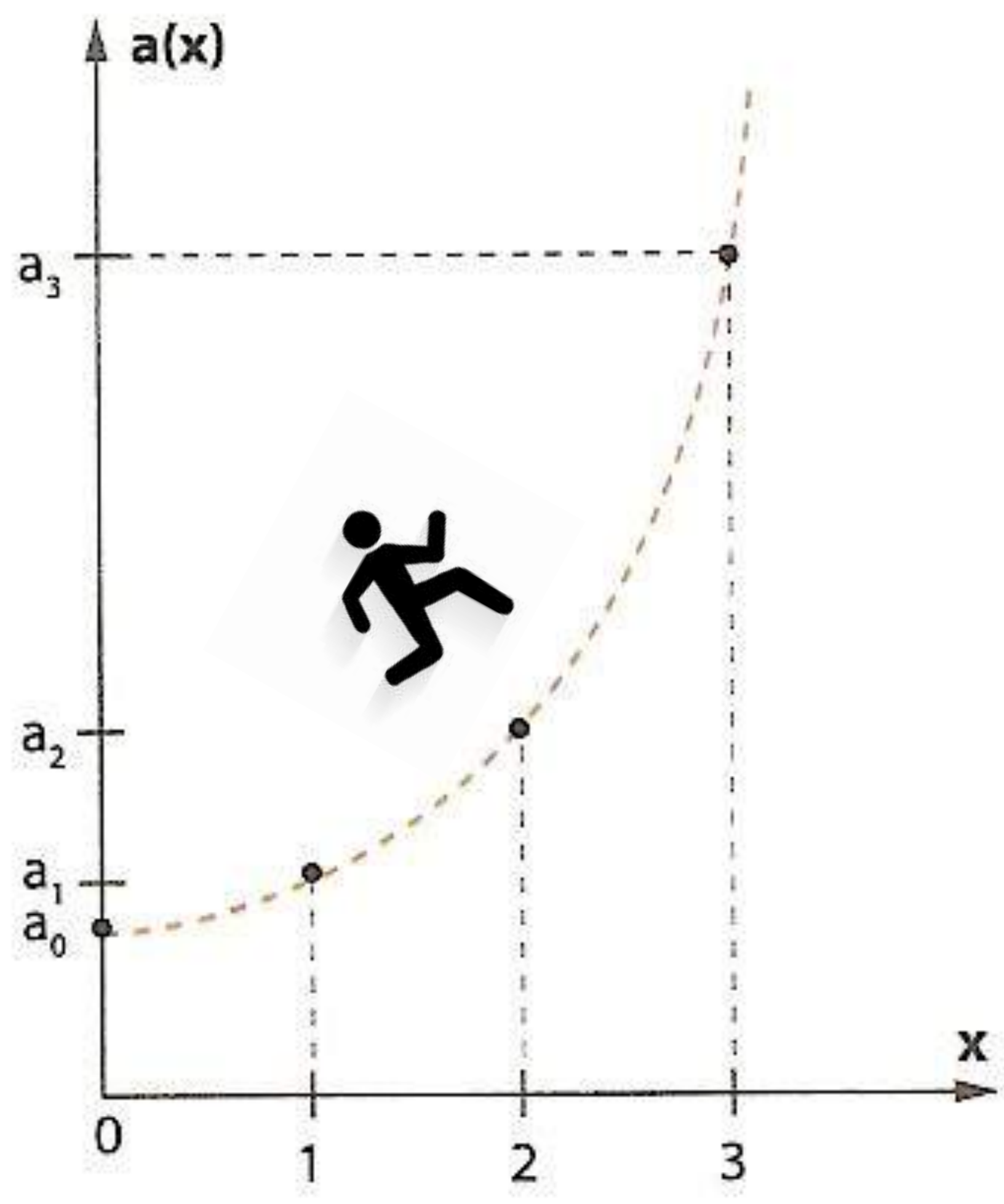
Table 1. Genetic mutations associated with primary atopic disorders.

Altered process	Genes
Impaired TCR signaling and cytoskeletal remodeling	ZAP70, CARD11, MALT1, WAS, WIPF1, ARPC1B, DOCK8, CARMIL2
Altered cytokine signaling	STAT3 ^{DN} , STAT1 ^{GOF} , STAT5B ^{LOF} , STAT5B ^{GOF} , JAK1 ^{GOF} , IL4RA ^{GOF} , TGFBR1, TGFBR2, ERBB2IP
T cell repertoire restriction	RAG1, RAG2, DCLRE1C, ADA, IL2RG, IL7RA, CHD7, LIG4, ZAP70, 22q11del
Tolerance failure	FOXP3, IL2RA, STAT5B ^{LOF} , TGFBR1, TGFBR2, WAS, CARD11, STAT1 ^{GOF}
Metabolic disturbance	PGM3, CARD11, MALT1
Skin barrier disruption	FLG, CDSN, DSG1, DSP, SPINK5
Mast cell deregulation	KIT, PLCG2, ADGRE2, TPSAB1

TABLE I. Currently defined human monogenic primary atopic disorders

Gene	Key clinical features	Mechanism	Molecular mechanism and inheritance	Year in which the PAD phenotype of the gene was reported
<i>TBX21</i>	Mycobacterial disease, persistent airway inflammation, eosinophilia	Altered cytokine signaling	AR, LOF	2021
<i>CARD14</i>	Asthma, allergy, atopic dermatitis, ↑ IgE level	Skin barrier dysfunction	AD, LOF	2019
<i>IL6R</i>	Eczema, eosinophilia, ↑ IgE level, recurrent infections	Altered cytokine signaling	AR, LOF	2019
<i>ZNF341</i>	Severe allergy and ↑ IgE level, chronic mucocutaneous candidiasis	Altered cytokine signaling	AR, LOF	2018
<i>ARPC1B</i>	Severe atopy, eosinophilia, poor growth, infections	Impaired T-cell receptor signaling and cytoskeletal remodeling	AR, LOF	2017
<i>CARD11</i>	Severe atopic dermatitis, eosinophilia, infections	Impaired T-cell receptor signaling	AD, DN	2017
<i>IL6ST</i>	Recurrent infections, eczema, bronchiectasis, ↑ IgE level, eosinophilia, connective tissue abnormalities	Altered cytokine signaling	AR, LOF	2017
<i>ERBIN</i>	Atopic dermatitis, ↑ IgE level, eosinophilic esophagitis, connective tissue abnormalities	Altered cytokine signaling	AD, LOF	2017
<i>JAK1</i>	Severe atopy, eosinophilia, poor growth	Altered cytokine signaling	AD, GOF	2017
<i>STAT5B (GOF)</i>	Severe atopy, eosinophilia, urticaria, diarrhea	Altered cytokine signaling	Somatic, GOF	2017
<i>CARMIL2</i>	Combined immunodeficiency associated with severe atopic dermatitis, ↑ IgE level, allergic asthma, food allergy, and cold urticaria	Impaired T-cell receptor signaling and cytoskeletal remodeling	AR, LOF	2016
<i>STAT3 (GOF)</i>	Lymphadenopathy, multiorgan autoimmunity, infections, short stature, eczema	Altered cytokine signaling	AD, GOF	2014
<i>PGM3</i>	Bronchiectasis, skin abscesses, developmental delay, ↑ IgE level	Metabolic disturbance	AR, LOF	2014
<i>MALT1</i>	Severe dermatitis, ↑ IgE level, poor growth, infections	Impaired T-cell receptor signaling	AR, LOF	2013
<i>DSG1</i>	Severe dermatitis and food allergies, ↑ IgE level, metabolic wasting	Skin barrier dysfunction	AR, LOF	2013
<i>TGFBR1</i>	Vascular and connective tissue abnormalities, atopy	Altered cytokine signaling	AD	2013
<i>TGFBR2</i>	Vascular and connective tissue abnormalities, atopy	Altered cytokine signaling	AD	2013
<i>STAT1</i>	Chronic mucocutaneous candidiasis, autoimmunity, enteropathy, eczema, short stature, vascular abnormalities	Altered cytokine signaling	AD, GOF	2013
<i>WIPF1</i>	Eczema, infections, thrombocytopenia, ↑ IgE level	Impaired T-cell receptor signaling and cytoskeletal remodeling	AR, LOF	2012
<i>PLCG2</i>	Cold urticaria, bacterial infection, autoimmunity, skin granulomas	Mast cell deregulation	AD, GOF	2012

<i>CDSN</i>	Peeling skin, diffuse ichthyosis, erythroderma, pruritus, food allergies, ↑ IgE level	Skin barrier dysfunction	AR, LOF	2010
<i>DOCK8</i>	Severe atopy, eosinophilia, infections, ↑ IgE level	Impaired T-cell receptor signaling and cytoskeletal remodeling	AR, LOF	2009
<i>ZAP70</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	AR, LOF	2009
<i>LIG4</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	AR, LOF	2008
<i>CHD7</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	AR, likely LOF	2008
<i>IL2RG</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	XL	2008
<i>STAT3 (LOF)</i>	Eczema, eosinophilia, ↑ IgE level, chronic mucocutaneous candidiasis, connective tissue abnormalities	Altered cytokine signaling	AD, DN LOF	2007
<i>IL2RA</i>	Severe autoimmune enteritis, viral infections, lymphoproliferation, eczema	Tolerance failure	AR, LOF	2007
<i>STAT5B (LOF)</i>	Growth failure, autoimmunity, eczema, ↑ IgE level	Altered cytokine signaling	AD or AR, LOF	2006, 2018
<i>IL7R</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	AR, LOF	2006
<i>KIT</i>	Systemic mastocytosis	Mast cell deregulation	AD, GOF	2005
<i>DCLRE1C</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	AR, LOF	2005
<i>TBX1</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	Haploinsufficiency	2004
<i>FOXP3</i>	Severe atopy, autoimmunity, enteropathy, eosinophilia, ↑ IgE level	Tolerance failure	XL, LOF	2001
<i>SPINK5</i>	Trichorrhexis invaginata, ichthyosis, ↑ IgE level, and atopy	Skin barrier dysfunction	AR, LOF	2000
<i>RAG1</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	AR, LOF	1998
<i>RAG2</i>	Erythroderma, eosinophilia, enteropathy, infections, ↑ IgE level*	T-cell repertoire restriction	AR, LOF	1998
<i>WAS</i>	Eczema, infections, thrombocytopenia, ↑ IgE level	Impaired T-cell receptor signaling and cytoskeletal remodeling	XL, LOF	1994
<i>ADA</i>	Diarrhea, dermatitis, infections, ↑ IgE level, multiorgan abnormalities	T-cell repertoire restriction	AR, LOF	1972



USIDNET Registration

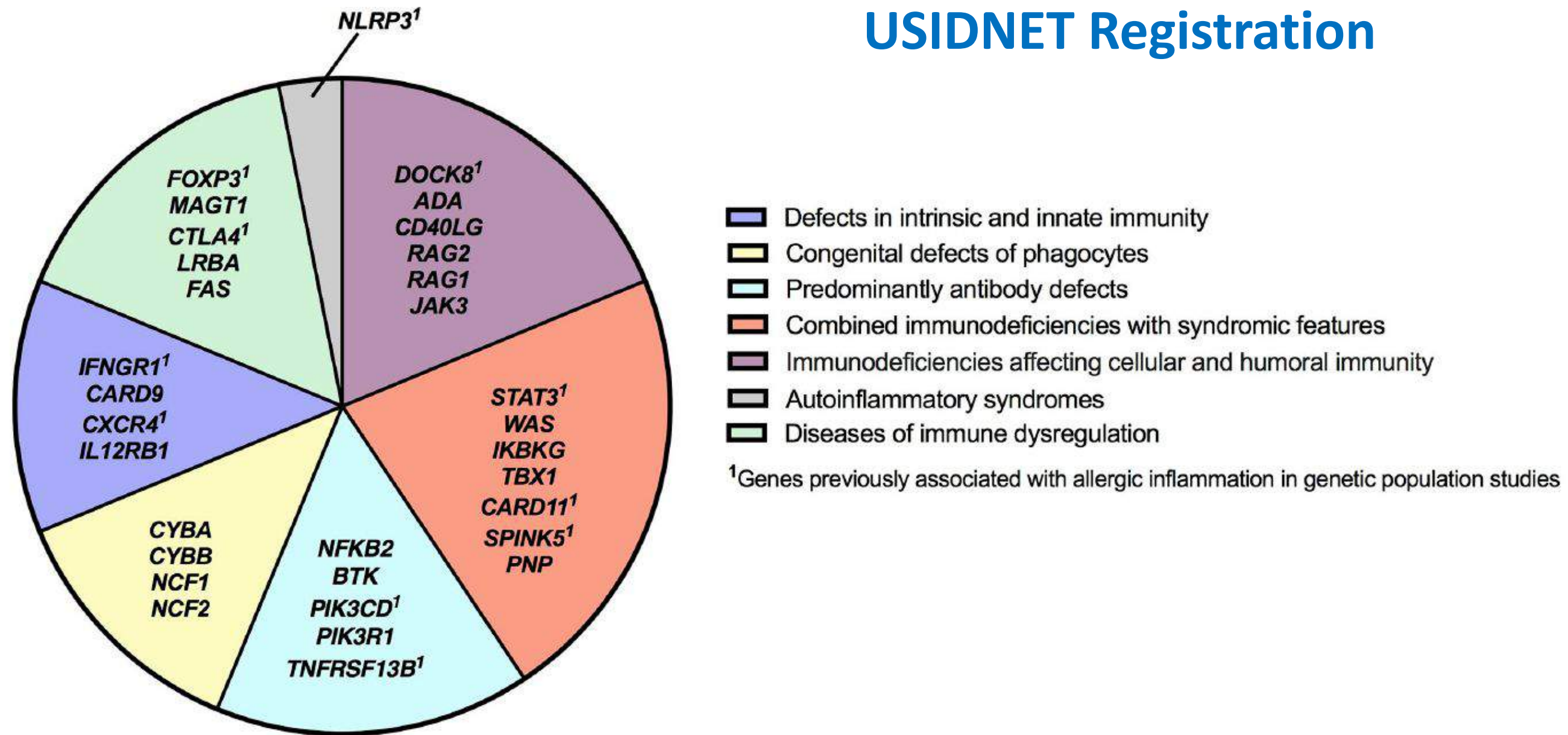
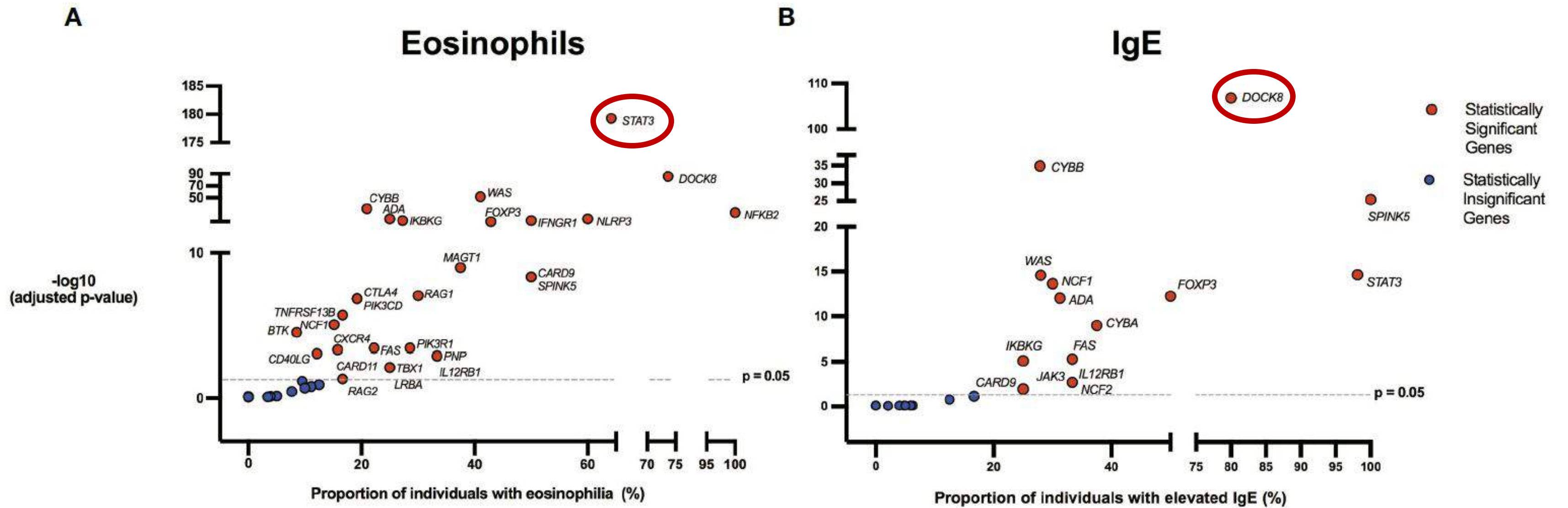


FIGURE 4 | Inborn errors of immunity genes associated with type 2 inflammation by disease category. IEI genes found to be associated with type 2 inflammation in our study are categorized according to IUIS Phenotypic Classification. HGNC gene symbols are used.

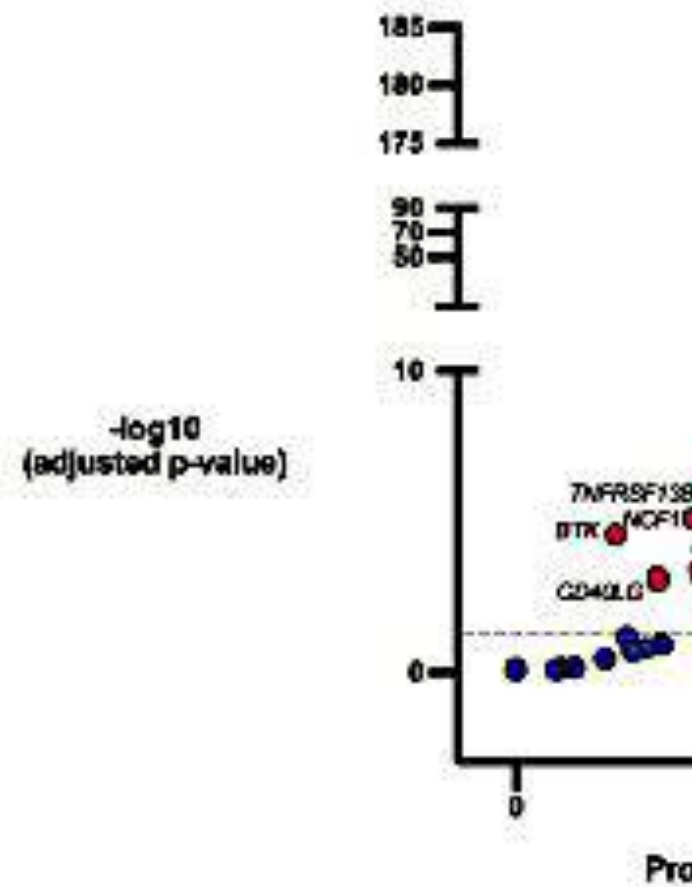
Table 1 Allergy manifestations and associated manifestations in different inborn errors of immunity.

Allergy manifestations	Associated manifestations	Inborn errors of immunity (name/gene)
Elevated IgE and eosinophilia	Bacterial skin and pulmonary infections (with pneumatoceles); chronic mucocutaneous candidiasis; altered inflammatory response (cold abscesses); connective tissue abnormalities (hypermotility, scoliosis, retention of primary teeth, fractures, typical facies, aneurysms); non-flexural eczematous dermatitis; exanthema in the neonatal period.	STAT3 defect - Hyper-IgE S.AD ^a (Job S.) Defects in the STAT3 pathway ZNF341, IL6ST, IL6R
Atopy (atopic dermatitis, asthma)/ food allergy/ anaphylaxis	Immune dysregulation; increased IgE and eosinophilia; viral skin infections; combined immunodeficiency (non-severe)	Actinopathies: Wiskott-Aldrich S. and defect in WIP ^b (thrombocytopenia with small platelets); defects in DOCK8, ARPC1B, CARMIL2 Defects in CARD9, CARD11, CARD14, MALT1 PGM3 defect
	Increased IgE and eosinophilia; scoliosis; bacterial lung and skin infections; myoclonus and cognitive delay; lymphopenia. Immune dysregulation (enteropathy); bacterial / viral infections; short stature	STAT5b LF ^c
	Important eosinophilia; impaired growth. Eosinophilia Lymphoproliferation (hepatosplenomegaly, lymphadenopathy); severe combined immunodeficiency; barrier defects, with major ichthyosis; increased IgE and eosinophilia; bamboo hair; increased metabolic expenditure.	JAK1 GF ^d Omenn S.
Severe atopic dermatitis and/or erythroderma / ichthyosis	Dermatitis with skin ulcers; increased IgE; bacterial skin and pulmonary infections; hepatosplenomegaly.	Comel-Netherton S. (SPINK5) Prolidase deficiency
Urticaria and anaphylaxis	Neonatal urticaria; very important eosinophilia; growth alteration. Early and severe hives; erythema and pruritus; anaphylaxis.	STAT5b GF ^d PLAID ^e (evaporative cooling; PLCG2 GF ^d) Familial vibratory urticaria (ADGRE2) Hereditary alpha-tryptasemia (TPSAB1)



USIDNET Registration

A



B

Eosinophils

IgE

Increase in both eosinophils and IgE:

ADA, CARD9, CYBB, NCF1, DOCK8, FOXP3,

STAT3, WASP, SPINK5, IKBKG

- Statistically Significant Genes
- Statistically Insignificant Genes

p = 0.05

100

USIDNET Registration

AD Hyper IgE Syndrome (Job Syndrome – STAT3 LOF)

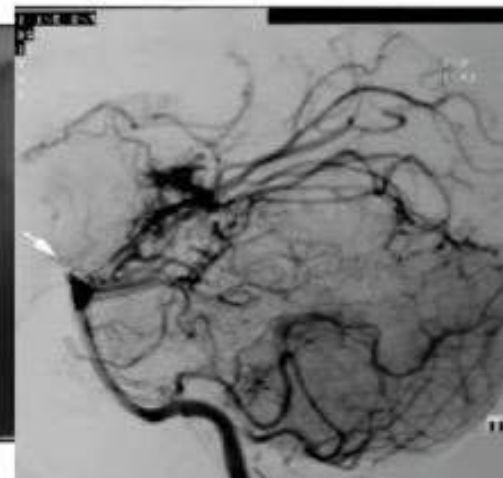


13 y/o

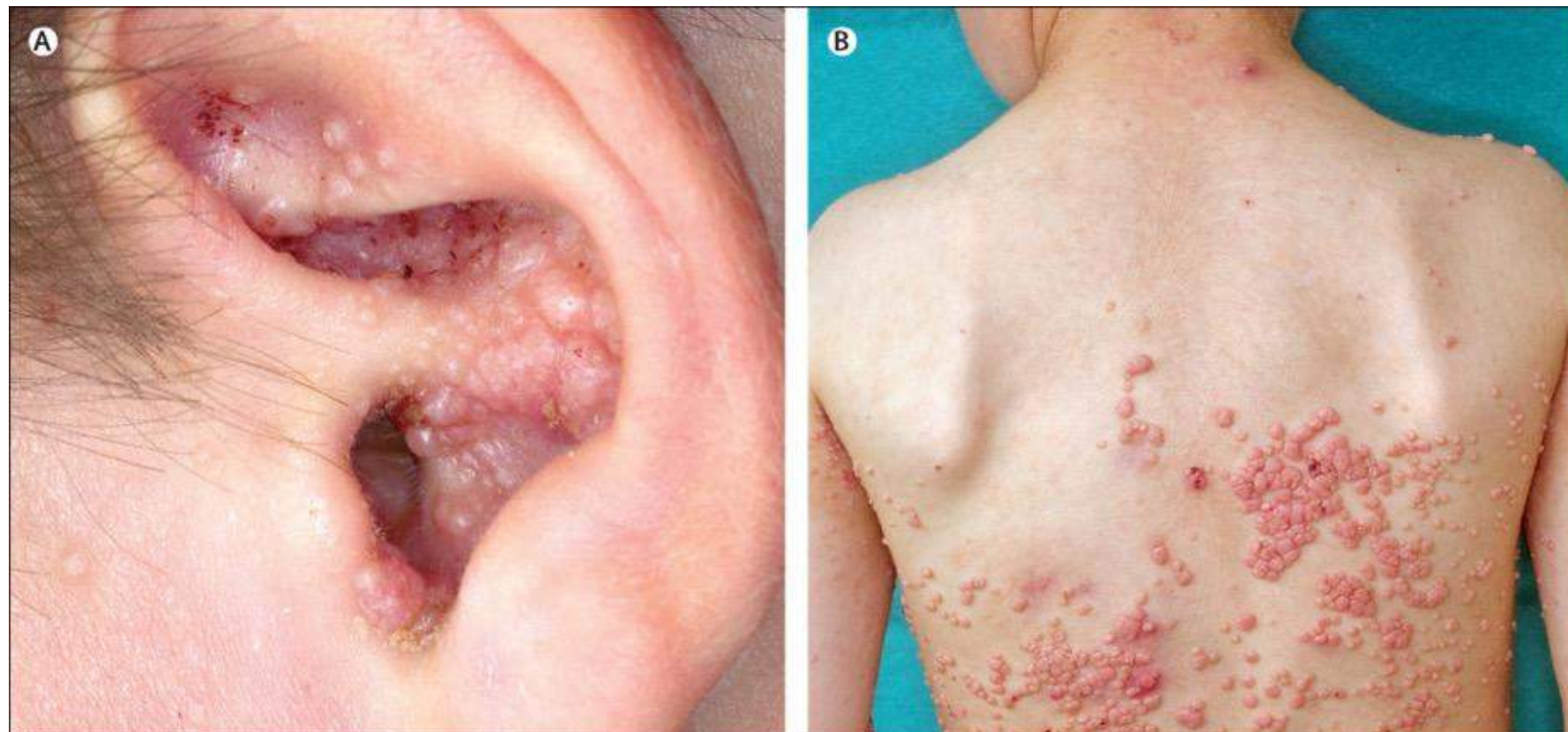
17 y/o

25 y/o

42 y/o



DOCK8 Deficiency



Asthma
Food allergy
CNS vasculitis
Severe respiratory/skin infections
Non-severe combined T and B defect –
lymphopenia and low IgM

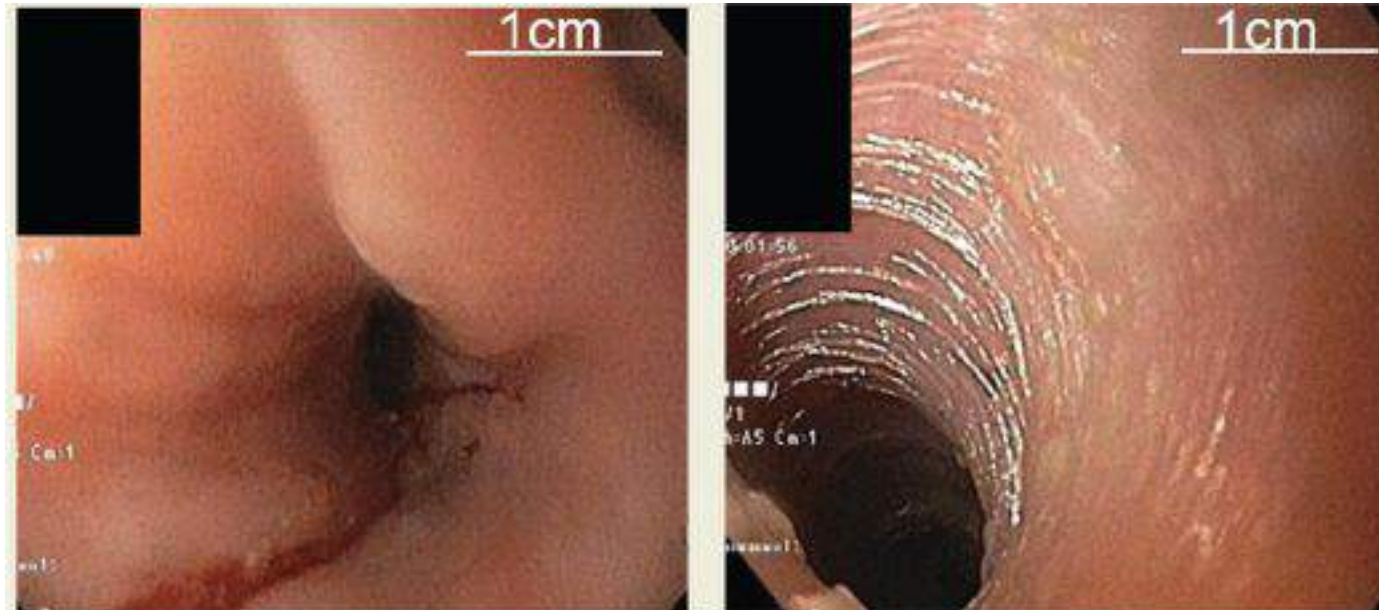
Purcell et al.
The Lancet. 2015; 386:9997

ARTICLE

Human germline heterozygous gain-of-function **STAT6** variants cause severe allergic disease



Early onset of multiple allergies



A	Clinical Feature	Value
	Patient Age Range	3-60 years
	Severe Atopic Disease – no. (%)	16 (100)
	Disease onset in early infancy	16 (100)
	Severe, widespread treatment-resistant atopic dermatitis	15 (94)
	Multiple food allergies	15 (94)
	Asthma	11 (69)
	Anaphylaxis	9 (56)
	Drug allergies	7 (44)
	Infection – no. (%)	8 (50)
	Recurrent skin infections (e.g. <i>S.aureus</i> , <i>C. albicans</i> , molluscum contagiosum)	7 (44)
	Recurrent respiratory infections	5 (31)
	Recurrent viral infections	2 (13)
	Gastrointestinal Disorders – no. (%)	11 (69)
	Eosinophilic gastrointestinal disease	10 (63)
	Early gastro-oesophageal reflux disease (GERD)	4 (25)
	Other GI issues (Constipation, Diarrhea)	3 (19)
	Skeletal Issues – no. (%)	5 (31)
	Osteoporosis, pathologic fractures	3 (19)
	Generalized hypermobility and joint pain	3 (19)
	Vascular anomalies – no. (%)	2 (13)
	B cell lymphoma – no. (%)	1 (6)
	IgE concentration >240 µg/L – no. (%)	15 (100)
	Eosinophil count >500/µL – no. (%)	15 (100)
	Mortality related to underlying disease – no. (%)	2 (13)
	Short stature (<3rd percentile for age)	7 (44)

Syndrome	Gene	Symptoms					
		Immunological Features	Infectious Susceptibilities	Atopic/ Allergic Manifestations	Musculoskeletal/ Connective Tissue	Th17 cell levels*	Other Clinical Features
AD (DN effect) Job's Syndrome	<i>STAT3</i>	Hyper IgE, High Eosinophils	Skin infections, Mucocutaneous candidiasis, Pulmonary infections	Severe eczema	Minimal trauma fractures, Retained primary teeth, connective tissue (like vascular tortuosity and aneurysm) and Skeletal tissue abnormalities.	reduced (215)	Malignancy
AR ZNF341 Deficiency	<i>ZNF341</i>	Hyper IgE, High Eosinophils	Skin infections, Mucocutaneous candidiasis	Severe eczema	Minimal trauma fractures, Retained primary teeth, Skeletal and connective tissue abnormalities.	normal or reduced (166)	
AR GPI30 deficiency	<i>IL6ST</i>	Hyper IgE, High Eosinophils	Skin infections, Mucocutaneous candidiasis, Pulmonary infections	Severe eczema	Minimal trauma fractures, Retained primary teeth, Skeletal and connective tissue abnormalities.	normal (17)	
AR IL-6 receptor deficiency	<i>IL6R</i>	Hyper IgE, High Eosinophils	Skin infections, Mucocutaneous candidiasis, Pulmonary infections	Severe eczema	Minimal trauma fractures, Retained primary teeth, Skeletal and connective tissue abnormalities.	normal or reduced (77)	
AR <i>DOCK8</i> deficiency	<i>DOCK8</i>	Hyper IgE, High Eosinophils	Skin infections, Mucocutaneous candidiasis, Warts, Herpes viridae infections	Severe eczema, [Severe] food allergies		reduced (216)	Malignancy
AR PGM3 deficiency	<i>PGM3</i>	Hyper IgE, High Eosinophils	Herpes viridae infections,	[Severe] food allergies, Asthma	Skeletal and connective tissue abnormalities.	reduced (176)	Malignancy, Neurocognitive delays
AD (DN effect) <i>CARD11</i> deficiency	<i>CARD11</i>	Hyper IgE, High Eosinophils	Molluscum, Pulmonary infections	Severe eczema, [Severe] food allergies, Asthma.		normal (121)	Malignancy, Bamboo hair
AR Comel-Netherton Syndrome	<i>SPINK5</i>	Hyper IgE, High Eosinophils		Severe eczema, [Severe] food allergies, Allergic rhinitis, Asthma		ND	Enteropathy
AD GOF <i>STAT6</i> syndrome	<i>STAT6</i>	Hyper IgE, High Eosinophils	Skin infections, Molluscum, Pulmonary infections	Severe eczema, [Severe] food allergies, Allergic rhinitis, Eosinophilic GI disease, Asthma.	Skeletal and connective tissue abnormalities	normal or reduced (217)	Malignancy, Enteropathy
AD Loey's-Dietz syndrome	<i>TGFBR</i>	Hyper IgE		Severe eczema	connective (like: thoracic aortic aneurysm) and Skeletal tissue abnormalities.	ND (218)	EBV-associated malignancy
AD <i>ERBIN</i> Deficiency	<i>ERBIN</i>	Hyper IgE, High Eosinophils		Severe eczema, Eosinophilic GI disease	Skeletal and connective tissue abnormalities.	normal (108)	EBV-associated malignancy

AD, Autosomal dominant; AR, Autosomal recessive, and the associated symptoms. *Th17 cell levels do not necessarily indicate normal differentiation. ND, No Data.

AlYafie et al.

Front. Immunol.2025 16:1516068.

Eczema

Hyper IgE
with real Allergies
Viral skin infections

DOCK8

Hiper IgE
with Allergies and
other features
similar to Job

PGM3
Loeys-Dietz
STAT6 GoF

Thrombocytopenia

Microplatelets – WAS
Normal or small platelets – WIP
Mild thombocytopenia with
normal platelets – ARPC1B

Autoimmunity

Endocrinopathies
Enteropathy
Food allergy
IPEX (FOXP3)
JAK1 GoF
IKZF1 GoF

Severe infections
Combined T and B
defects

CARD11
MALT1

IPEX

Autoimmunity
Eczema – Allergies (food)
Endocrinopathy
Enteropathy
X-linked

Park et al.
Autoimmunity Reviews. 2020;19:102526

IPEX-like: mutations in IL2RA, CTLA4, LRBA, STAT5B

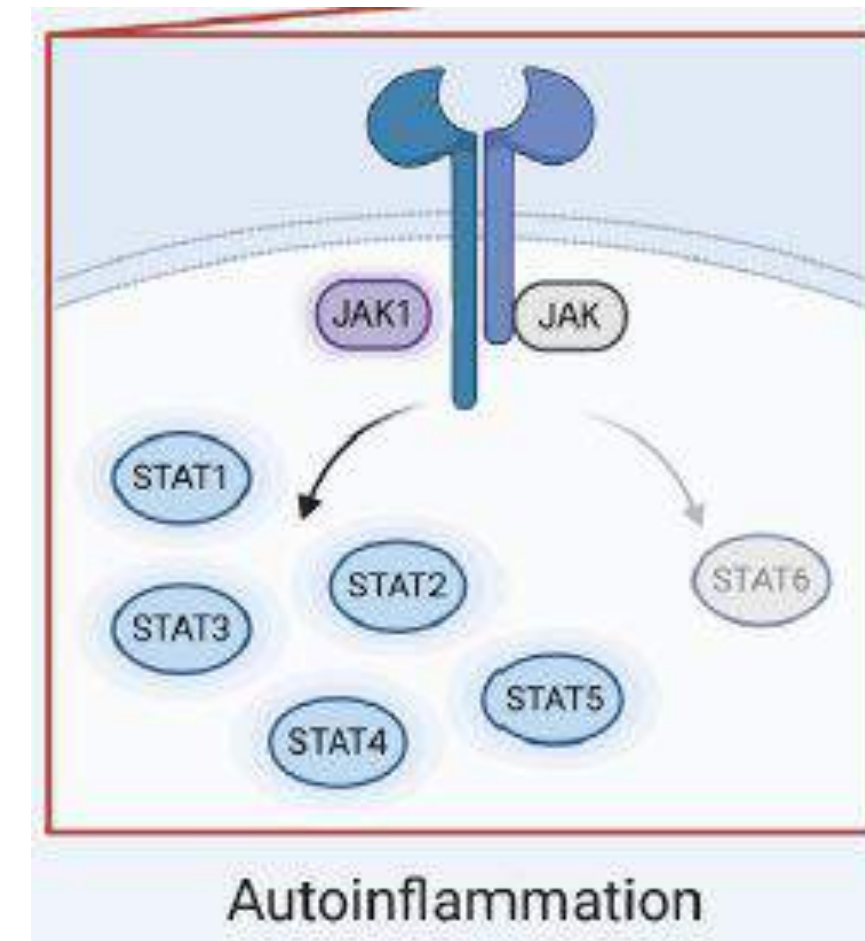


JAK1 GoF

Complex immunodysregulation syndrome

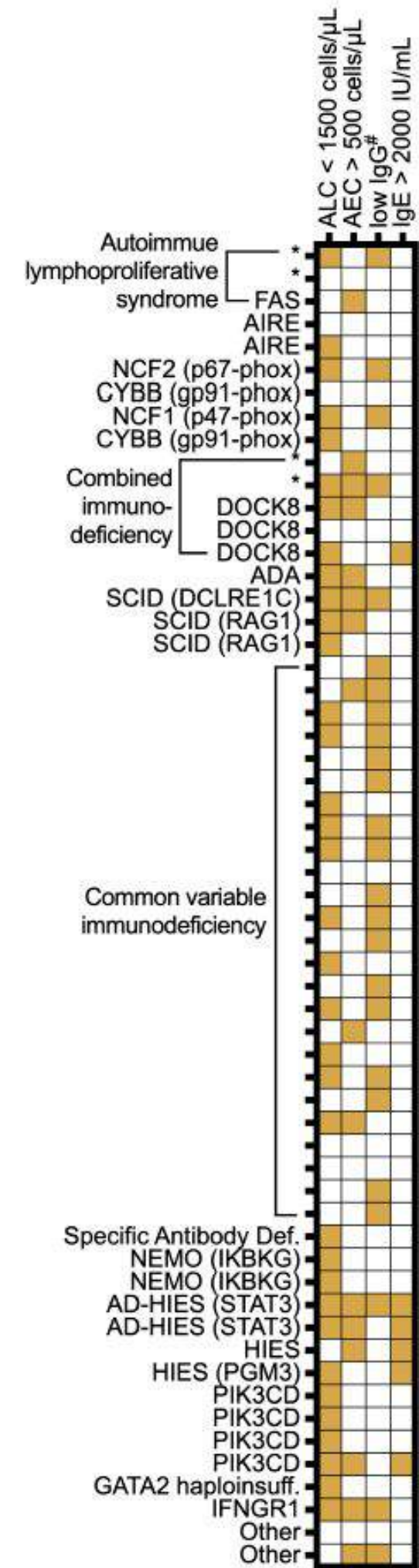
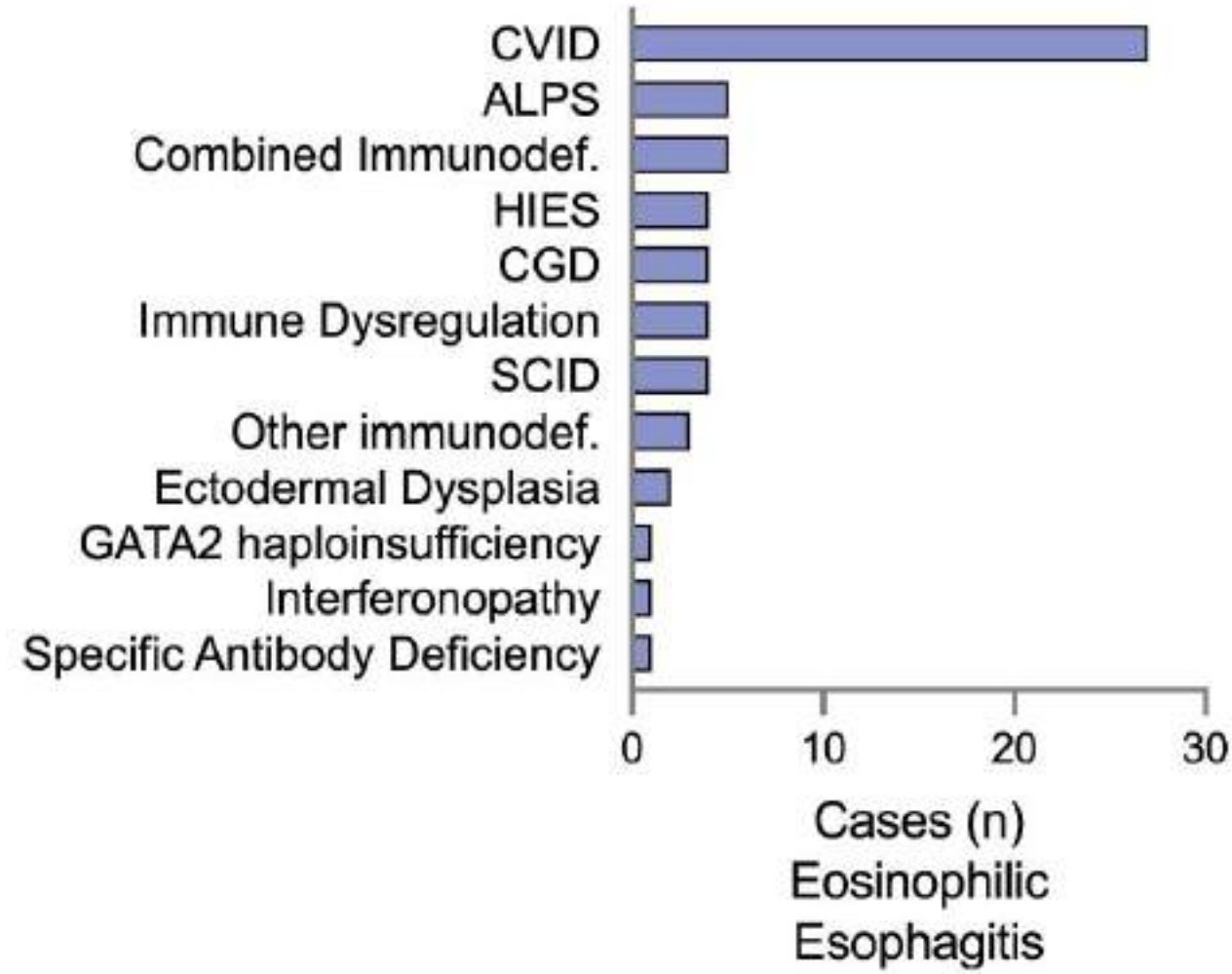
TABLE E1. Clinical features associated with autosomal-dominant *JAK1* GoF mutations

Hematologic abnormalities	Eosinophilia
Autoimmunity	Autoimmune hypothyroidism
Atopy	Asthma
	Atopic dermatitis
	Food allergy
	Environmental allergies
Infections	Recurrent viral infections
Organ involvement	Hepatosplenomegaly
	Prenatal liver cysts
	Eosinophilic infiltration of the gastrointestinal tract
Growth abnormalities	Failure to thrive (pediatric)
	Short stature (adult)
Treatments and response	Corticosteroids (poor response)
	Ruxolitinib (favorable response)

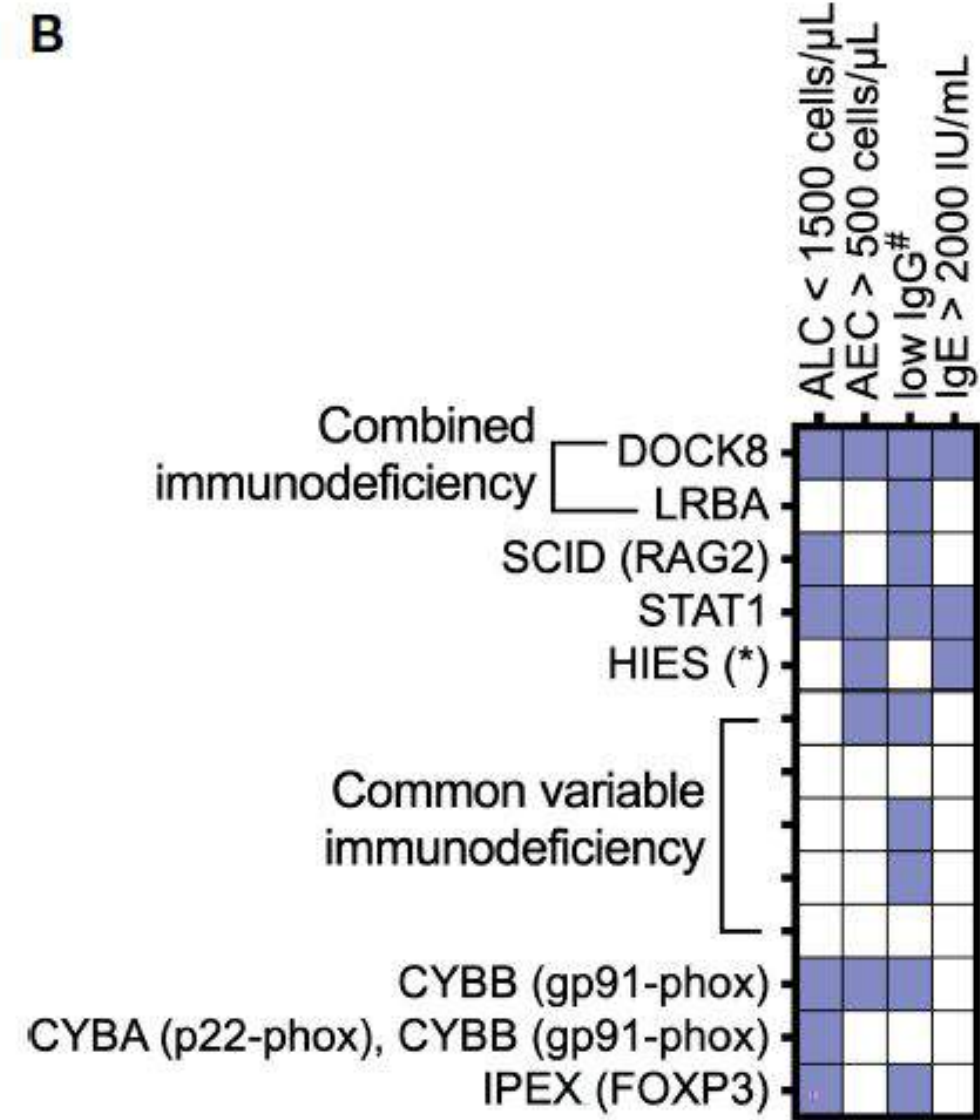
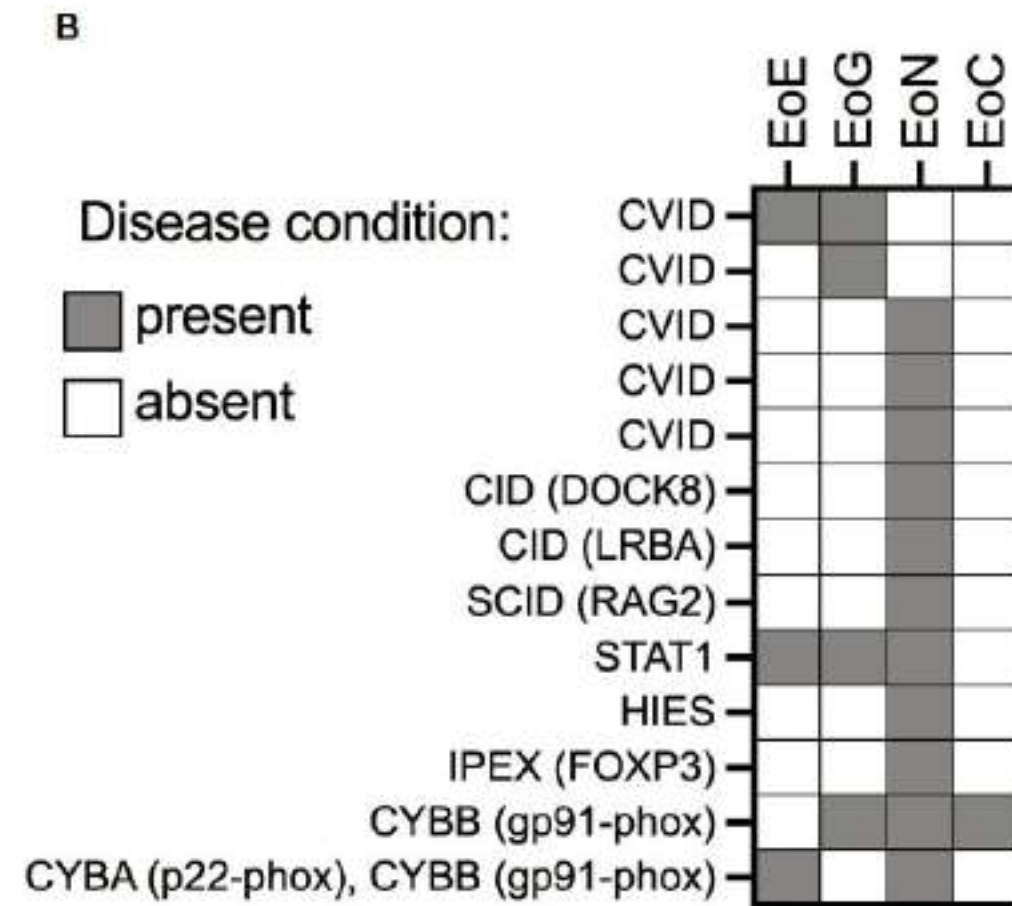
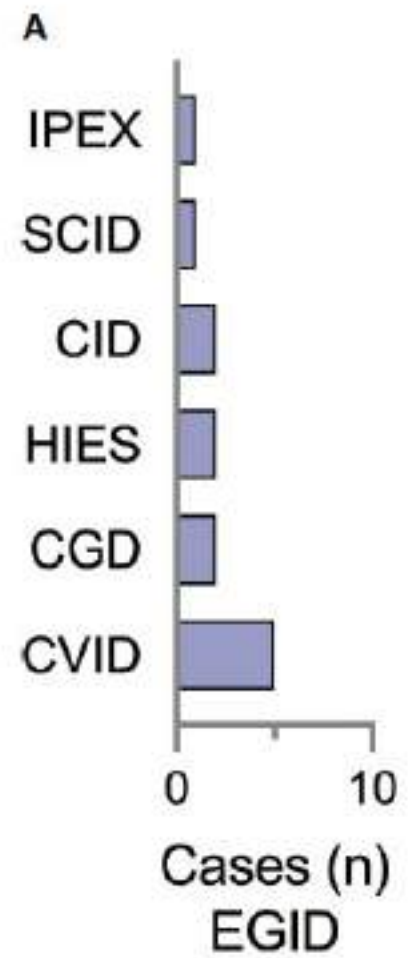


Gruber et al. Immunity, 2020; 53:672–684

EoE



Extraesophageal GI eosinophilia



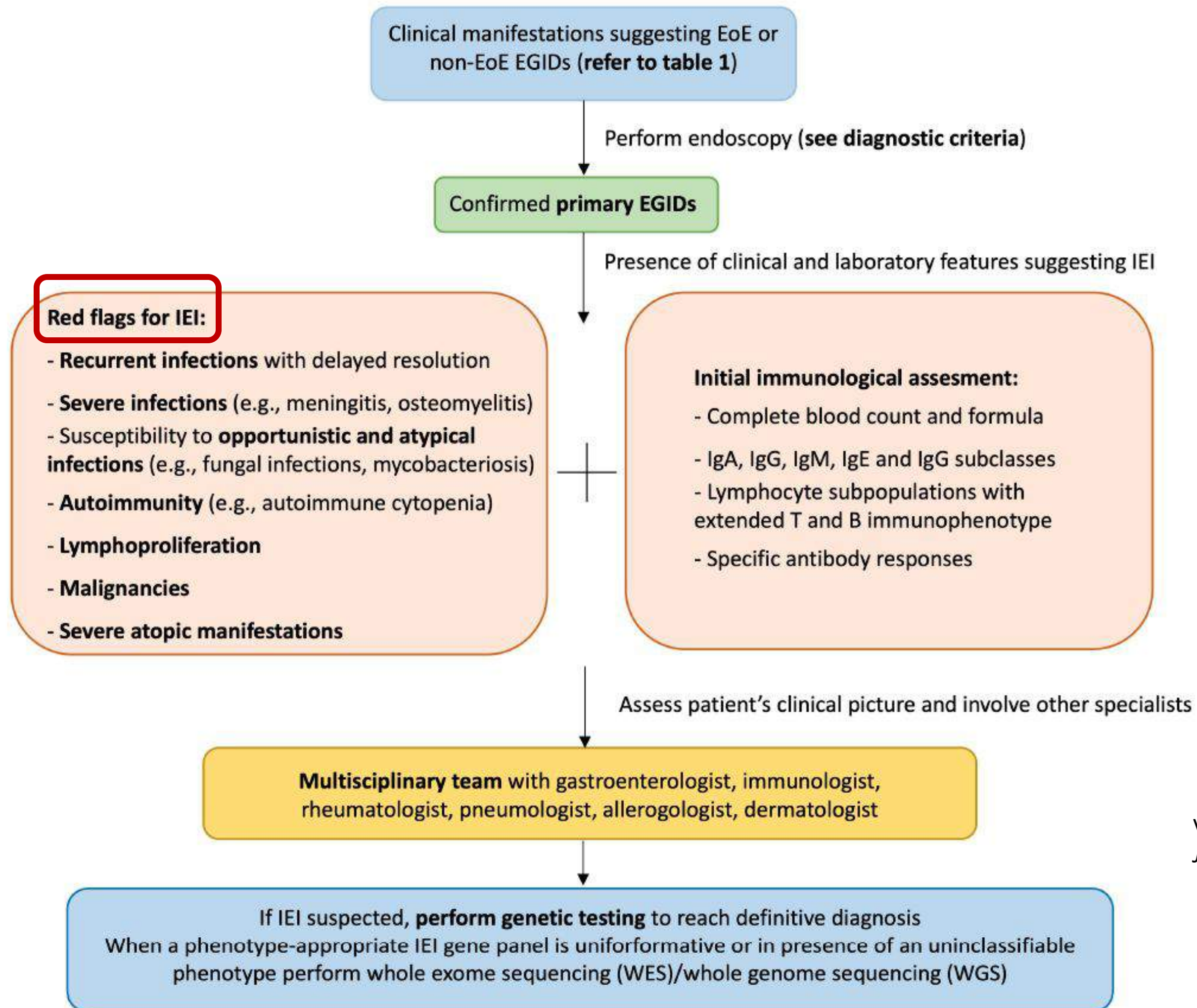


Table 1 Allergy manifestations and associated manifestations in different inborn errors of immunity.

Allergy manifestations	Associated manifestations	Inborn errors of immunity (name/gene)
Elevated IgE and eosinophilia	Bacterial skin and pulmonary infections (with pneumatoceles); chronic mucocutaneous candidiasis; altered inflammatory response (cold abscesses); connective tissue abnormalities (hypermotility, scoliosis, retention of primary teeth, fractures, typical facies, aneurysms); non-flexural eczematous dermatitis; exanthema in the neonatal period.	STAT3 defect - Hyper-IgE S.AD ^a (Job S.) Defects in the STAT3 pathway ZNF341, IL6ST, IL6R
Atopy (atopic dermatitis, asthma)/ food allergy/ anaphylaxis	Immune dysregulation; increased IgE and eosinophilia; viral skin infections; combined immunodeficiency (non-severe) Increased IgE and eosinophilia; scoliosis; bacterial lung and skin infections; myoclonus and cognitive delay; lymphopenia. Immune dysregulation (enteropathy); bacterial / viral infections; short stature Important eosinophilia; impaired growth. Eosinophilia Lymphoproliferation (hepatosplenomegaly, lymphadenopathy); severe combined immunodeficiency; barrier defects, with major ichthyosis; increased IgE and eosinophilia; bamboo hair; increased metabolic expenditure. Dermatitis with skin ulcers; increased IgE; bacterial skin and pulmonary infections; hepatosplenomegaly.	Actinopathies: Wiskott-Aldrich S. and defect in WIP ^b (thrombocytopenia with small platelets); defects in DOCK8, ARPC1B, CARMIL2 Defects in CARD9, CARD11, CARD14, MALT1 PGM3 defect STAT5b LF ^c JAK1 GF ^d Omenn S. Comel-Netherton S. (SPINK5) Prolidase deficiency
Severe atopic dermatitis and/or erythroderma / ichthyosis		
Urticaria and anaphylaxis	Neonatal urticaria; very important eosinophilia; growth alteration. Early and severe hives; erythema and pruritus; anaphylaxis.	STAT5b GF ^d PLAID ^e (evaporative cooling; PLCG2 GF ^d) Familial vibratory urticaria (ADGRE2) Hereditary alpha-tryptasemia (TPSAB1)

Omenn Syndrome



Hepatosplenomegaly, lymphadenopathy, eosinophilia.

AR or XL

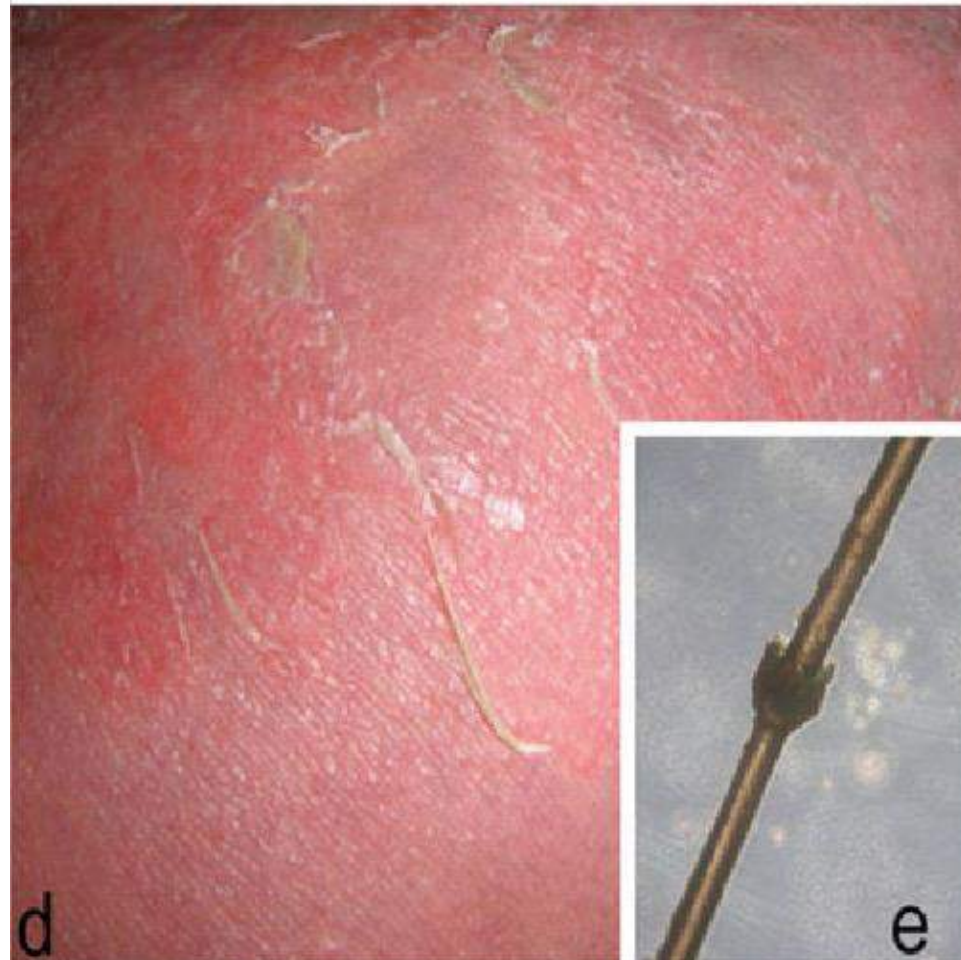
Multiple genes, mainly RAG1/RAG2, ARTEMIS, DNAligase



Siala et al.

Acta Dermatovenerol Croat. 2013;21(4):259-62.

Comèl-Netherton Syndrome



Bamboo hair –
trichorrhexis invaginata,
enteropathy, bacterial
infections
High IgE and IgA
AR
SPINK5



FIGURA 1: Lesões eritemato-serpiginosas e policíclicas, com margens apresentando dupla borda escamosa na perna da paciente

S. Comèl – Netherton

Linear circumflex ichthyosis

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Allergy manifestations	Associated manifestations	Inborn errors of immunity (name/gene)
Elevated IgE and eosinophilia	Bacterial skin and pulmonary infections (with pneumatoceles); chronic mucocutaneous candidiasis; altered inflammatory response (cold abscesses); connective tissue abnormalities (hypermotility, scoliosis, retention of primary teeth, fractures, typical facies, aneurysms); non-flexural eczematous dermatitis; exanthema in the neonatal period.	STAT3 defect - Hyper-IgE S.AD ^a (Job S.) Defects in the STAT3 pathway ZNF341, IL6ST, IL6R
Atopy (atopic dermatitis, asthma)/ food allergy/ anaphylaxis	Immune dysregulation; increased IgE and eosinophilia; viral skin infections; combined immunodeficiency (non-severe) Increased IgE and eosinophilia; scoliosis; bacterial lung and skin infections; myoclonus and cognitive delay; lymphopenia. Immune dysregulation (enteropathy); bacterial / viral infections; short stature Important eosinophilia; impaired growth. Eosinophilia Lymphoproliferation (hepatosplenomegaly, lymphadenopathy); severe combined immunodeficiency; barrier defects, with major ichthyosis; increased IgE and eosinophilia; bamboo hair; increased metabolic expenditure. Dermatitis with skin ulcers; increased IgE; bacterial skin and pulmonary infections; hepatosplenomegaly. Neonatal urticaria; very important eosinophilia; growth alteration. Early and severe hives; erythema and pruritus; anaphylaxis.	Actinopathies: Wiskott-Aldrich S. and defect in WIP ^b (thrombocytopenia with small platelets); defects in DOCK8, ARPC1B, CARMIL2 Defects in CARD9, CARD11, CARD14, MALT1 PGM3 defect STAT5b LF ^c JAK1 GF ^d Omenn S. Comel-Netherton S. (SPINK5) Prolidase deficiency STAT5b GF ^d PLAID ^e (evaporative cooling; PLCG2 GF ^d) Familial vibratory urticaria (ADGRE2) Hereditary alpha-tryptasemia (TPSAB1)
Severe atopic dermatitis and/or erythroderma / ichthyosis		
Urticaria and anaphylaxis		

Urticaria and Anaphylaxis

STAT5b GoF

PLAID (PLCG2)

Familial vibratory urticaria (EMR2)

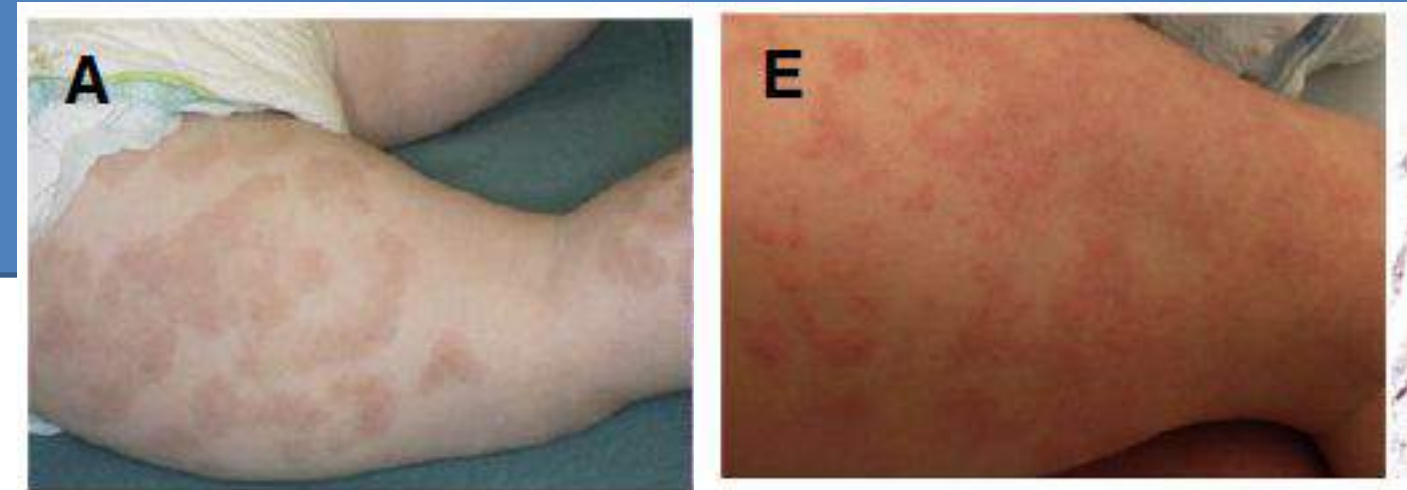
KARS

α hereditary tryptasemia (TPSAB1)

Urticaria and Anaphylaxis


STAT5b GoF →
PLAID (PLCG2)
Urticária vibratória familiar (EM)
KARS
 α triptasemia hereditária (TPSA)

Persistent urticaria
Erythema annular migrans
Atopic dermatitis
Food allergy (angioedema)



Ma et al. Blood, 2017; 129(5):650-3

Urticaria and Anaphylaxis

STAT5b GoF
 PLAID (PLCG2) 
 Urticária vibratória familiar (EMR2)
 KARS
 α triptasemia hereditária (TPSAB1)

A Evaporative Cooling Test



Ice Cube Test Negative

Panel A shows the results of an evaporative cooling test in one subject. Cold urticaria was provoked with droplets of ethanol (E) or air-blown water (A) but not with droplets of unblown water (W) or covered water (C). In Panel B,

Table 1. Summary of the Clinical Manifestations of Phospholipase C γ_2 -Associated Antibody Deficiency and Immune Dysregulation in the Subjects.

Clinical Manifestation	Frequency no./total no. (%)
Cold urticaria evaporation	27/27 (100)
Recurrent sinopulmonary infection	12/27 (44)
Antibody deficiency*	15/20 (75)
Common variable immunodeficiency	3/27 (11)
Symptomatic autoimmune disease†	7/27 (26)
Positive test for antinuclear antibodies‡	13/21 (62)
Symptomatic allergic disease	15/27 (56)

Ombrello et al.
N Engl J Med 2012;366:330-8.

Urticaria and Anaphylaxis

STAT5b GoF

PLAID (PLCG2)

Urticária vibratória familiar (EMR2)

KARS

reditária (TPSA)

B Forearm Vortex Challenge



Vibration-induced mast cell degranulation
Also headache, facial flushing, metallic taste
EMR2 or ADGR2 (transmembrane epidermal growth factor) mutation
Autosomal dominant inheritance

Boyden et al. N Engl J Med 2016;374:656-63.

Urticaria and Anaphylaxis

STAT5b GoF

PLAID (PLCG2)

Urticária vibratória familiar

KARS



α triptasemia hereditária

Severe anaphylaxis after hymenoptera bite.

KARS – canonical pathway of protein synthesis and non-canonical antigen-dependent activation of mast cells Fc ϵ RI

Ribó et al. J Allergy Clin Immunol.2021;147:1855-64.

Hereditary alpha tryptasemia (HαT) is an autosomal dominant genetic trait characterized by increased copy number of the TPSAB1 gene encoding α-tryptase, resulting in elevated basal serum tryptase levels.

This genetic variant is present in approximately 4–6% of the general population, but its prevalence is significantly higher among patients with systemic mastocytosis and other mast cell disorders.

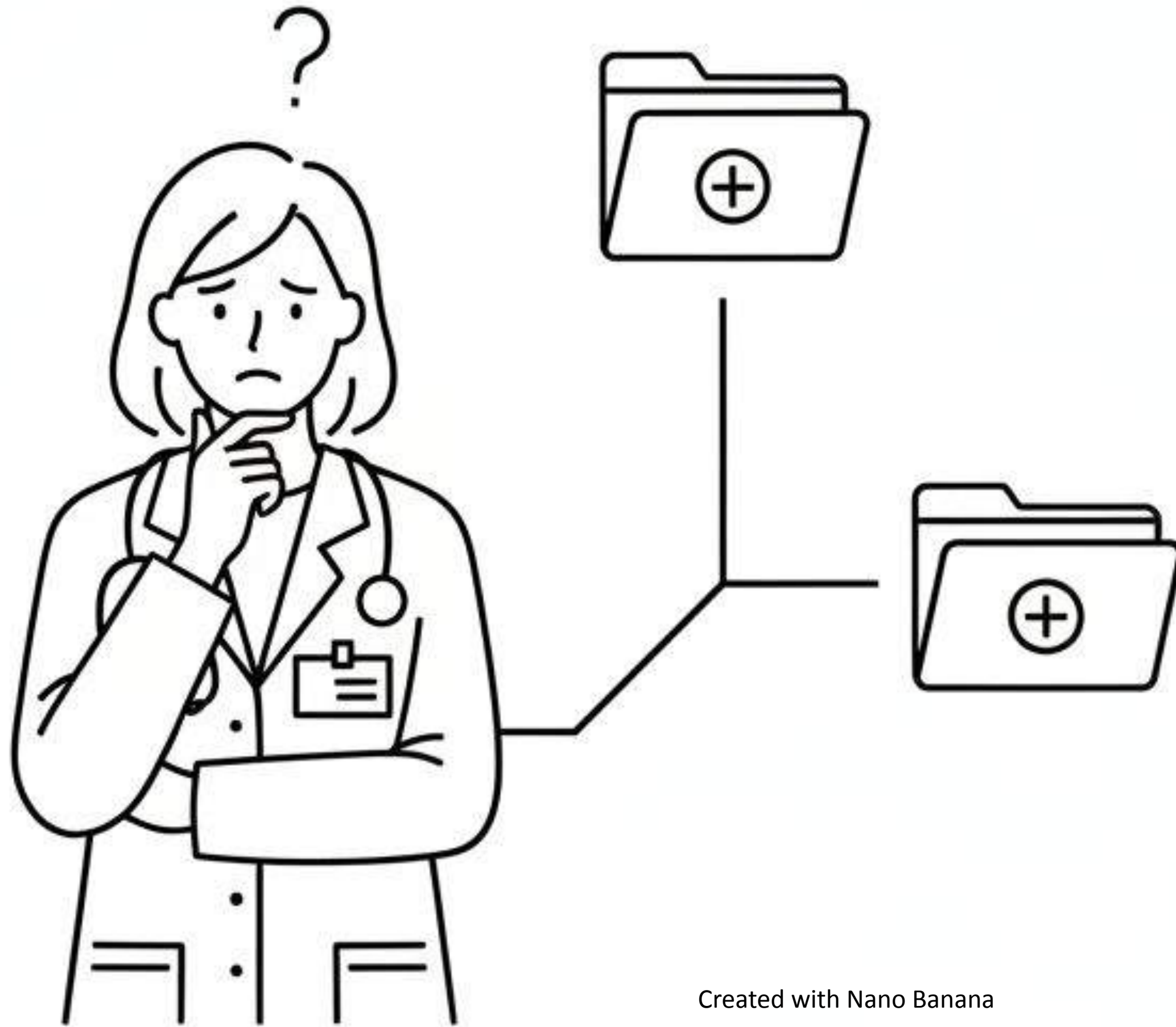
The gene dosage effect—i.e., the number of additional TPSAB1 copies—correlates with both the degree of tryptase elevation and the severity of clinical manifestations.

Rüfer et al. Swiss Medical Weekly. 2025;155:3679.

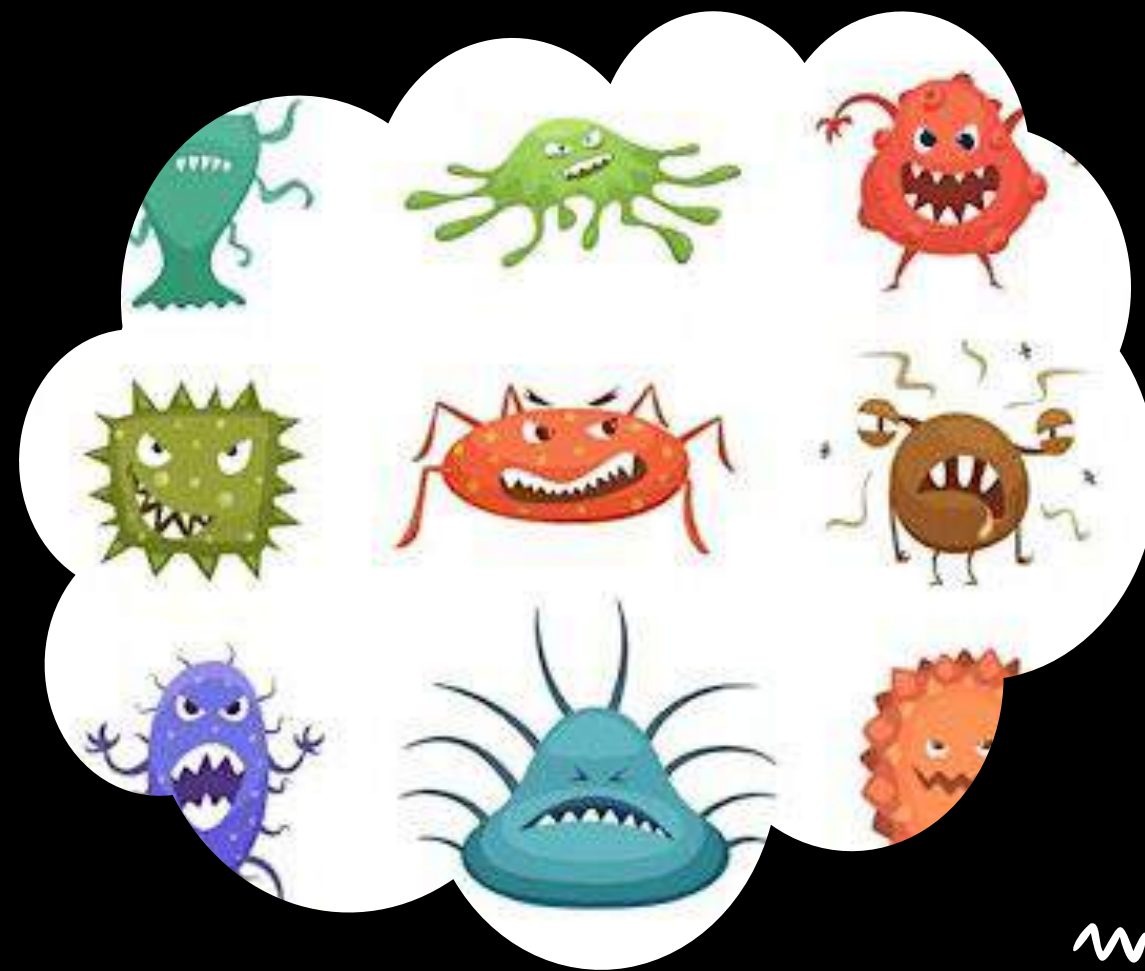
Incorporate specific TPSAB1 genotyping early in the evaluation of elevated BST, severe anaphylaxis (especially venom), and suspected mast cell disease; interpret acute events with the universal 20%+2 rule.

HαT acts as a risk modifying factor, mainly in IgE mediated allergy and mastocytosis; risk stratification and counseling should reflect this.

*“Commonly appearing allergic disease
may well be monogenic in some cases.”*



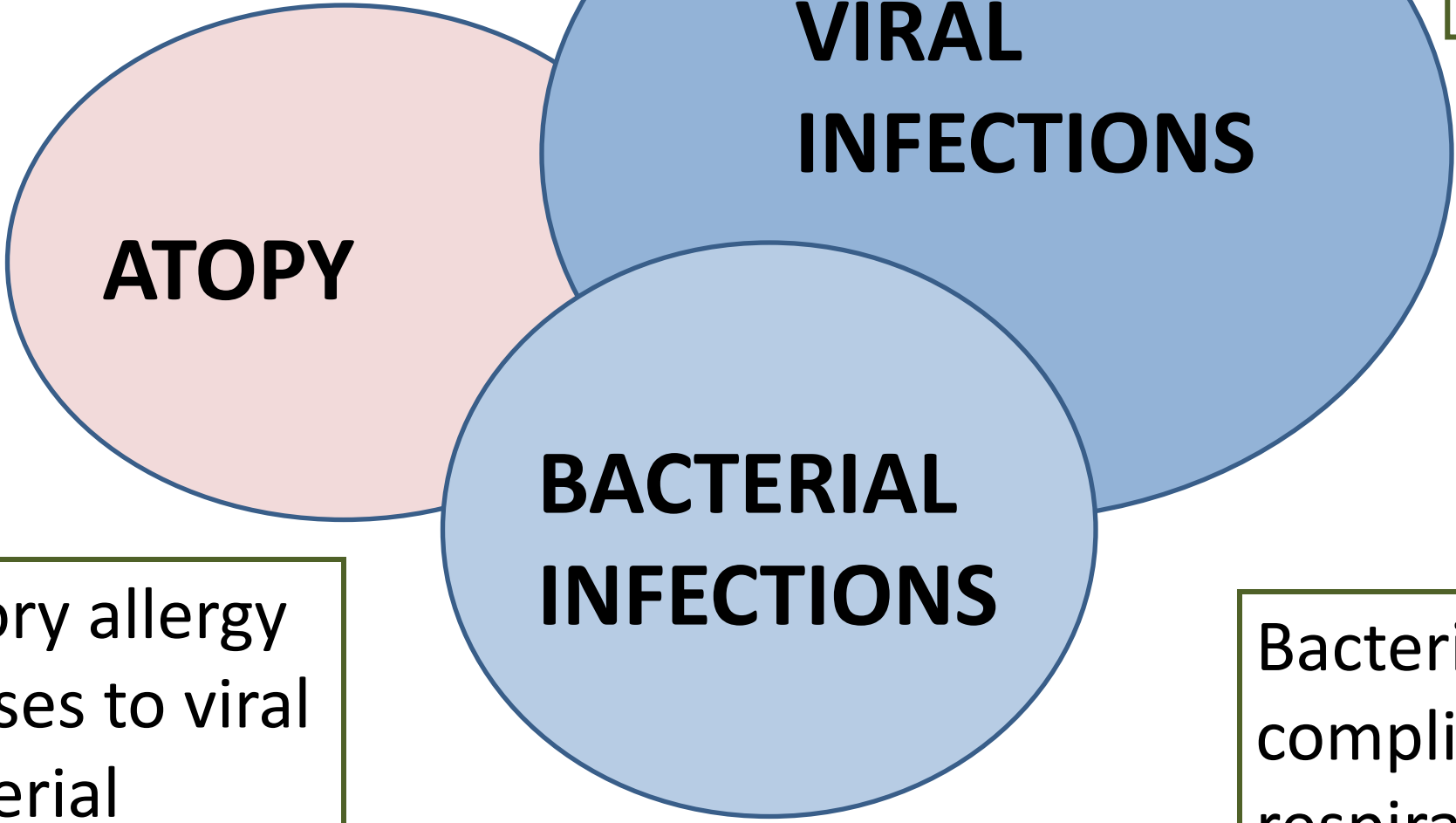
Infections !!!!!



Symptoms of Acute Respiratory Infections are confused with those of respiratory allergy, or trigger them.

Viral acute respiratory infections are prevalent in children, particularly up to 3 to 5 years of age.

Physiological Immunological Immaturity



Respiratory allergy predisposes to viral and bacterial infections

Bacterial infections may complicate acute viral respiratory infections

Primary Atopic Disorders



Monogenic diseases in which allergy or atopy are the most important manifestations.



True allergy

or

Activation of T2 mechanisms due to defects in
different pathways of the immune system

Early-onset atopic disease, usually at birth or in the first months of life

Severe atopic disease, usually not responsive to standard therapy (e.g. severe and recalcitrant eczema)

High levels of Th2 biomarkers (e.g. increased total serum IgE, eosinophilia)

Presence of other affected family members (inheritance pattern, including family history for primary immunodeficiencies and/or familial severe atopic diathesis), family history of consanguinity

Associated clinical features^a

Associated immunological abnormalities^a

Efficacy of targeted therapies

Table 1. Common features of inborn errors of immunity with atopic phenotypes *a. See Table 2, Red flags*

Serum total IgE >2000 kU/L, especially in the first 3 months of life

Neonatal erythroderma

Congenital ichthyosis

AD

+ Serum total IgE >2000 kU/L
+ recurrent skin and pulmonary infections
± skeletal abnormalities
± neurodevelopmental delay

Atopic diathesis *

+ recurrent/severe infections (especially due to opportunistic pathogens and Herpesviridae, including CMV, EBV, HHV-6)

AD

+ autoimmunity
± recurrent infections

Atopic diathesis *

+ lymphopenia

Atopic diathesis *

+ cytopenias (neutropenia/thrombocytopenia/anemia)

AD

+ diarrhea
+ endocrinopathy
± failure to thrive

AD

+ diarrhea
+ bleeding
± failure to thrive

EGID

+ severe eosinophilia (>1500 cells/mm³)
± atopic diathesis

Red Flags

Castagnoli et al.

WAO Journal. 2021; 14:100513

* **Atopic diathesis** denotes a constitutional, often genetically determined, tendency to develop atopic diseases, characterized by increased IgE-mediated sensitization and a spectrum of clinical allergic disorders.



¡Muchas gracias por la
invitación y por la atención!

egoudouris@gmail.com

Severe early-onset atopic dermatitis/erythroderma

- *Likely IEI: SPINK5/Netherton; DSG1/SAM; STAT3 LOF and ZNF341; DOCK8; PGM3; WAS; hypomorphic RAG/Omenn; ADA-SCID variants; IPEX (FOXP3), IL2RA, STAT5B [1,2,5,11,14,16,18,20,23,24,26].*
- *Red flags: neonatal onset; failure to thrive; alopecia/hair shaft defects; microthrombocytopenia; skeletal/dental hallmarks; extensive viral warts/molluscum; lymphadenopathy/organomegaly*

Multiple food allergy and/or anaphylaxis

- *Likely IEI: DOCK8; STAT6 GOF; IL4RA GOF; CARD11 DN; PGM3; WAS; IPEX/IL2RA/STAT5B; LRBA/CTLA4; TGF β -pathway (Loeys–Dietz) and ERBIN [1,2,5,8,16,17,28].*
- *Red flags: trace-exposure anaphylaxis; concomitant severe eczema/EGID; cutaneous viral infections; autoimmunity/enteropathy; connective-tissue/syndromic signs*

Severe/difficult-to-control asthma

- *Likely IEI: STAT6 GOF; IL4RA GOF; DOCK8; PI3K' GOF (PIK3CD/PIK3R1); CARD11 DN; PGM3; STAT3 LOF (fungal/ABPA-like) [1,2,5,16].*
- *Red flags: early-onset severe asthma with recurrent sinopulmonary infections, bronchiectasis, lymphoproliferation, hepatosplenomegaly, extrapulmonary autoimmunity*

Chronic urticaria/angioedema

- *IEI/mimics: PLCG2 (PLAID—cold-induced urticaria with CVID-like features; APLAID—autoinflammation/uveitis); STAT3 GOF; CTLA4/LRBA; autoinflammatory CAPS (NLRP3); hereditary angioedema (C1 INH) as a comparator [1,2,5,16].*
- *Red flags: infantile cold-triggered urticaria; urticaria with hypogammaglobulinemia/recurrent infections; angioedema without wheals; systemic inflammation*

EGIDs/enteropathies

- *Likely IEI: STAT6 GOF; IL4RA GOF; DOCK8; CARD11 DN; PGM3; WAS; IPEX/IL2RA/STAT5B; LRBA/CTLA4; PI3K' GOF [1,2,5,13,16,28].*
- *Red flags: failure to thrive; protein-losing enteropathy; early-onset severe eosinophilic esophagitis/gastroenteritis with extra-GI immune dysregulation*