Primary immunodeficiency diseases

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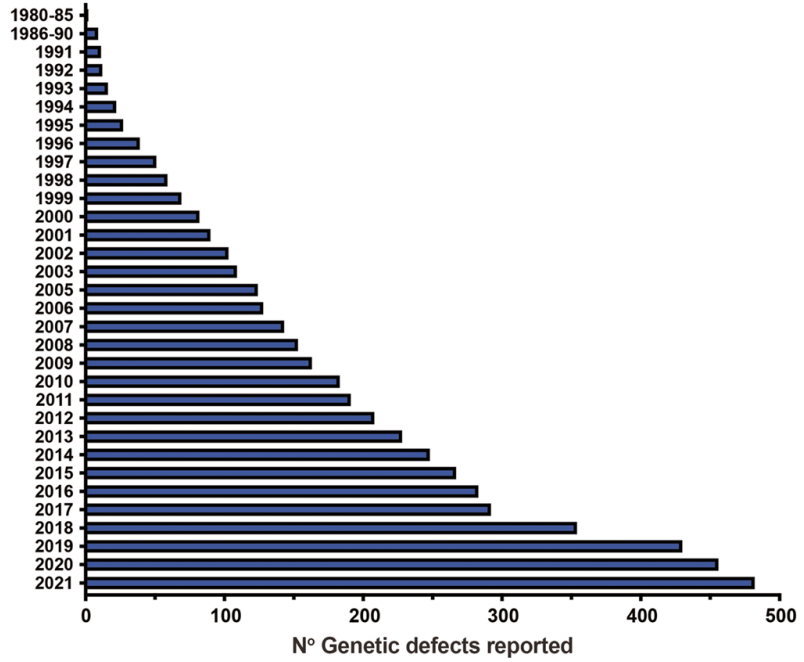
Inborn errors of immunity

The scene….

- >480 defects described
- Defect in the development or in the function of the immune system
- Mutations in the same gene
  - Different mode of inheritence
  - Different phenotypes
  - Different pathogenesis
- "Pattern" recognition of disease



J Clin Immunol 42, 1473–1507 (2022). https://doi.org/10.1007/s10875-022-01289-3

Single patients is a challenge!

Rare diseases but all together frequent… 1/2000 birth.

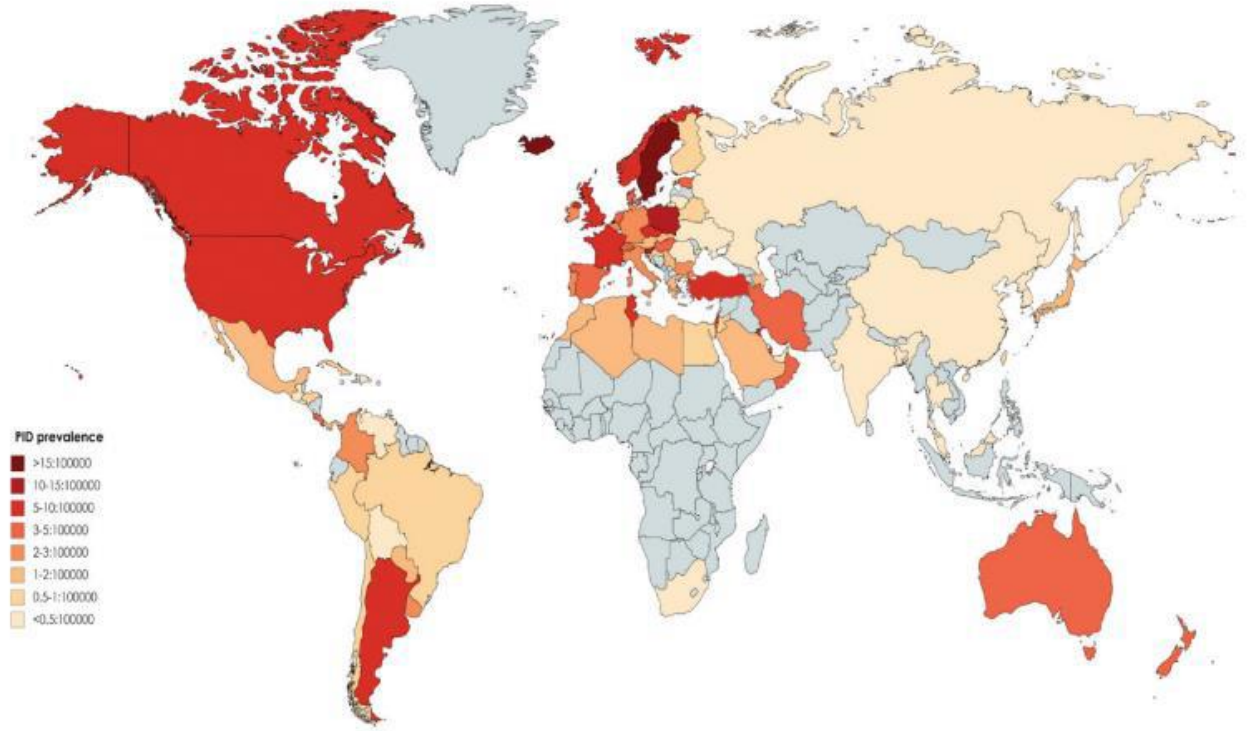
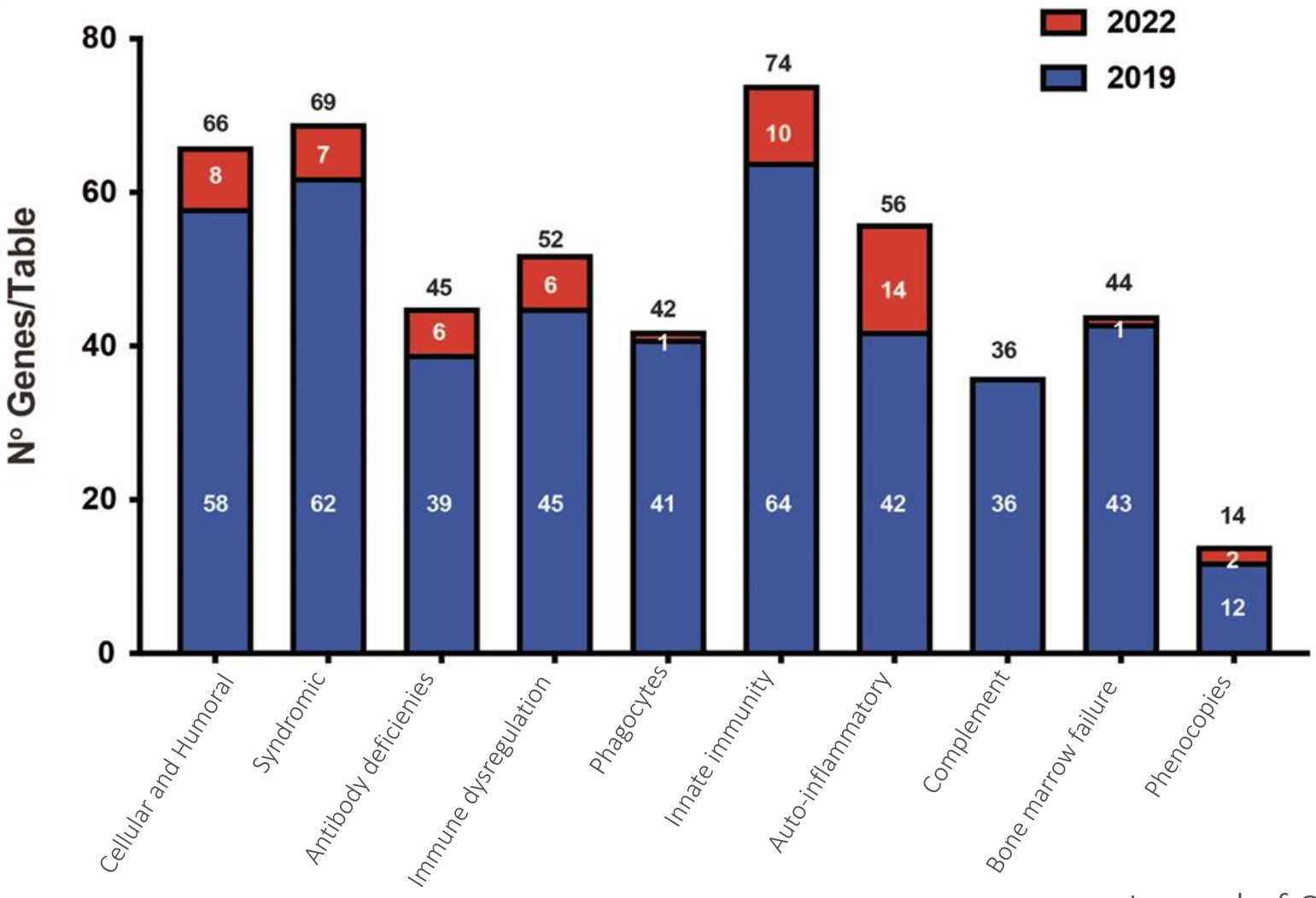


Figure 1. Distribution of primary immunodeficiency prevalence in the world based on the number of reported patients per 100000 individuals (Gray color represents countries without registry or without published report).



16/55 come from a single patient

STRONG validation necessary!

Journal of Clinical Immunology (2022) 42:1473–1507

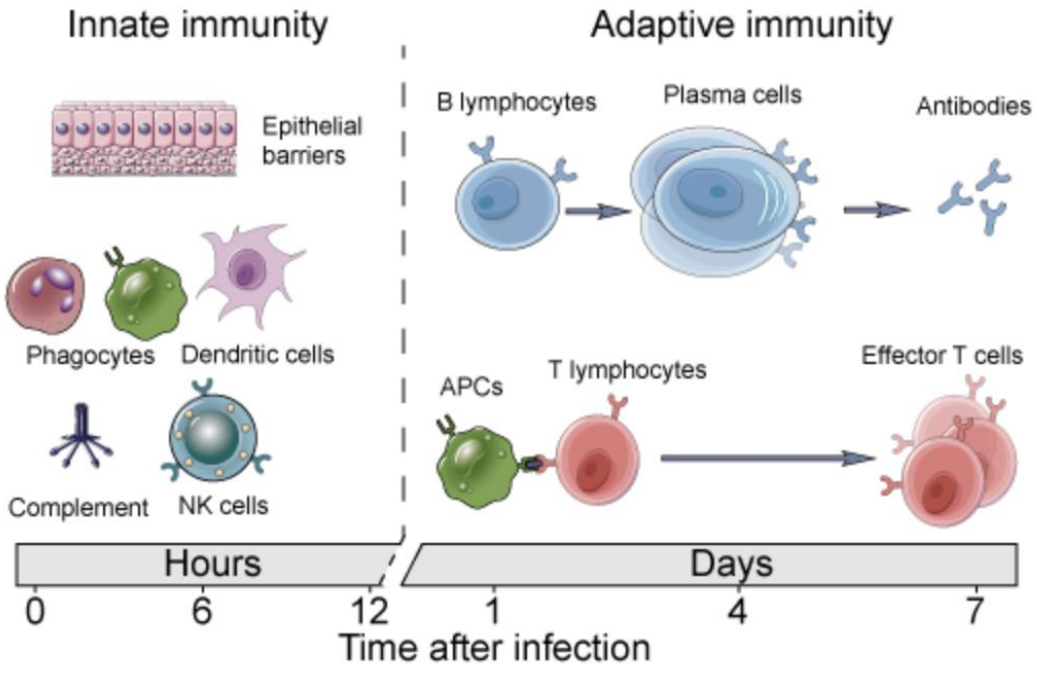
Inborn errors of immunity (IEI)

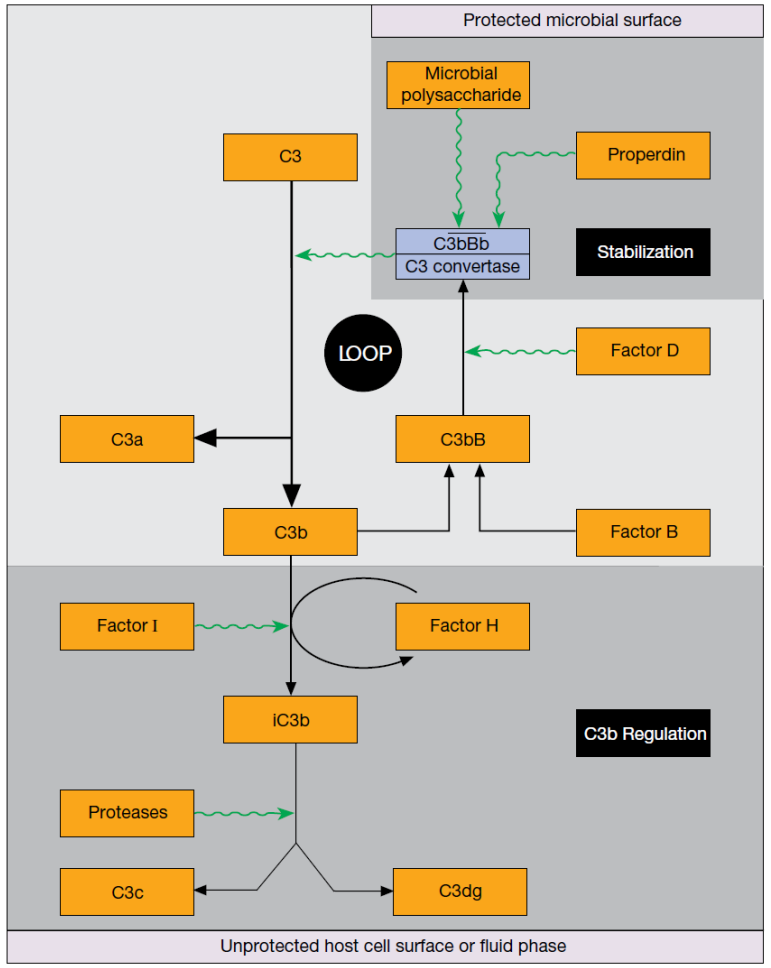
Exponential progress

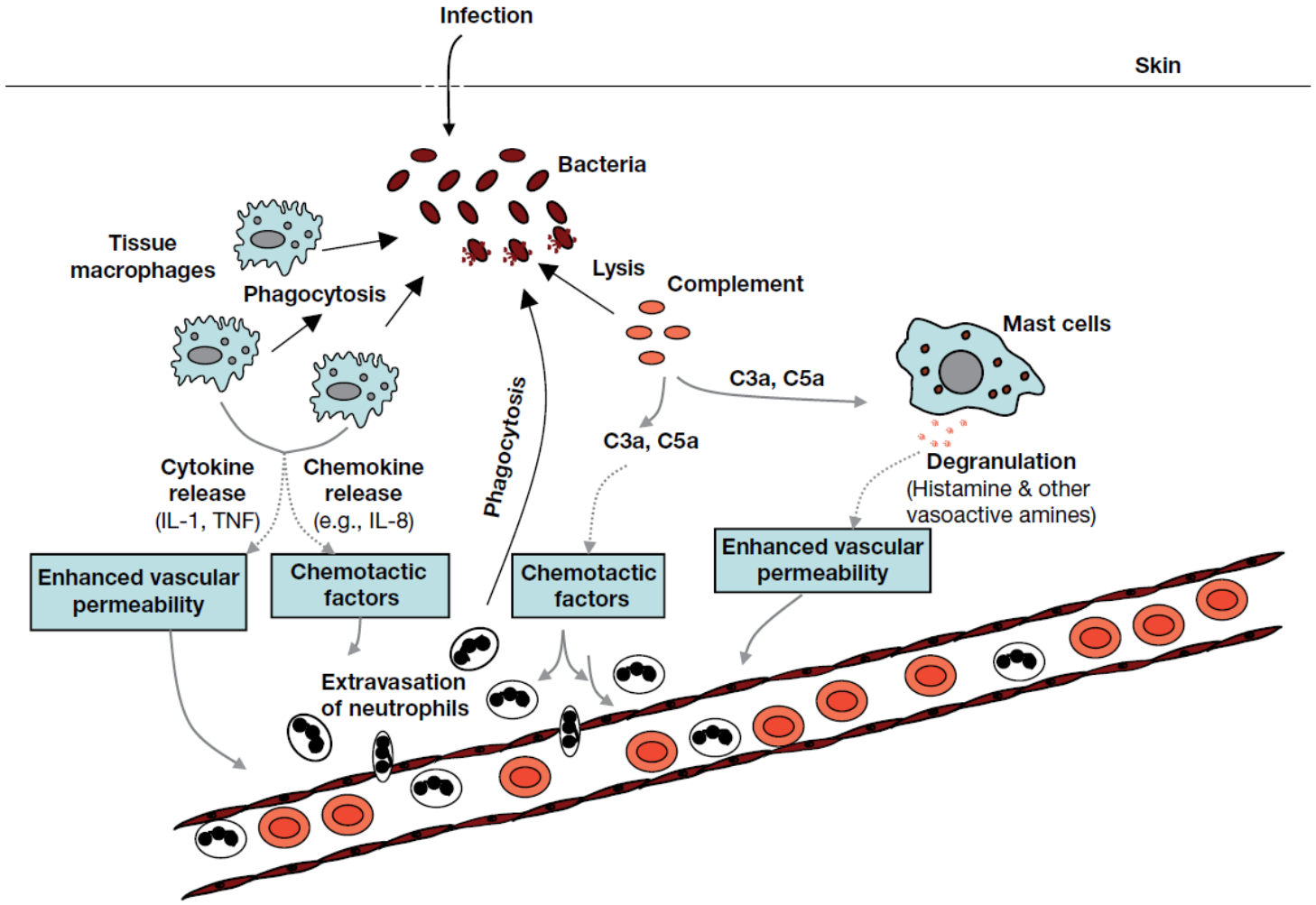
- Kids are reaching adulthood
- First diagnosis of IEI in adults

- MOLECULAR basis of diseases understood
- New TAGETED THERAPY
- Next generation sequencing and other tools

A crash course on immunology

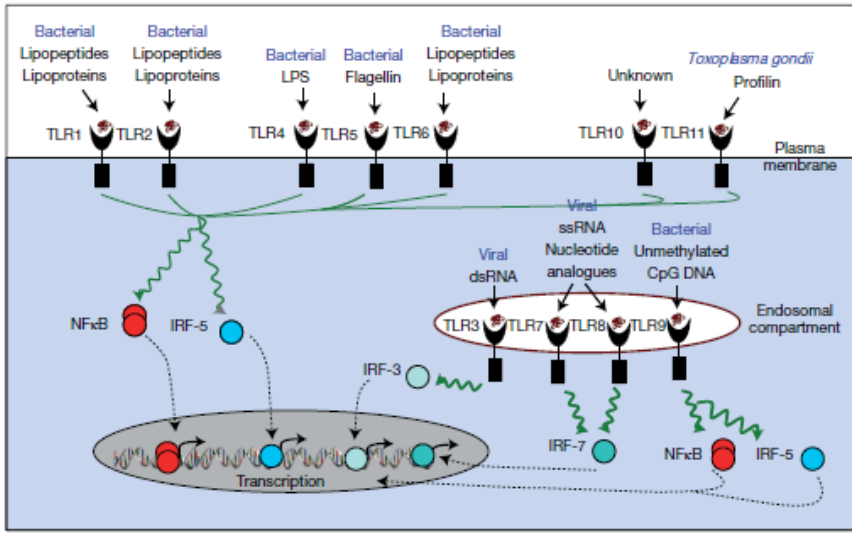


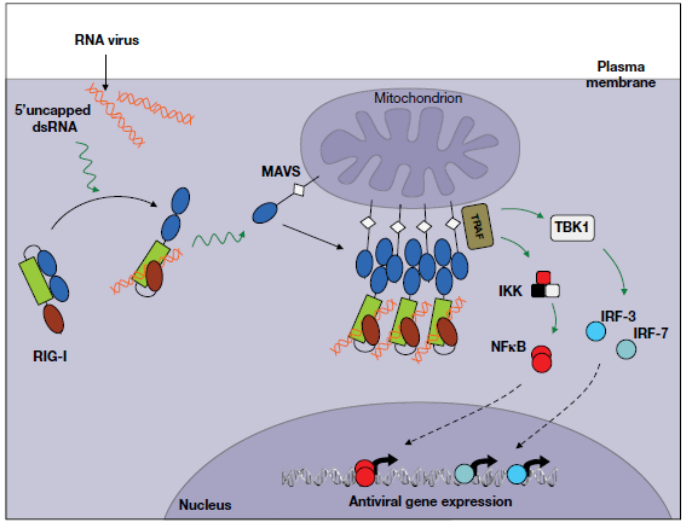


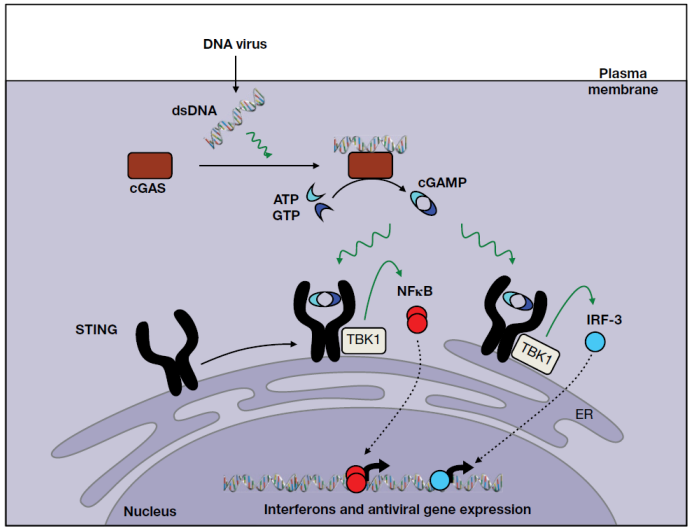

Infection
Skin
Bacteria
Tissue macrophages
Phagocytosis
Lysis
Complement
Mast cells
C3a, C5a
C3a, C5a
Phagocytosis
Cytokine release (IL-1, TNF)
Chemokine release (e.g., IL-8)
Degranulation (Histamine & other vasoactive amines)
Enhanced vascular permeability
Chemotactic factors
Chemotactic factors
Enhanced vascular permeability
Extravasation of neutrophils

Decoding the nature of infection

Pathogen-associated molecular patterns (PAMPs) and PRRs: Interferon Regulated Factor and NFKB transcription factors

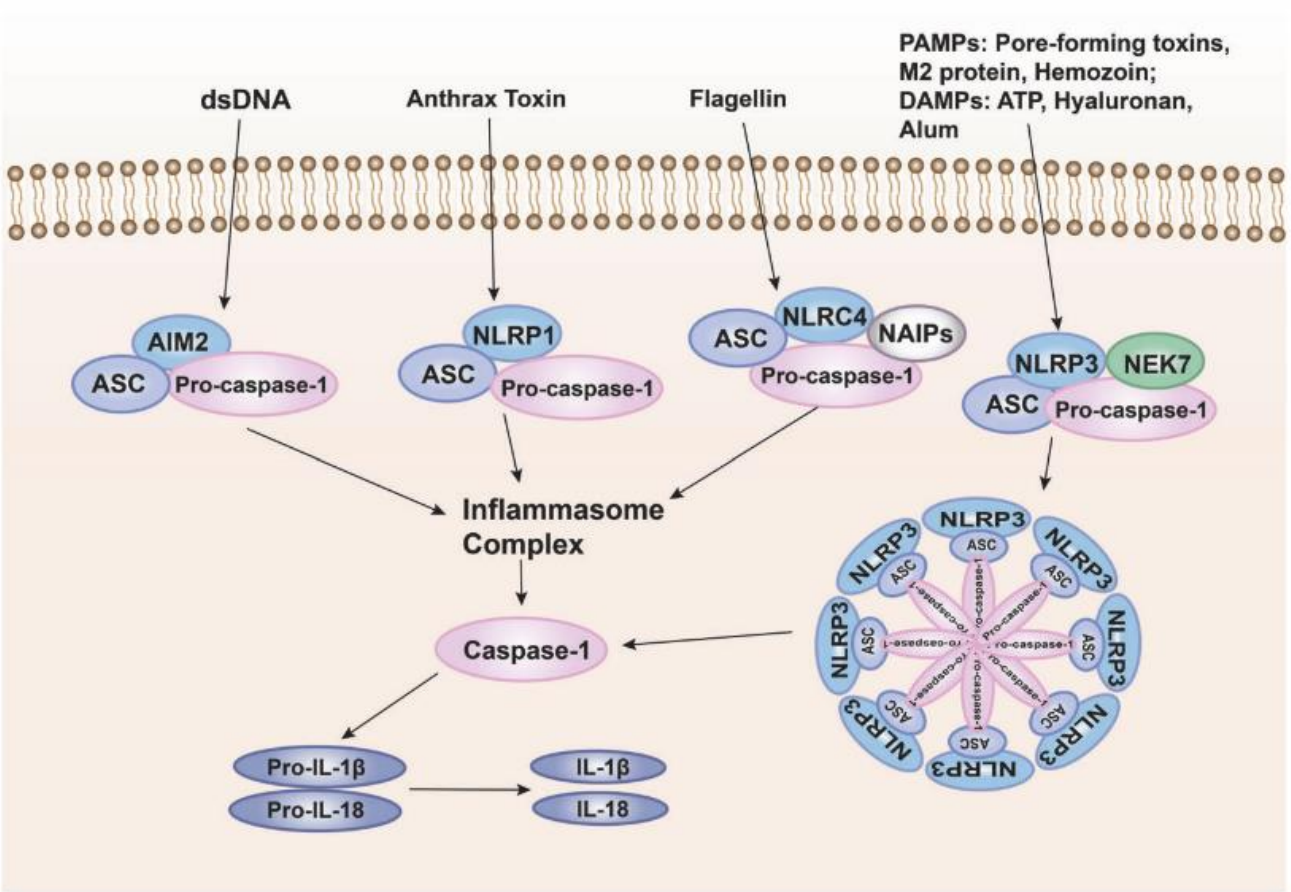






Decoding the nature of infection

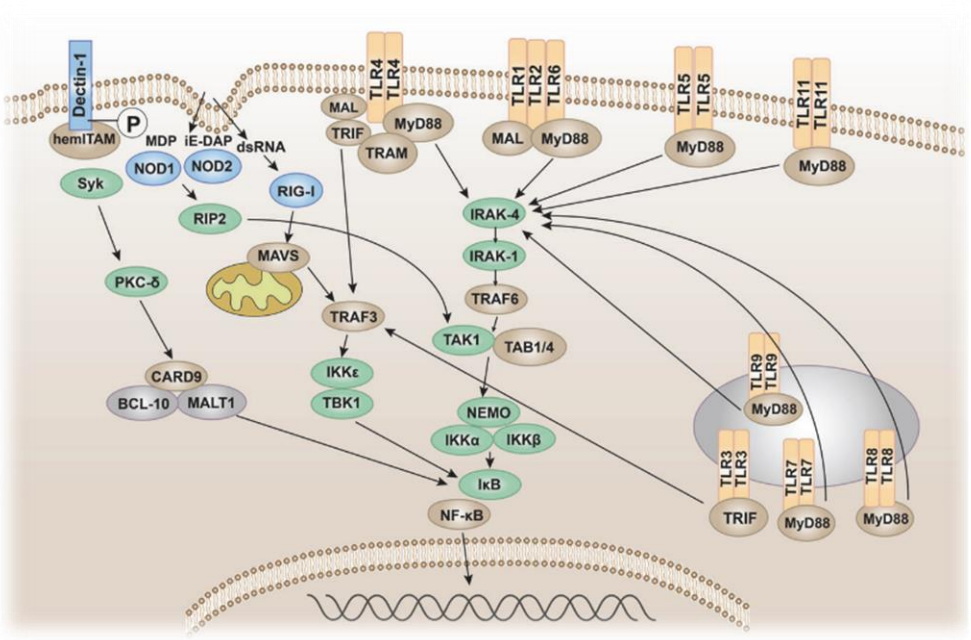
Pathogen-associated molecular patterns (PAMPs) and PRRs: Inflammasome



Decoding the nature of infection

Immune responses are tailored towards particular types of infection

Because of the diversity of infectious agents, all of which have their own strategies to evade and neutralize the best efforts of our immune systems, we have responded by evolving multiple ways of dealing with intruders (whether viral, extracellular bacterial, intracellular bacterial, worm, fungal, etc.)



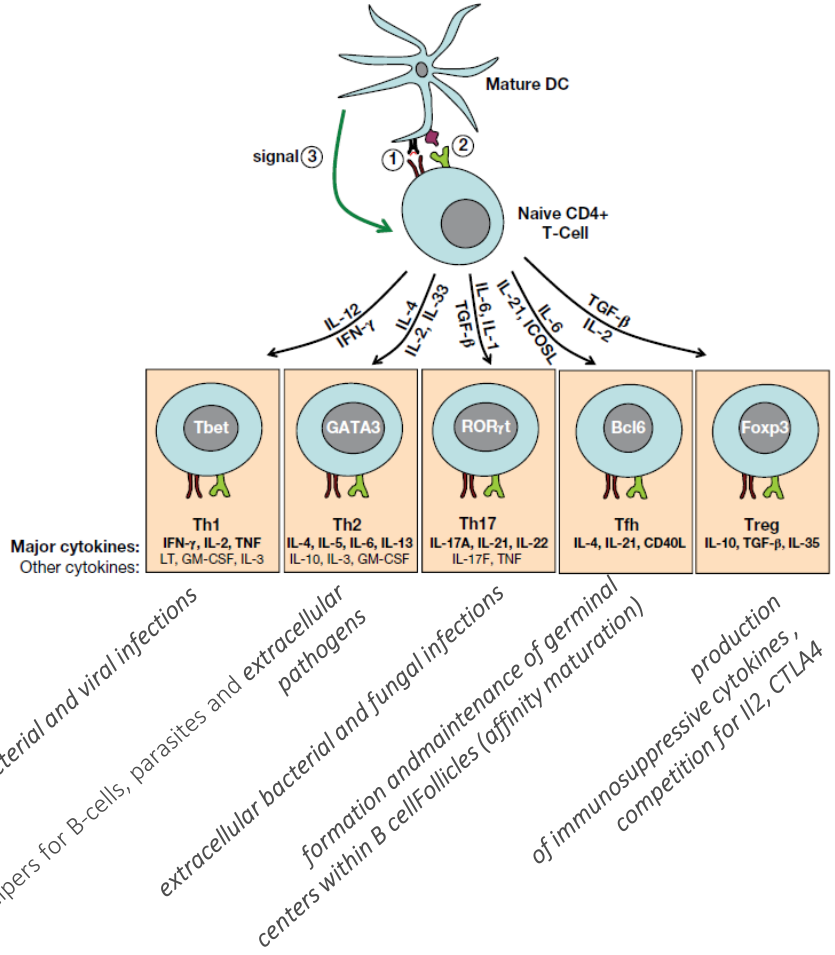
Cell-associated PRRs decode the nature of infection

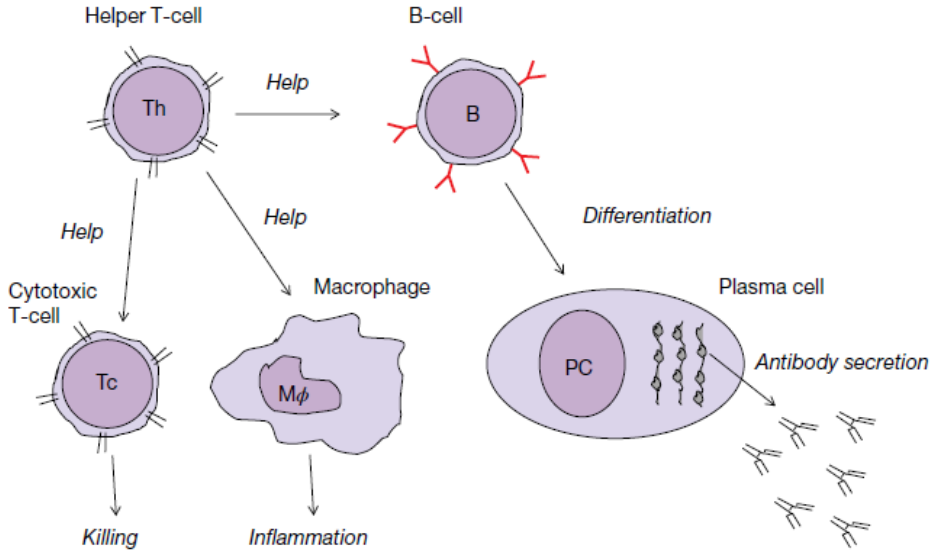
Engagement of several categories of PRR simultaneously may be required for effective immune responses

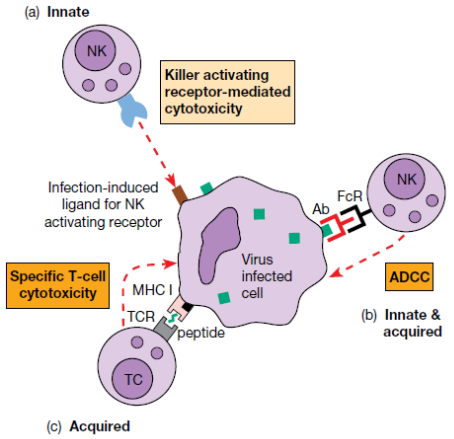
PRR engagement results in cell activation and proinflammatory cytokine production

Adaptative immune response

T-cell polarization







To make a long story short

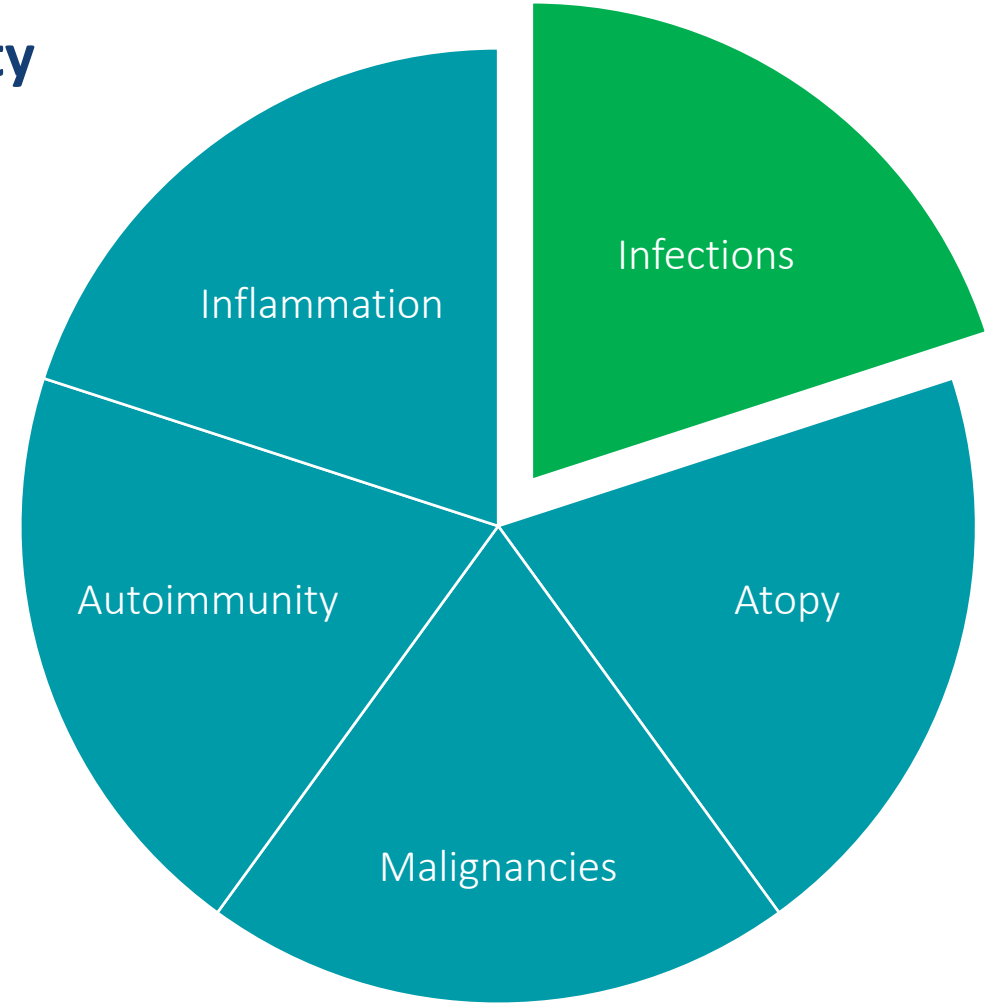
Virus
- T cells
- NK cells
- Antibodies

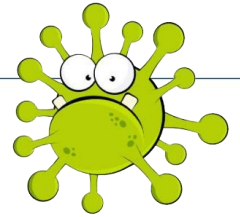
Bacteria
- **Antibodies**
- Complement
- Neutrophiles

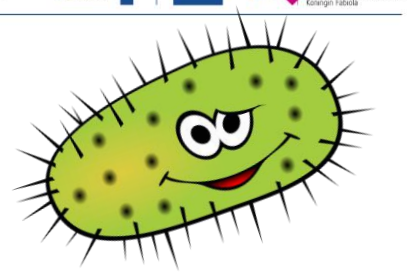
Fungi
- T cells
- Neutrophiles

Inborn errors of immunity

Not just infection susceptibility!







Warning signs…..

Pediatric and adult warning signs

- Four or more new ear infections within 1 year.
- Two or more serious sinus infections within 1 year.
- Two or more months on antibiotics with little effect.
- Two or more pneumonias within 1 year.
- Failure of an infant to gain weight or grow normally.
- Recurrent, deep skin or organ abscesses
- Persistent thrush in mouth or fungal infection on skin.
- Need for intravenous antibiotics to clear infections.
- Two or more deep-seated infections including septicemia.
- A family history of PI.

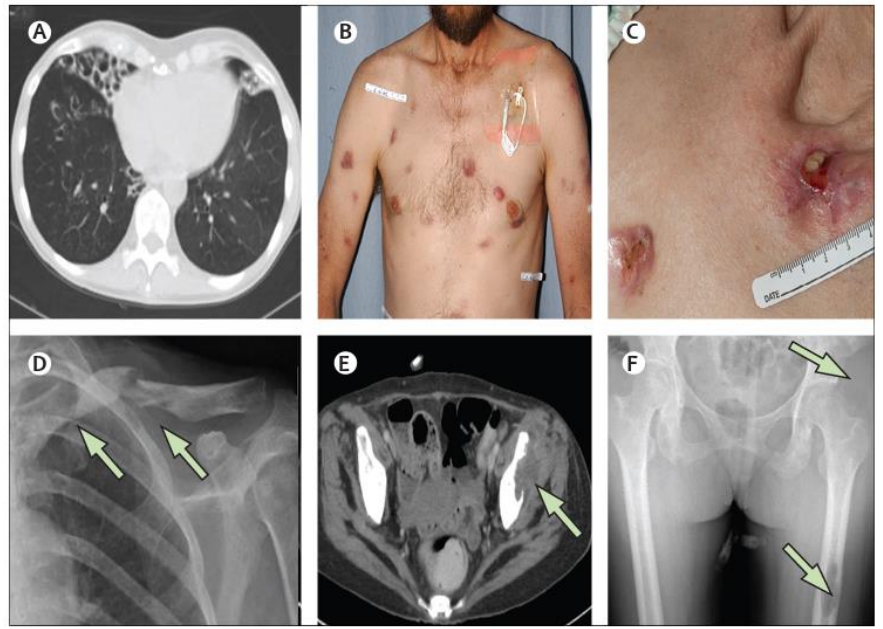
- Four or more infections requiring antibiotics within one year (otitis, bronchitis, sinusitis, pneumonia)
- Recurring infections or infection requiring prolonged antibiotic therapy
- Two or more severe bacterial infections (osteomyelitis, meningitis, septicemia, cellulitis)
- Two or more radiologically proven pneumonia within 3 years
- Infection with unusual localization or unusual pathogen
- PID in the family

Is this an unusual infection?

Severe infectious diseases of childhood and adulthood as monogenic inborn errors of immunity

- Susceptibility to specific infections
  - Mendelian Susceptibility to (not only) Mycobacterial Diseases (MSMD)

	Inheritance	Disease onset	BCG infection	Systemic salmonella infection	Other possible infections	Granuloma formation	Response to antimicrobial therapy	Indication for immunotherapy	Prognosis
Early onset									
IFNGR1/R2									
Complete[16,24,26,30,31]	AR	Infancy/early childhood	Yes	Yes	Listeriosis, herpes virus, respiratory syncytial virus, parainfluenza virus infections, tuberculosis	No	Very poor	No	Poor
Partial[32–39]	AR	Late childhood	Yes	Yes	Tuberculosis	No report	Favourable	Variable	Good
Partial[26,40–42]	AD	Late childhood/ adolescence	Yes	Yes	Histoplasmosis, tuberculosis	Yes	Favourable	Yes	Good
IL12B[43,44]	AR	Infancy/early childhood	Yes (97%)	Yes (25%)	CMC, disseminated tuberculosis, nocardia, *Klebsiella* spp infection	Yes	Favourable	Yes	Fair
IL12RB1[45–48]	AR	Early childhood	Yes (76%)	Yes (43%)	Tuberculosis, CMC (24%), *Klebsiella* spp infection	Yes	Favourable	Yes	Fair
STAT1 LOF									
Complete[49–51]	AR	Infancy (die early without HSCT)	Yes	No	Tuberculosis, fulminant viral infection (mainly herpes)	Yes	Poor	No	Poor
Partial[27,28,52–54]	AR	Infancy/early childhood/ adolescence	Yes	Yes (50%)	Severe, curable viral infection (mainly herpes)	No report	Favourable	Yes	Fair
Partial[55–58]	AD	Infancy/early childhood/ adolescence	Yes	No	Tuberculosis	Yes	Favourable	Yes	Good
IRF8[59]	AR	Infancy	Yes	No	CMC	Poorly formed	Poor	No	Poor
IRF8[59]	AD	Late infancy	Yes	No	No report	Yes	Favourable	No	Good
ISG15[60]	AR	Infancy	Yes	Yes	No report	No report	Favourable	Yes	Good
NEMO[61–64]	XR	Early to late childhood	Yes	No	Invasive Hib infection, tuberculosis	Yes	Variable	Yes	Fair
CYBB[15]	XR	Infancy/early childhood	Yes	No	Tuberculosis	Yes	Fair	No	Fair
Late onset									
GATA2[65–69]	AD	Late childhood/ adulthood	No	No	HPV, CMV, EBV, *Clostridium difficile* infections, histoplamosis, aspergillosis	Yes	Poor	Yes	Poor
Anti-interferon-γ autoantibodies[70–73]	Acquired	Young adult to elderly	No	Yes	*Salmonella* spp, *Penicillium* spp, *Histoplasma* spp, *Cryptococcus* spp, *Burkholderia pseudomallei*, VZV, CMV infections	Yes	Poor	No	Fair



Is this an unusual infection?

Severe infectious diseases of childhood and adulthood as monogenic inborn errors of immunity

VI. Defects in Intrinsic and Innate immunity. (b) Predisposition to Bacterial, Fungal and Parasitic Infections

Predisposition to Invasive Bacterial infections (pyogens):
Meningitis, *sepsis, arthritis, osteomyelitis and abscesses, often in the absence of fever.*

Predominant pathogens (S. pneumoniae, S. aureus and Pseudomonas aeruginosa). Non-invasive bacterial infections (skin infections and upper respiratory tract infections). Improve with age. Routine Usual screening tests are normal. Specific screening tests (lack of proinflammatory cytokine production and CD62L shedding) : available only in specialized clinical immunology laboratories.
IRAK4 def . ***IRAK4*** AR
MyD88 def . ***MYD88*** AR.

Isolated congenital asplenia.
Bacteremia (encapsulated bacteria). No spleen.
RPSA AD.
HMOX* AR. Hemolysis, nephritis, inflammation

IRAK-1 def. *IRAK1 XL.*** Bacterial infections, X-linked MECP2 deficiency-related syndrome due to a large de novo Xq28 chromosomal deletion encompassing both *MECP2 andIRAK1*

TIRAP def. *TIRAP AR.***
Staphylococcal disease during childhood.

Predisposition to Parasitic and Fungal infections

Predisposition to Chronic Mucocutaneous Candidiasis (CMC)
without ectodermal dysplasia

STAT1 GOF. *STAT1* AD. Various fungal, bacterial and viral (HSV) infections, autoimmunity (thyroiditis, diabetes, cytopenias), enteropathy, squamous cell carcinoma and cerabral aneurysms.

IL-17RA deficiency. *IL17RA* AR. Folliculitis. Susceptibility to mucocutaneous *S aureus* (skin and lung) and chronic bacterial infections, abolished responses of fibroblasts to IL-17A, IL-17F.

IL-17RC deficiency*. *IL17RC* AR. Abolished responses of fibroblasts to IL-17A, IL-17F

IL-17F deficiency*. *IL17F* AD. Folliculitis.

ACT1 deficiency*. *ACT1* AR. Blepharitis, folliculitis and macroglossia. Abolished responses of fibroblasts to IL-17A IL-17F

JNK1 haploinsufficiency def*. *MAPK8* AD (haplo-insufficiency). Connective tissue disorder (similar to Ehlers-Danlos syndrome). ↓ Th17 cells ex vivo, in vitro, ↓ responses of fibroblasts to IL-17A, IL-17F

CARD9 def. *CARD9* AR.
Predisposition to Invasive Fungal Diseases.
Invasive candidiasis infection, deep dermatophytoses, other invasive fungal infections.

Trypanosomiasis *APOL1* AD. Trypanosomiasis.

Mendelian Susceptibility to Mycobacterial Disease: MSMD

Severe phenotypes :
Complete IFNGR1 Def and **IFNGR2 Def. *IFNGR1, IFNGR2.***
AR. Serious disseminated BCG and environmental mycobacterial infections (soft tissue, bone marrow, lungs, skin, bones and lymph nodes), *Salmonella* spp., *Listeria monocytogenes* and viruses
IFNG deficiency*. *IFNG* AR LOF.

Moderate phenotypes:
With Susceptibility to *Salmonella*
IL-12 and IL-23 receptor b1 chain def. *IL12RB1* AR.
IL-12p40 (IL-12 and IL-23) def. *IL12B* AR.
IL-12Rb2 deficiency. *IL12RB2 AR***
IL-23R deficiency. *IL23R AR.***
STAT1 LOF *STAT1* (AD)
Partial IFNγR1, *IFNGR1* AR.
Partial IFNγR2, *IFNGR2* AR.
AD IFNGR1 *IFNGR1* AD. Mycobacterial osteomyelitis
SPPL2a deficiency*. *SPPL2A* AR.
Tyk2 deficiency, *TYK2* AR. Susceptibility to viruses, +/- elevated IgE. multiple cytokine signaling defect.
P1104A TYK2 homozygosity MSMD or tuberculosis.

Macrophage gp91 phox def. *CYBB XL*
IRF8 def. *IRF8* AD.
ISG15 def. *ISG15* AR. Brain calcification. IFNg production defect.
IRF8 def. *IRF8* AR. Multiple other infectious agents. Myeloproliferation
RORγt def*. *RORC* AR. Susceptibility to *Candida*. IFNg productiondefect, complete absence of IL-17A/F-producing Tc
JAK1 (LOF)*, *JAK1* AR. Susceptibility to viruses, urothelial carcinoma. ↓ IFNg production.
T-bet def. *TBX21*** AR LOF. Upper airway inflammation

Others

Hydradenitis suppurativa.

PSENEN AD.
NCSTN AD. + acne
PSEN AD. + hyperpigmentation

Acute liver failure due to NBAS def. *NBAS* AR.

Fever induces liver failure

Acute necrotizing encephalopathy.
RANBP2 AD.

Fever induces acute encephalopathy

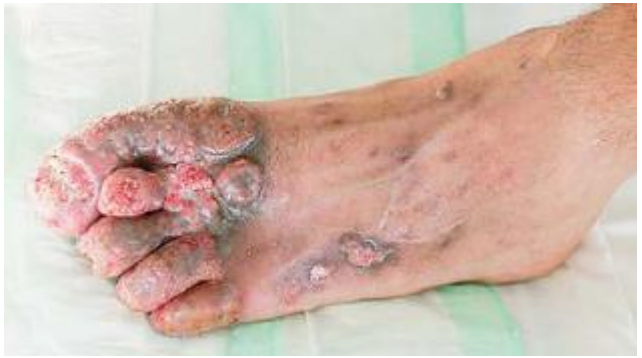
IRF4 haploinsufficiency*.
IRF4 AD.

Whipple's disease

Is this an unusual infection?

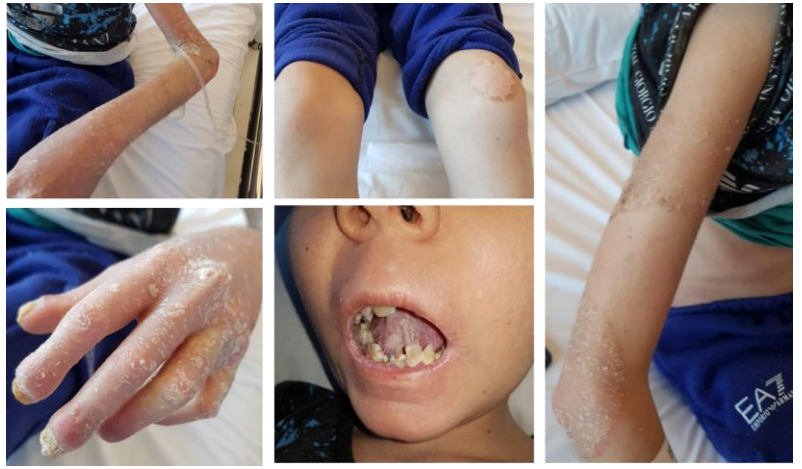
Severe infectious diseases of childhood and adulthood as monogenic inborn errors of immunity

- Opportunistic infections
  - Invasive fungal infections (Aspergillus, Tinea crurum…)



R101C/R101C (CARD9)

  - Chronic mucocutaneous candidiasis

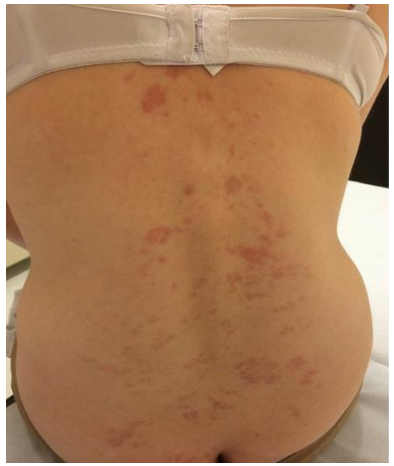


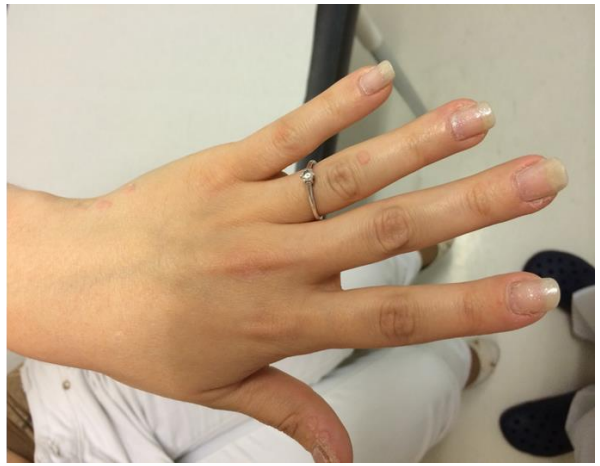
c.863C>T (p.Thr288Ile) (STAT1 GOF)

Is this an unusual infection?

Severe infectious diseases of childhood and adulthood as monogenic inborn errors of immunity

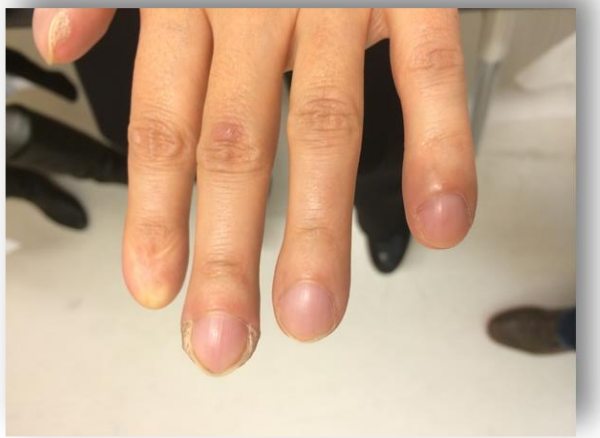
- HPV and warts





Both cases with monocytopenia, myelodysplasia and severe condylomatosis (VIN3, AIN3)

GATA2



Is this an unusual infection?

Severe infectious diseases of childhood and adulthood as monogenic inborn errors of immunity

VI. Defects in Intrinsic and Innate immunity. (a) Predisposition to Viral infection

Predisposition to Herpes simplex Encephalitis

Dominant clinical phenotype is *Herpes simplex* encephalitis (HSE) during primary infection with herpes simplex virus type 1 (HSV1), usually between 3 months and 6 years of age. Incomplete clinical penetrance for all etiologies listed here.
Routine screening tests are normal.
Specific tests examining the TLR3 pathway: marked decrease in the ability of patient's fibroblasts to produce IFN-α and β in response to HSV1 infection.

UNC93B1 (AR), **TRAF3**** (AD), **TICAM1 *(TRIF)**** (AR,AD), ***TBK1**** (AD), ***IRF3**** (AD)

SNORA31* AD. Forebrain HSV-1 encephalitis.

TLR3 (AD,AR) + severe pulmonary influenza, VZV, COVID19.

DBR1* (AR) + other viral infections of the brainstem

Mollaret's meningitis : recurrent lymphocytic meningitis due to HSV2, history of multiple episodes of meningitis.
ATG4A* . AD
MAP1LC3B2*. AD

Predisposition to HPV

Epidermodysplasia verruciformis
HPV group B1 infections and cancer of the skin
EVER1 def. ***TMC6*** AR.
EVER2 def. ***TMC8*** AR.
CIB1 def. ***CIB1*** AR.

WHIM (Warts, Hypogammaglobulinemia, infections, myelokathexis) sd.
CXCR4 AD GOF.
Warts (HPV) infection, neutropenia, low B cell number, hypogammaglobulinemia.

RHOH def.** ***RHOH*** AR.
HPV infection, lung granulomas, molluscum contagiosum, lymphoma. Low naïve T cells, restricted repertoire, poor proliferation to CD3.

Predisposition to Severe Viral Infection

STAT1 def. ***STAT1*** AR LOF. *(+ Mycobacteria)*

STAT2 def*. ***STAT2*** *AR.*
Disseminated vaccine-strain measles

MDA5 def (LOF)*. ***IFIH1*** *AR.*
Rhinovirus and other RNA viruses

IFNAR1 def*. ***IFNAR1*** AR.
Severe disease caused by Yellow Fever vaccine and Measles vaccine

IFNAR2 def*. ***IFNAR2*** AR.
Disseminated vaccine-strain measles, HHV6. No response to IFN-α.

RNA poymerase III def*. ***POLR3A. POLR3C. POLR3F.*** AD. Severe VZV infection.

IRF7 def.** ***IRF7*** AR.
IRF9 def*. ***IRF9*** AR.
Severe influenza disease.

IL-18BP def.** ***IL18BP.*** AR.
Fulminant viral hepatitis

ZNFX1 def. ***ZNFX1.*** AR.
Severe infections by RNA/DNA viruses, mycobacteria; early-onset severe inflammation affecting liver, brain, kidneys, lungs; virally triggered Inflammatory episodes, hepatosplenomegaly, lymphadenopathy

Severe COVID19. ***TLR7*** XL. ***TLR3*** AD, ***UNC93B1*** AD, ***TICAM1*** AD, ***TBK1*** AD, ***IRF3*** AD, ***IRF7*** *AR/AD,* ***IFNAR1*** AR/AD ***and IFNAR2*** AD

CD16 def*. ***FCGR3A*** *AR.*
Severe herpes viral infections, particularly VZV, EBV, and HPV.

CD28 def*. ***CD28*** AR.
Susceptibility to HPV infection. Nl Tc, ↓NKc, Nl Bc. Nl serum IgM,G,A.

NOS2 def.** ***NOS2*** AR.
Severe susceptibility to CMV-induced disease, fatal pneumocystis pneumonia secondary to CMV, apparent intact responses to infection with other herpes viruses (EBV, VZV, HSV). ↓CD4+ Tc; ↓NKc (mostly all immature cells), Nl CD8+ Tc. ↓Bc.

Predominantly antibody deficiencies

UUIS 2022

III. Predominantly Antibody deficiencies. (b) Other Antibody deficiencies

Severe Reduction in Serum IgG and IgA with Normal or elevated IgM and Normal Numbers of Bc : Hyper IgM Syndromes

AID deficiency.
AICDA. AR or AD.
Bacterial infections, enlarged lymph nodes and GC. Nl memory Bc, but lacking somatic hypermutation in AR form.

UNG deficiency. ***UNG*** *AR.*
Enlarged lymph nodes and germinal centers.

MSH6 def. ***MSH6*** *AR.*
Family or personal history of cancer. Variable IgG, defects, increased IgM in some, Nl Bc, low switched memory Bc.

INO80 def*. ***INO80*** *AR.*
Severe bacterial infections.

Isotype, Light Chain, or Functional Deficiencies with Generally Normal Numbers of Bc

Selective IgA deficiency. ***Unknown.***
May be asymptomatic. Bacterial infections, autoimmunity mildly increased. Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies.

Transient hypogammaglobuliemia of infancy. Unknown.
Usually not associated with significant infections, normal ability to produce antibodies to vaccine antigens. IgG and IgA decreased.

IgG subclass deficiency with IgA deficiency. ***Unknown.***
Recurrent bacterial infections. May be asymptomatic. Reduced IgA with decrease in one or more IgG subclass.

Isolated IgG subclass deficiency. ***Unknown.***
Usually asymptomatic, a minority may have poor antibody response to specific antigens and recurrent viral/bacterial infections. Reduction in one or more IgG subclass.

Specific antibody deficiency with normal Ig levels and normal B cells. ***Unknown.***
Reduced ability to produce antibodies to specific antigens. Ig: Nl.

Ig heavy chain mutations and deletions.
Mutation or chromosomal deletion at 14q32 AR.
May be asymptomatic. One or more IgG and/or IgA subclasses as well as IgE may be absent.

Selective IgM deficiency. ***Unknown.*** Pneumococcal / bacterial infections. Absent serum IgM.

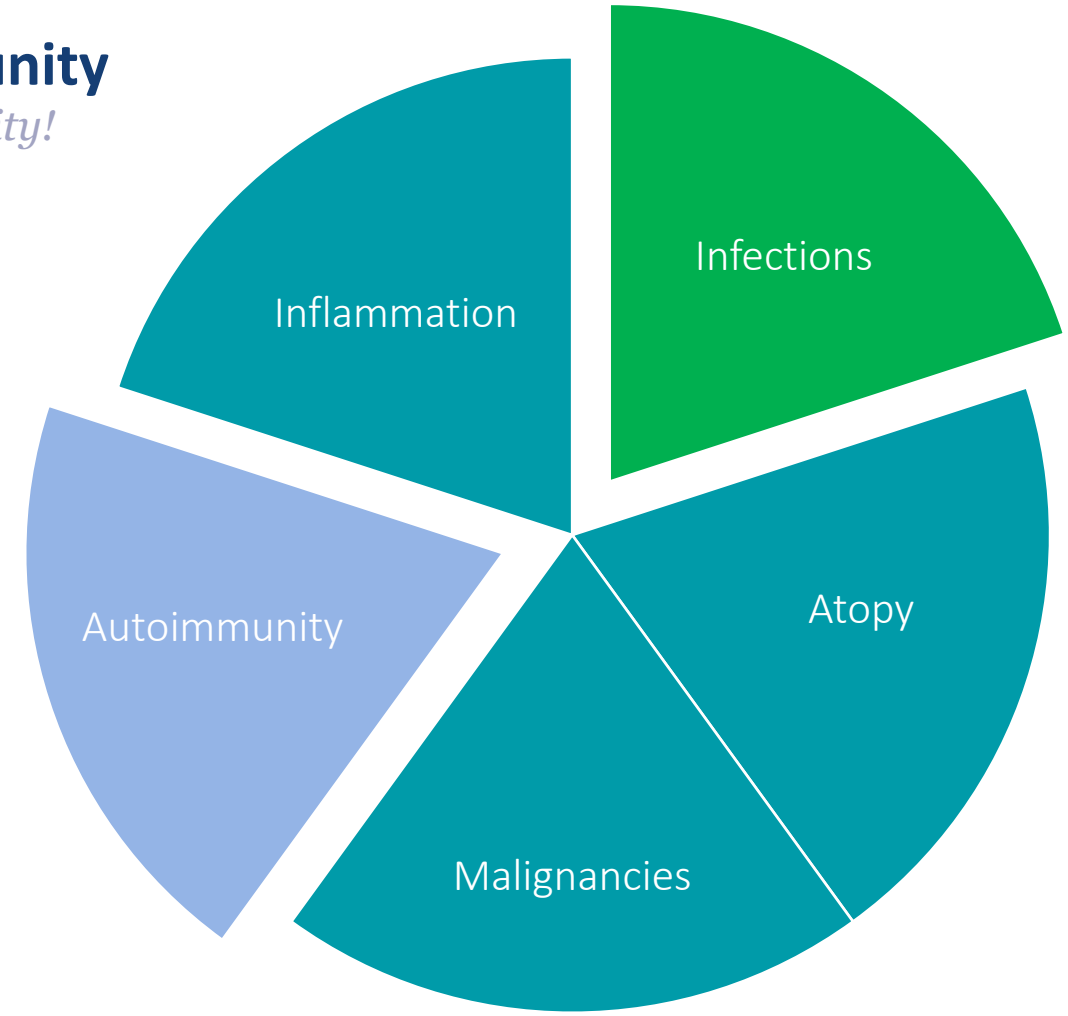
Kappa chain deficiency*. ***IGKC*** *AR.*
Asymptomatic. All immunoglobulins have lambda light chain.

High Bc numbers due to constitutive NF-κB activation

CARD11 GOF . ***CARD11.*** AD GOF .
BENTA syndrome.
Splenomegaly, lymphadenopathy, poor vaccine responses.

Inborn errors of immunity

Not just infection susceptibility!



Infections are not the only warning signs

Autoimmunity is part of some inborn errors of immunity

- Immune dysregulation in many primary immunodeficiency syndromes leads to autoimmune disease manifestations
- Mutations in various genes can lead to immunodeficiencies, as well as to autoimmunity
- Specific knowledge of these genetic alterations and their pathophysiological consequences will enable the development of new therapeutic approaches
- Knowledge of primary immunodeficiency syndromes will enable a better understanding of potential infection-related adverse events when DMARDs are usedto treat rheumatic diseases

Schmidt RE, Grimbacher B, Witte T. Autoimmunity and primary immunodeficiency: two sides of the same coin? Nat Rev Rheumatol. 2017;14(1):7-18

Autoimmunity and inflammation

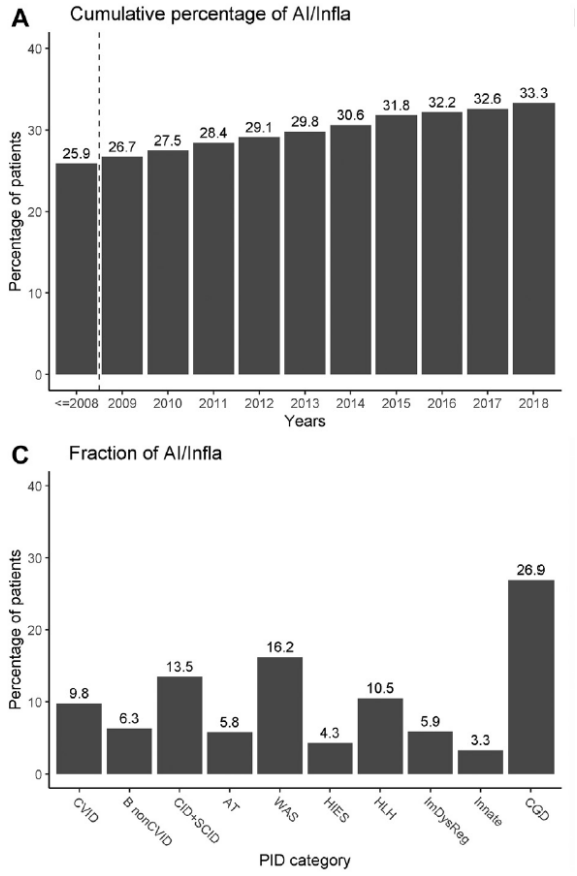


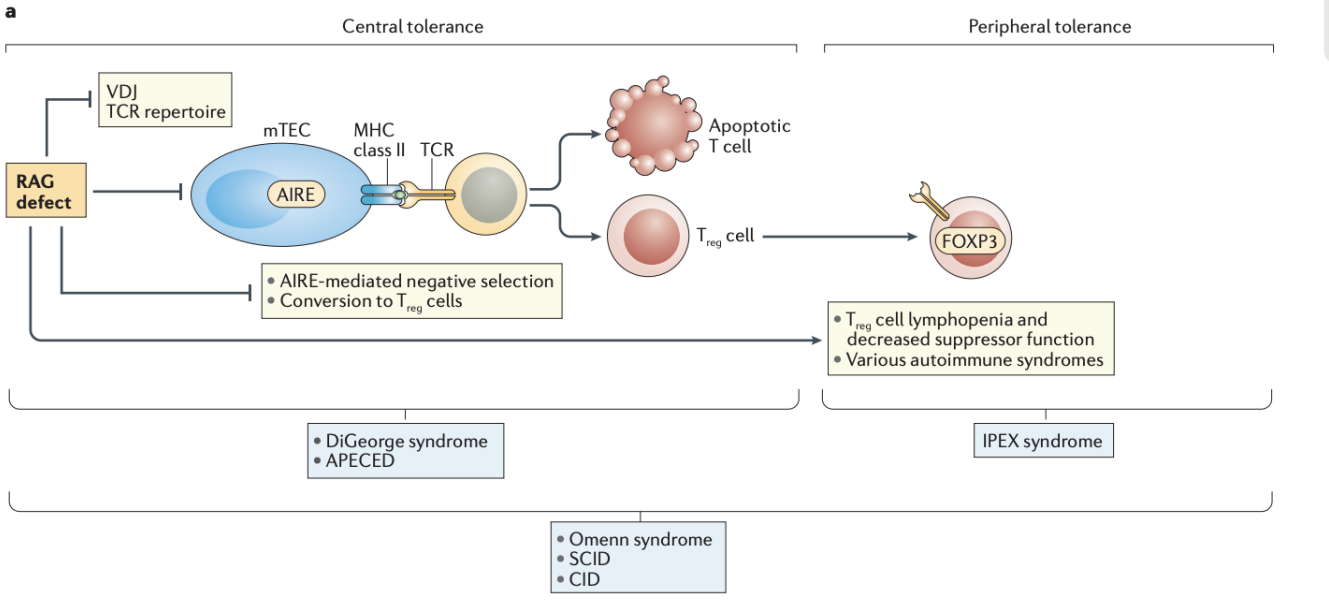
TABLE III. The relative risk of autoimmune disease in patients with PID

	Prevalence per 1 × 10^5 patients with PIDs	Prevalence per 1 × 10^5 of the general population	Relative risk
Cytopenia	12,000	100	120
Autoimmune hemolytic anemia (children, France)†	2,500	3	830
Immune thrombocytopenia (France)‡	6,000	100	60
Rheumatologic disorders*	5,000	860	6
Rheumatoid arthritis (children, France)§	800	20	40
Inflammatory bowel disease (adults, France)‖	7,800	180	43
Inflammatory bowel disease (children, France)‖	5,500	70	80
Skin*	6,000	600	10
Endocrine disorders*	3,000	1,000	3
Eye*	700	100	7
Kidney*	500	63	8
Vasculitis and other systemic disorders*	250	17.5	13
Neurologic disorders*	400	130	3

Fischer A et al. J Allergy Clin Immunol 2017
Alligon M et al. . J Allergy Clin Immunol. 2022 Jun;149(6):2116-2125. doi: 10.1016/j.jaci.2021.12.790.

Basic immunology to understand

Immune pathway	Gene(s)	Syndrome(s)
T cell development and tolerance	• *RAG1* and *RAG2* • *RAG1*, *RAG2* and *DCLRE1C* • *AIRE* • *FOXP3*	• SCID, CID and CVID • Omenn syndrome • APECED • IPEX and IPEX-like syndromes



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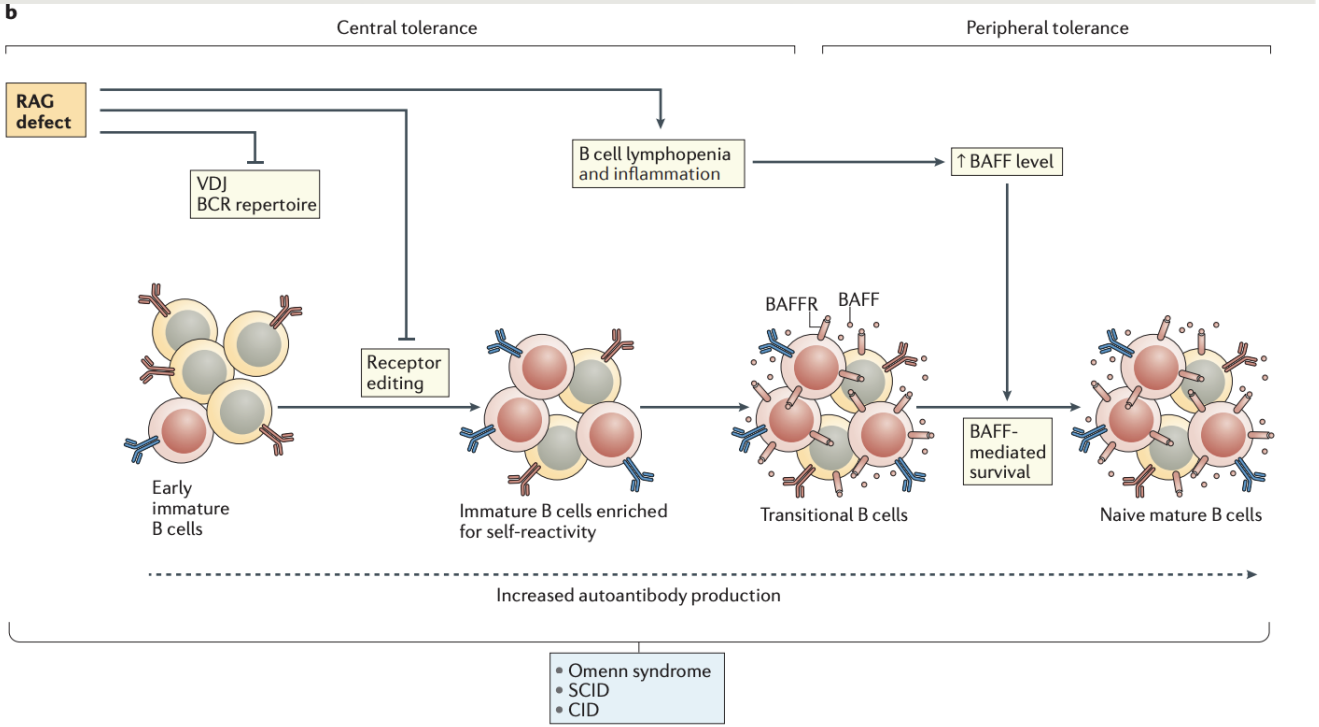


Diseases of immune dysregulation

IV. Diseases of immune dysregulation. (b) Syndromes with Autoimmunity and Others

Syndromes with Autoimmunity

ALPS: Autoimmune Lymphoproliferative Sd *Chronic adenopathy Splenomegaly, defective lymphocyte apoptosis.*

ALPS-FAS. ***TNFRSF6***. AD or AR. Autoimmune cytopenias, increased lymphoma risk, Nl/increased IgA/IgA, elevated serum FasL, IL-10, vitamin B12.

ALPS-FASLG. ***TNFSF6.AR.*** Autoimmune cytopenias, SLE, soluble FasL is not elevated

ALPS-Caspase10*. ***CASP10.*** AD.

Regulatory T Cell Defects ?

No

APECED : Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APS-1) . *AIRE.* AR/ AD. Hypoparathyroidism hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction and other endocrine abnormalities, chronic mucocutaneous candidiasis, dental enamel hypoplasia, alopecia, enteropathy, pernicious anemia.

FADD deficiency.* *FADD.* AR. Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction.

JAK1 GOF. *JAK1.*** AD GOF. HSM, eosinophilic enteritis, thyroid disease, viral infections. Eosinophilia,

Caspase 8 def*. *CASP8.* *AR.* Bacterial/viral infections, Hypogamma, defective lymphocyte activation. Slightly increased DNT cells.

PDCD1 deficiency. *PDCD1.*** AR. Tuberculosis, autoimmunity (T1D, hypothyroidism and JIA), fatal pulmonary autoimmunity, HSM, ↑IgG/IgA, anti-insulin autoAb. Mildly lymphopenia. ↑DNT. Nl Bc.

ITCH deficiency. *ITCH.* *AR.* Early-onset chronic lung disease (interstitial pneumonitis), thyroiditis, type I diabetes, chronic diarrhea, enteropathy, and hepatitis, developmental delay, dysmorphic facial features.

Prolidase deficiency. *PEPD.* AR. Chronic skin ulcers, eczema, infections. Auto-abs common.

SOCS1 deficiency. *SOCS1.* AD (haploinsufficiency) Recurrent bacterial infections, severe multisystemic autoimmunity, ITP, AIHA, SLE, GN, HSM, psoriasis, arthritis, thyroiditis, hepatitis, risk of COVID19/MIS-C, neutropenia, lymphopenia, incomplete penetrance. ↓CD4/CD8 Tc. ↑naïve Bc; ↓sw memory.

Tripeptidyl-Peptidase II Deficiency. *TPP2.*** *AR.* Variable lymphoproliferation, severe autoimmune cytopenias, hypergamma, recurrent infections. Decreased Tc and Bc.

Yes

IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked. *FOXP3* XL. Autoimmune enteropathy, early onset diabetes, thyroiditis hemolytic anemia, thrombocytopenia, eczema, ↑IgE/IgA. Lack and/or impaired function of $CD4^+$ $CD25^+$ $FOXP3^+$ Tregs.

LRBA deficiency. *LRBA.* AR. Recurrent infections, inflammatory bowel disease, autoimmunity. ↓IgG/IgA in most. ↓ or Nl Bc. ↓ or Nl CD4 numbers, Tc dysregulation.

STAT3 GOF mutation. *STAT3.* AD. Lymphoproliferation, solid organ autoimmunity, recurrent infections. Enhanced STAT3 signaling, leading to increased Th17 cell differentiation, lymphoproliferation and autoimmunity. ↓ Tregs and impaired function. ↓ Tc and Bc.

FERMT1 deficiency. *FERMT1* AR. Dermatosis (congenital blistering, skin atrophy, photosensitivity, skin fragility, and scaling). Intracellular accumulation of IgG, IgM, IgA, and C3 in colloid bodies under the basement membrane

IKAROS GOF*. *IKZF1.* AD GOF. Multiple autoimmune features (diabetes, colitis, thyroiditis), allergy, lymphoproliferation, Evans Syndrome, recurrent infections. Normal/mildly decreased Bc.

CTLA4 deficiency (ALPSV). ***CTLA4*** AD. Autoimmune cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration recurrent infections . Impaired function of Tregs. ↓ Tc and Bc.

BACH2 deficiency. *BACH2* AD. Lymphocytic colitis, sinopulmonary infections. Impaired memory Bc development. Progressive Tc lymphopenia.

CD25 deficiency*. *IL2RA* AR. Lymphoproliferation, autoimmunity, impaired Tc proliferation. No CD4+C25+ cells with impaired function of Tregs cells.

CD122 deficiency. *IL2RB* AR. Lymphoproliferation, lymphadenopathy, HSM, AIHA, dermatitis, enteropathy. Hypergamma, viral (EBV, CMV) infections

DEF6 deficiency*. *DEF6* AR. HSM, enteropathy, cardiomyopathy, recurrent infections. ↓Tc, ↓ or Nl Bc.

Immune Dysregulation with Colitis

IL-10R def. AR. Folliculitis, recurrent respiratory diseases, arthritis, lymphoma.
IL10RA Leukocytes unresponsive to IL-10.
IL10RB. Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29

RIPK1 def. *RIPK1.* AR. Reccurrent infections, progressive polyarthritis. Low Tc , low or nl Bc.

IL-10 def*. *IL10.* AR. Folliculitis, recurrent respiratory diseases, arthritis. No functional IL-10 secretion.

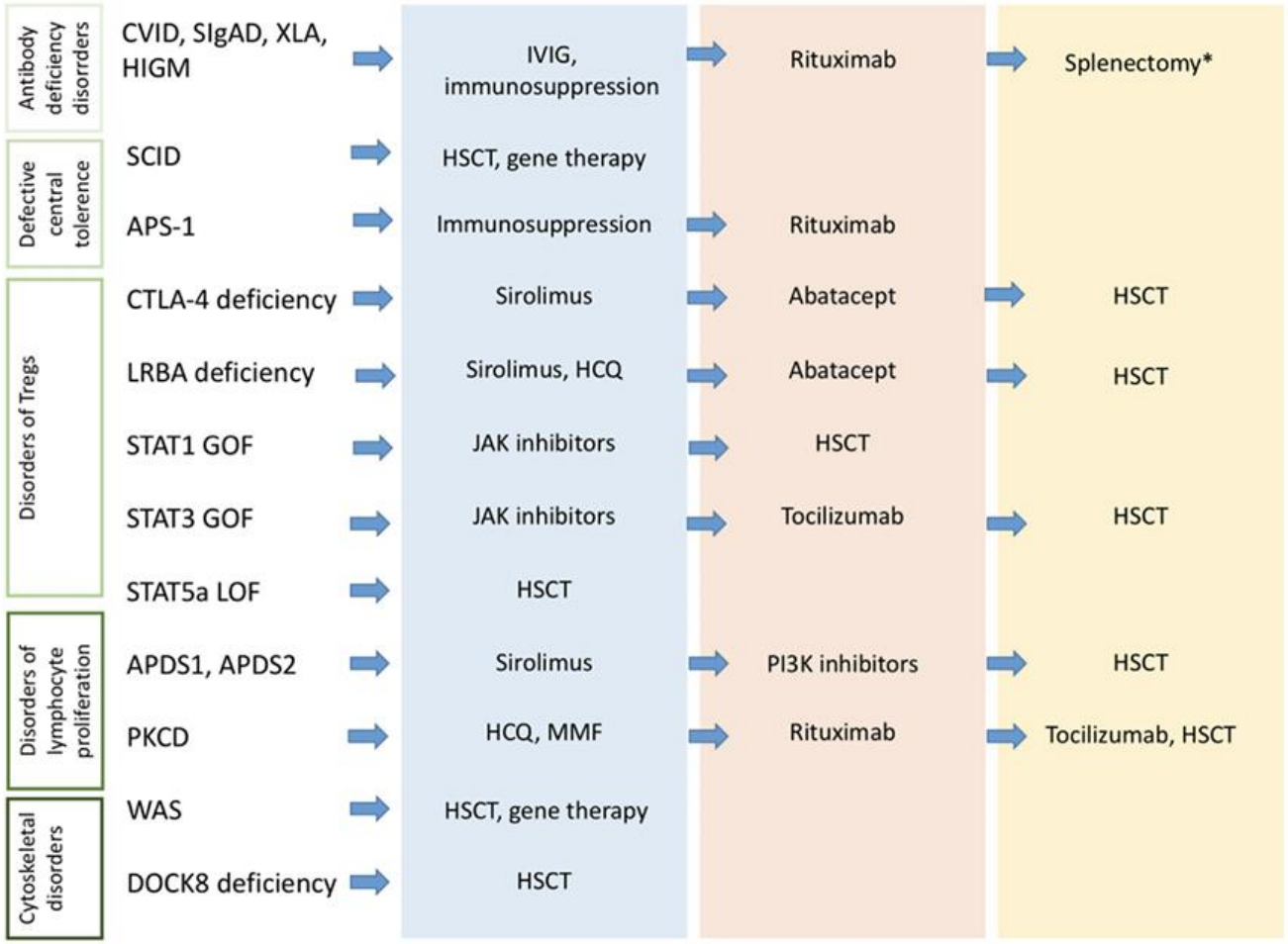
TGFB1 def*. *TGFB1.* AR. Recurrent viral infections, microcephaly, and encephalopathy. Decreased T cell proliferation in response to anti-CD3

ELF4 def*. *ELF4 .* XL. Early onset mucosal autoinflammation/ IBD, fevers and ulcers, hyper inflammatory macrophages. Nl IgM, G, A. ↓responses to live viral vaccines. Nl Tc and Bc.

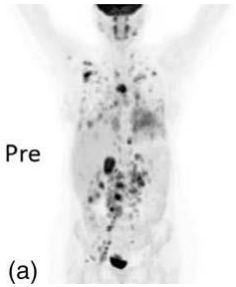
NFAT5 haploinsufficiency. *NFAT5.*** AD. Recurrent Sinopulmonary infections. Decreased memory Bc and plasmablasts.

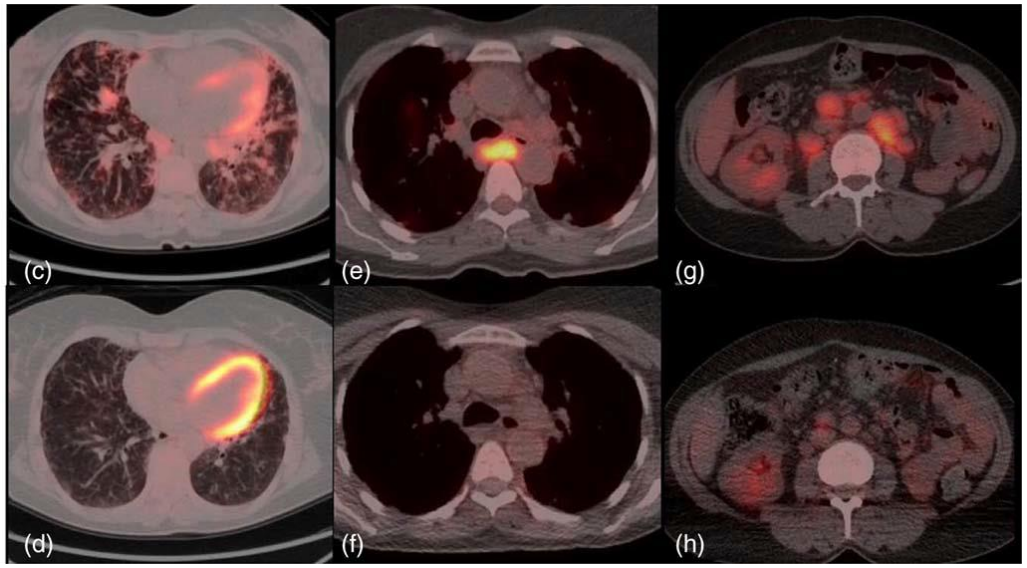
IL21 def. *IL21* AR. Severe early onset colitis. Tc : NL / low function. Hypogamma-globulinemia, poor specific antibody responses;↑ IgE

Therapeutics



Granulomatous lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID)



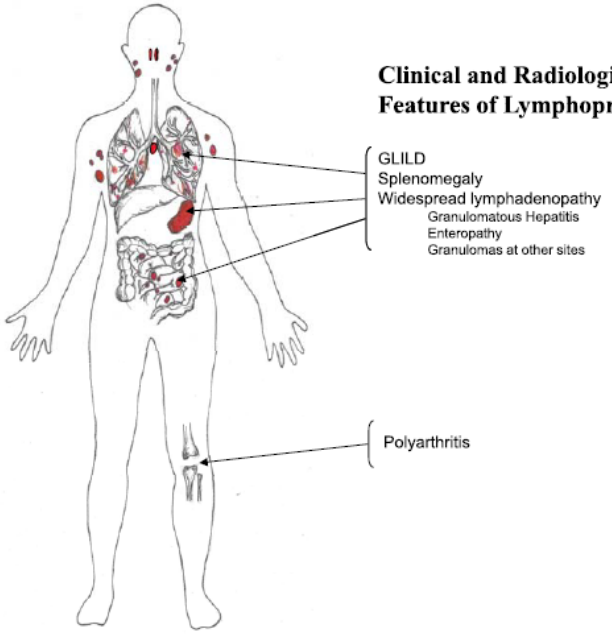


Laboratory biomarkers of GLILD and Lymphoproliferation

Elevated IgM
Suboptimal IGRT
Inversely related to IgA
Episodes of thrombocytopenia
Elevated β-2 microglobulin (>3mg/ml)
(sIL-2R is a similar marker)

B cell biomarkers
Low smB- <2%
$IgD^{-}IgM^{+}CD27^{+}$ of $CD19^{+}$ B cells
Expansion of transitional B cells
(Tr^{hi} >9% $CD38^{hi}IgM^{hi}$)
$CD21^{low}$ B cells (> 10% of B cells)

T cell biomarkers
CD4 T cells < 200 x 10^{6} cells/l*
Reduced niave CD4 T cells*
Reduced Regulatory T cells



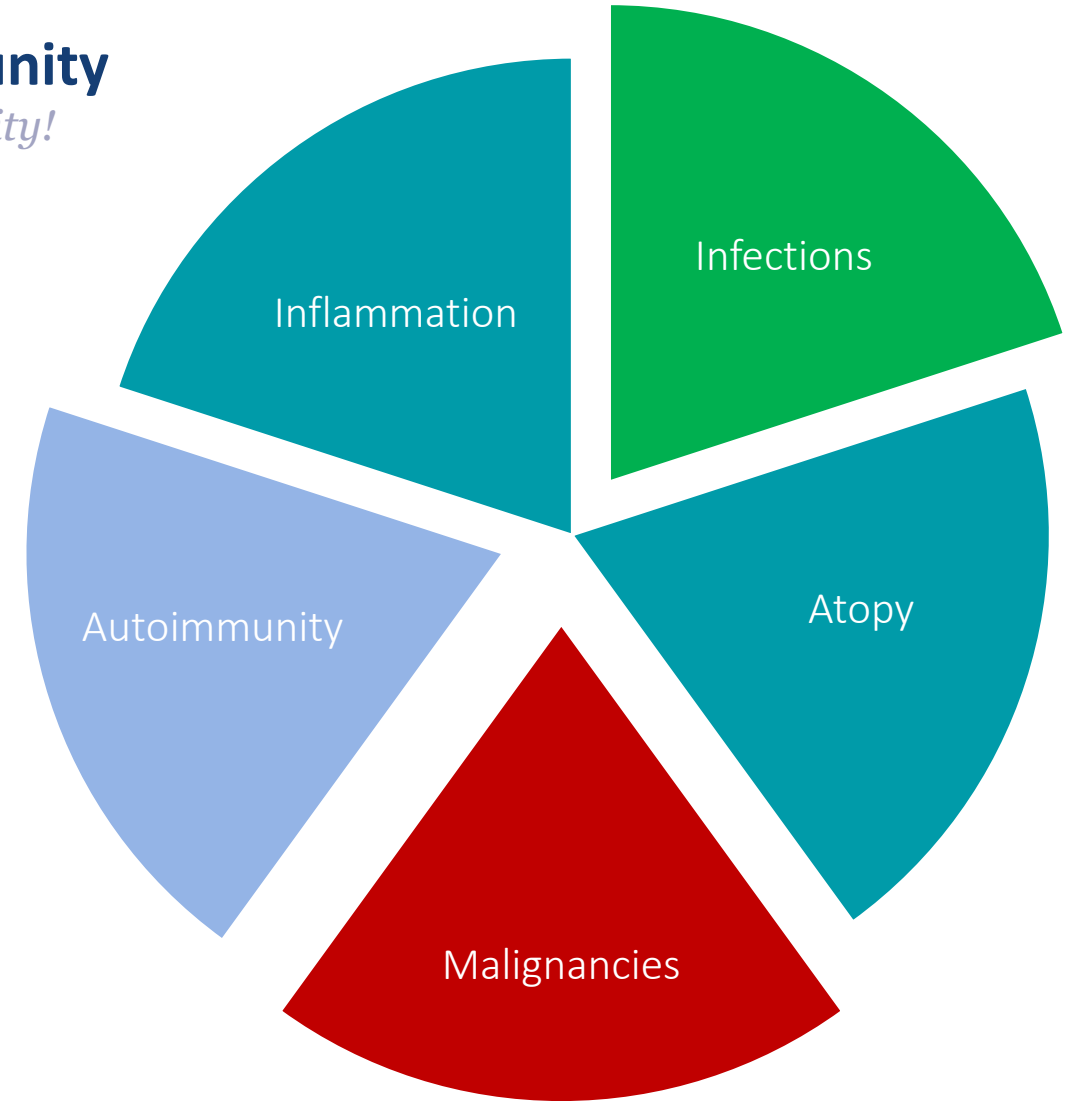
Clinical and Radiological Features of Lymphoproliferation

GLILD
Splenomegaly
Widespread lymphadenopathy
Granulomatous Hepatitis
Enteropathy
Granulomas at other sites

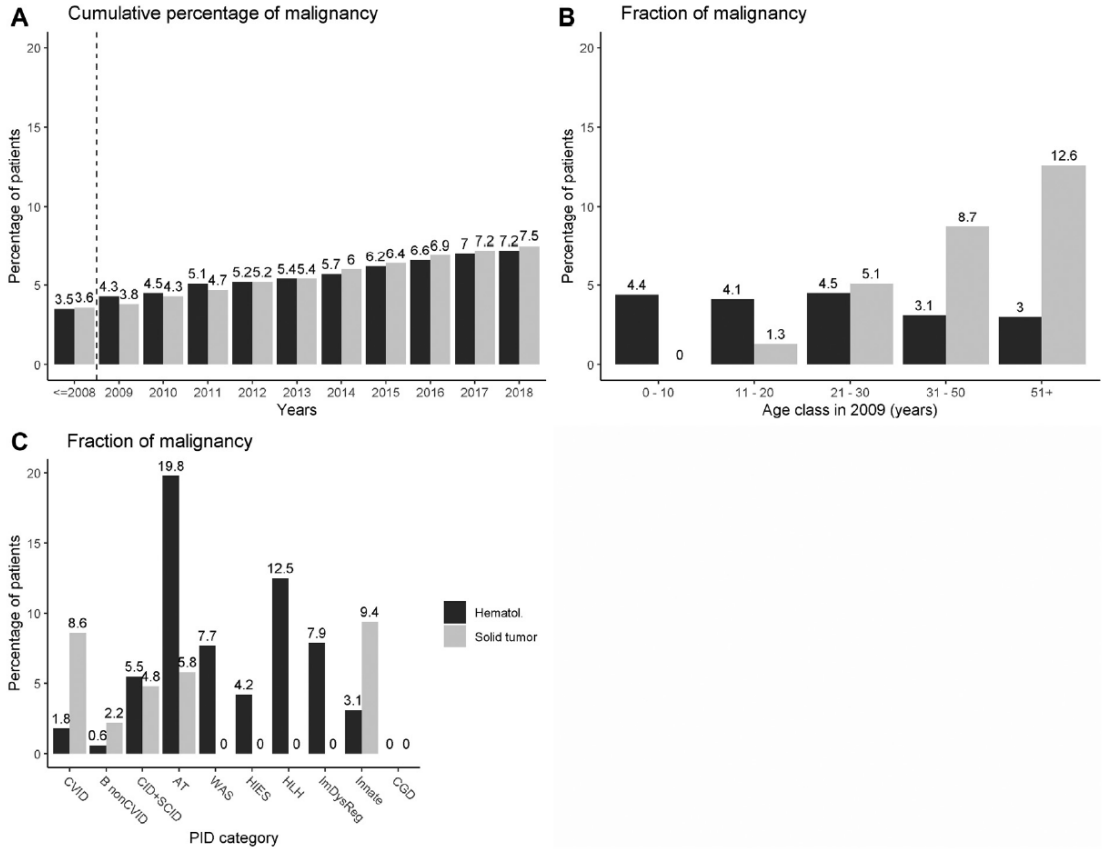
Polyarthritis

Inborn errors of immunity

Not just infection susceptibility!



Malignancy in PID



1151 patients

Most patients experienced a single malignancy.

Malignancies occurred at all ages and in all PID categories

PID categories with the highest frequency of malignancies were

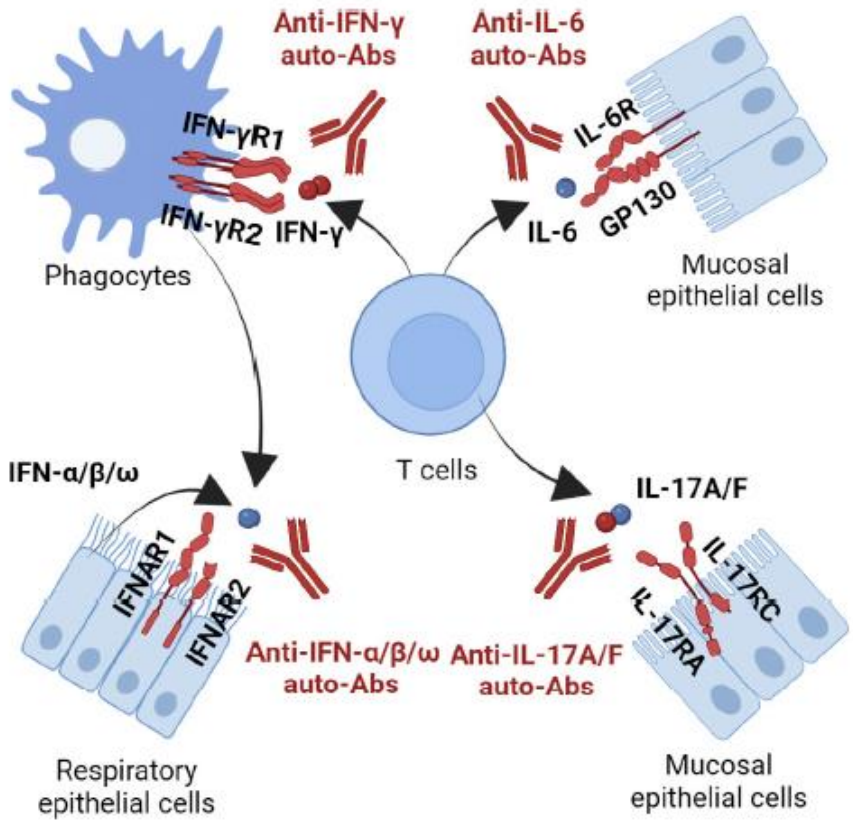
B-cell deficiencies (both CVID and non-CVID)

Ataxia telangiectasia

Phenocopies of inborn errors of immunity

Table 1. **Inborn errors of cytokines or their receptors, their corresponding autoimmune phenocopies (anti-cytokine auto-Abs), and monoclonal antibodies used in therapeutics, together with the associated infectious phenotypes**

Cytokine	Receptor of cytokine	Inborn error of immunity	Main infectious disease	Phenocopies (auto-Abs)	Infectious disease	Therapeutic with monoclonal Abs	Infectious disease
Type II IFN (IFN-γ)	IFN-γR1 IFN-γR2	*IFNG* *IFNG-R1* *IFNGR2*	- Disseminated *M. bovis*–BCG disease - Disseminated environmental mycobacteria disease	Auto-Abs to IFN-γ	- Disseminated environmental mycobacteria disease - Disseminated *tuberculosis* - Salmonellosis	- Emapalumab - Fontolizumab - AMG811	- Disseminated histoplasmosis - Disseminated salmonellosis
Type I IFNs (IFN-α/β)	IFNAR1 IFNAR2	*IFNAR1* *IFNAR2*	- Herpes virus encephalitis - Severe influenza - Yellow fever - Life-threatening COVID-19 pneumonia	Auto-Abs to IFN-α2, other IFN-α, IFN-β, IFN-ω	- Life-threatening COVID-19 pneumonia - Yellow fever vaccine disease	- Sifalimumab/ MEDI545 - Rontalizumab/ RG-7415 - AGS-009 - S95021/19D11 -Anifrolimab/ MEDI-546	- Respiratory tract infections - Herpes zoster
IL-17A IL-17F	IL-17RA IL-17RC	*IL17F* *IL17RA* *IL17RC*	Chronic mucocutaneous candidiasis	Auto-Abs to IL-17A, IL-17F	- Chronic mucocutaneous candidiasis	- Secukinumab/ AIN457 - Ixekizumab/ LY2439821 - Brodalumab/ AMG 827 - Bimekizumab	- Chronic mucocutaneous candidiasis
IL-6	IL-6R GP130/ IL6ST	*IL6R* *IL6ST*	Staphylococcal cutaneous infections	Auto-Abs to IL-6	- Staphylococcal cutaneous infections	- Tocilizumab - Sarilumab - Satralizumab - Sirukumab - Siltuximab	- Staphylococcal cellulitis - Pneumonia by *S. aureus*
GM-CSF[a]	CSF2RA CSF2RB	*CSF2RA* *CSF2RB*	- Nocardiosis? - Cryptococcosis?	Auto-Abs to GM-CSF	- Pulmonary and extra-pulmonary cryptococcosis - Pulmonary and extra-pulmonary nocardiosis	- Lenzilumab - Namilumab - Gimsilumab - Otilimab - Mavrilimumab	- Nasopharyngitis without microbe isolation



Inborn errors of immunity: non mendelian inheritance

Conclusion

- 1 gene ➔ Different phenotype
- 1 phenotype ➔ different genes
- Incomplete penetrance
- Variable expression

- Only 30% with a documented genetic defect

Inborn errors of immunity: non mendelian inheritance

Hereditary Angioedema

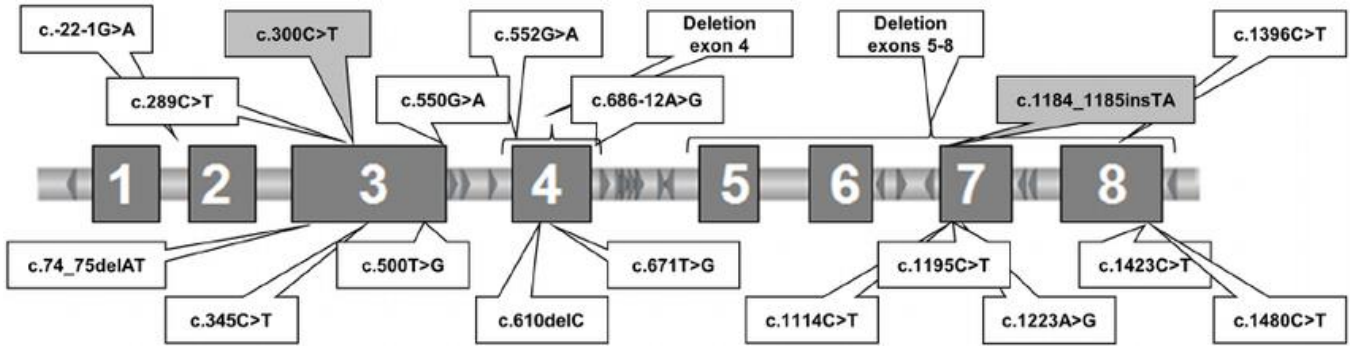
Prof JC Goffard
Hôpital Universitaire de Bruxelles
Médecine interne
Unité de traitement,des immunodéficiences

Hereditary Angioedema (HAE) and Targets for Available Therapy.

Deficiency of functional C1 inhibitor (due to a mutation in SERPING1)

C1-Inh regulates multiple proteases involved in

- Complement
- contact-system
- Coagulation
- fibrinolytic pathways



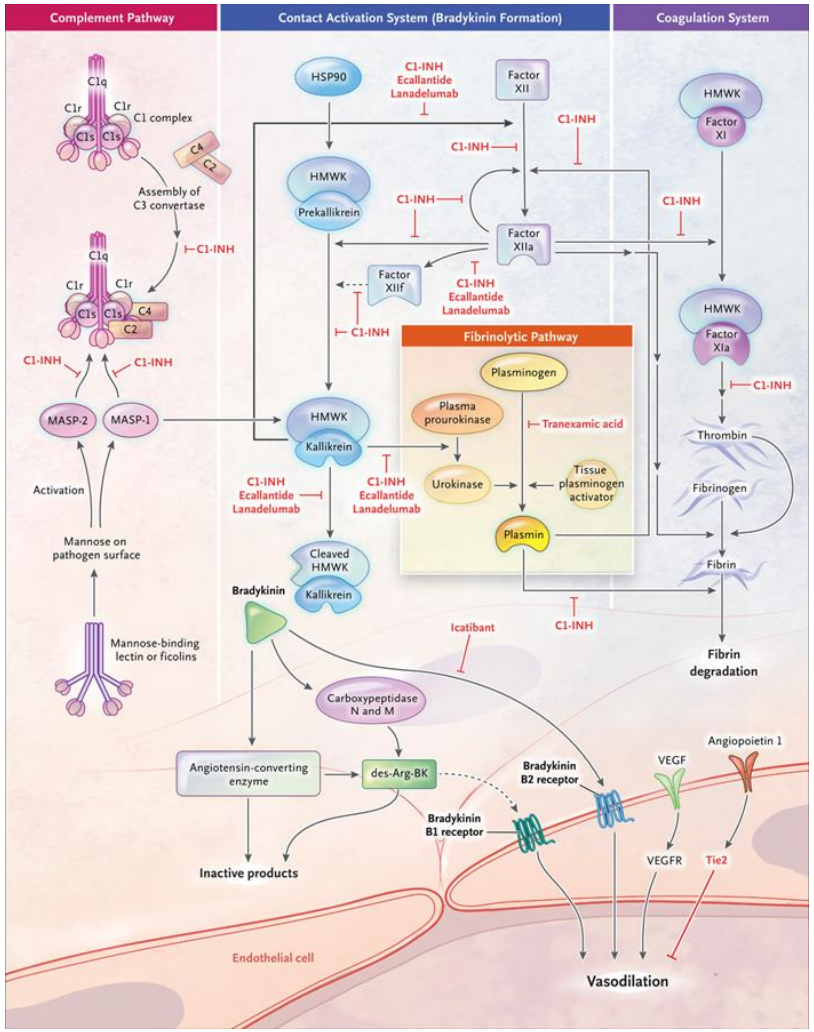


Table 1. Clinical and Laboratory Features of Bradykinin-Mediated Angioedema, According to Type.*

Variable	HAE-C1-INH†	HAE-nl-C1-INH‡	INHA	Acquired C1-INH Deficiency	ACE-Inhibitor–Induced HAE
Clinical features	Recurrent cutaneous and submucosal angioedema without urticaria Attacks prolonged (>48 hr) Physical prodrome of erythema marginatum in approximately one third of patients	Phenotypic presentation similar to HAE-C1-INH Absence of erythema marginatum Rare cutaneous hemorrhage May have more disease-free intervals than with HAE-C1-INH	Similar to HAE-C1-INH	Phenotypic presentation similar to HAE-C1-INH Associated antibodies to C1-INH§ Cancer (e.g., non-Hodgkin's B-cell lymphoma)§	More common in blacks and smokers Less common in patients with diabetes
Genetic features	AD, full penetrance Approximately 75% of patients have positive family history; 25% have de novo mutation (no family history)	AD, incomplete penetrance, female predominance (males can be silent carriers, particularly in subtype HAE-XII)	None	None	None
Attack location	Extremity and abdominal attacks more frequent than facial attacks	Facial attacks most frequent, then extremity attacks, then abdominal attacks More cutaneous and abdominal attacks in subtype HAE-FXII than in HAE-U Characteristic tongue swelling in subtype HAE-PLG	Face and periorbital areas	Facial attacks most frequent, followed by peripheral, abdominal, and oral attacks	Head (tongue) and neck
Age at onset	Childhood or young adulthood, worsening in puberty	Usually after childhood	Usually about 30–40 yr	Usually >40 yr	Usually >40 yr
Triggers	Often unpredictable; stress, trauma, infection, estrogen, fatigue	Often unpredictable; stress, trauma, infection, estrogen, fatigue; greater influence of estrogen in HAE-FXII than in HAE-U	Unknown	May be affected by underlying disorder Often unpredictable; stress, trauma, infection, estrogen, fatigue	ACE-inhibitor use; ARBs are usually associated with an acceptable side-effect profile
C4	Decreased	Normal	Normal	Decreased more than with HAE-C1-INH	Normal
Antigenic C1-INH	Subtype I, decreased; subtype II, normal	Normal	Normal	Decreased or normal	Normal
Functional C1-INH	Decreased	Normal	Normal	Decreased	Normal
C1q	Normal¶	Normal	Normal	Normal or decreased‖	Normal
C3	Normal	Normal	Normal	Normal or decreased	Normal

* Information in the table is modified from Wu et al.[30] ACE denotes angiotensin-converting enzyme, AD autosomal dominant, ARB angiotensin-receptor blocker, C1-INH C1 inhibitor, HAE hereditary angioedema, HAE-C1-INH HAE with low functional C1-INH, HAE-FXII HAE with coagulation factor XII mutation, HAE-KNG1 HAE with kininogen-1 mutation, HAE-nl-C1-INH HAE with normal C1-INH, HAE-PLG HAE with plasminogen mutation, HAE-U HAE with unknown mutation, and INHA idiopathic nonhistaminergic angioedema.
† Subtypes are HAE type I and HAE type II.
‡ Subtypes are HAE-U, HAE-FXII, HAE-PLG, HAE-ANGPT-1, and HAE-KNG1.
§ This feature is seen in some patients and should therefore be included in the evaluation.
¶ On rare occasions, a decrease in homozygous HAE occurs.[31-33]
‖ C1q may be normal in some patients.

Table 2. Diagnosis of Hereditary Angioedema with Normal C1 Inhibitor Levels.

Consensus criteria*

History of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema
Normal or near-normal C4 level and C1 inhibitor antigen level and function
Documented lack of response to high-dose antihistamines (e.g., second-generation antihistamines given 4 times/day)
Either a known genetic mutation (factor XII, angiopoietin-1, plasminogen, or kininogen-1) or a family history of angioedema†

Supportive data

History of no response to epinephrine and glucocorticoids
History of prompt and durable responses to a bradykinin-targeted medication‡
Documented, visible angioedema or, in patients with predominantly abdominal symptoms, evidence of bowel-wall edema identified by computed axial tomography or magnetic resonance imaging§

Emerging biomarkers

Threshold-stimulated kallikrein activity¶

* All four criteria must be met. If there is no family history and no biomarker has been determined, compelling supportive data may suggest the diagnosis.
† Mutational analysis for plasminogen, angiopoietin-1, and kininogen-1 is available only at a limited number of research facilities.
‡ Prompt, durable responses are those that occur within 30 to 120 minutes after administration of the medication and that last for more than 6 hours.
§ Ultrasonography could be used, although it is less sensitive. In the case of negative findings, we recommend computed axial tomography or magnetic resonance imaging.
¶ The assay for this biomarker has been described by Li et al.[44]

Gene to be tested in Normal C1 inhibitors level

Autosomal dominant inheritance pattern with incomplete penetrance.

Men can be silent carriers of the disease.

Hormonal influences of pregnancy or exogenous estrogens may be pronounced, particularly in patients who have HAE with a factor XII mutation.

- factor XII
- angiopoietin-1
- Plasminogen
- kininogen-1 heavy chain
- unknown genetic mutation

Treatment

Table 3. First-Line Treatments for Hereditary Angioedema with C1 Inhibitor Deficiency.*

Drug (Trade Name, Manufacturer)	Approved Indications†	Dose	Mechanism of Action	Potential Side Effects
Plasma-derived C1 inhibitor (Berinert, CSL Behring)	Acute attacks in all age groups, including women who are pregnant or breast-feeding	20 U/kg IV	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Recombinant human C1 inhibitor (Ruconest, Pharming)	Acute attacks in adolescents and adults, including women who are pregnant or breast-feeding	50 U/kg IV (maximum dose, 4200 U)	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis (among rabbit-sensitized persons) Theoretical: transmission of infectious agent
Ecallantide (Kalbitor, Takeda)	Acute attacks in patients ≥12 yr of age	30 mg SC	Inhibits plasma kallikrein	Common: prolonged PTT‡ Rare: risk of anaphylaxis§ Uncommon: antidrug antibodies
Icatibant (Firazyr, Takeda)	Acute attacks in patients ≥18 yr of age¶	Adults: 30 mg SC Children: 12–25 kg, 10 mg SC 26–40 kg, 15 mg SC 41–50 kg, 20 mg SC 51–65 kg, 25 mg SC >65 kg, 30 mg SC	Bradykinin B2 receptor antagonist	Common: discomfort at injection site
Plasma-derived C1 inhibitor (Cinryze, Takeda)	Prophylaxis in patients ≥6 yr of age‖	Children (6–11 yr): 500 U IV every 3–4 days; doses up to 1000 U IV every 3–4 days may be needed Adolescents >12 yr of age and adults: 1000 U IV every 3–4 days; doses up to 2500 U IV every 3–4 days may need to be considered on the basis of a patient's response	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Plasma-derived C1 inhibitor (HAEGARDA, CSL Behring)	Prophylaxis in patients ≥12 yr of age	60 U/kg SC twice weekly	Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Common: mild injection-site reaction Rare: risk of anaphylaxis Theoretical: transmission of infectious agent
Lanadelumab (Takhzyro, Takeda)	Prophylaxis in patients ≥12 yr of age	300 mg SC every 2 wk; 300 mg every 4 wk may be considered if patient is attack-free for >6 mo	Inhibits plasma kallikrein	Common: mild injection-site reaction, dizziness, prolonged PTT‡ Rare: risk of anaphylaxis

* IV denotes intravenously, PTT partial-thromboplastin time, and SC subcutaneously.
† The listed indications are those approved by the Food and Drug Administration.
‡ A prolonged PTT is not clinically significant. The increase is due to inhibition of "feedback" for activation of factor XII by kallikrein.
§ This agent must be administered by a medical professional who is prepared to treat anaphylaxis.
¶ In Europe, this agent is approved for use in patients 2 years of age or older.
‖ This agent is approved in Europe for short-term, on-demand treatment in patients 2 years of age or older.