Fem viktiga vetenskapliga publikationer 2024 - 2025

SLIPIs årsmöte 3-5 september 2025
Båstad

Kim Ramme

The 2024 update of IUIS phenotypic classification of human inborn errors of immunity

Klinisk och fenotypisk klassificering

- 559 immunbrister
- 67 nya monogena sjukdomar
- 2 nya phenocopies

Algoritm som klinisk vägledning

Tabeller med de viktigaste kliniska fynden och laboratoriefynden

ARTICLE

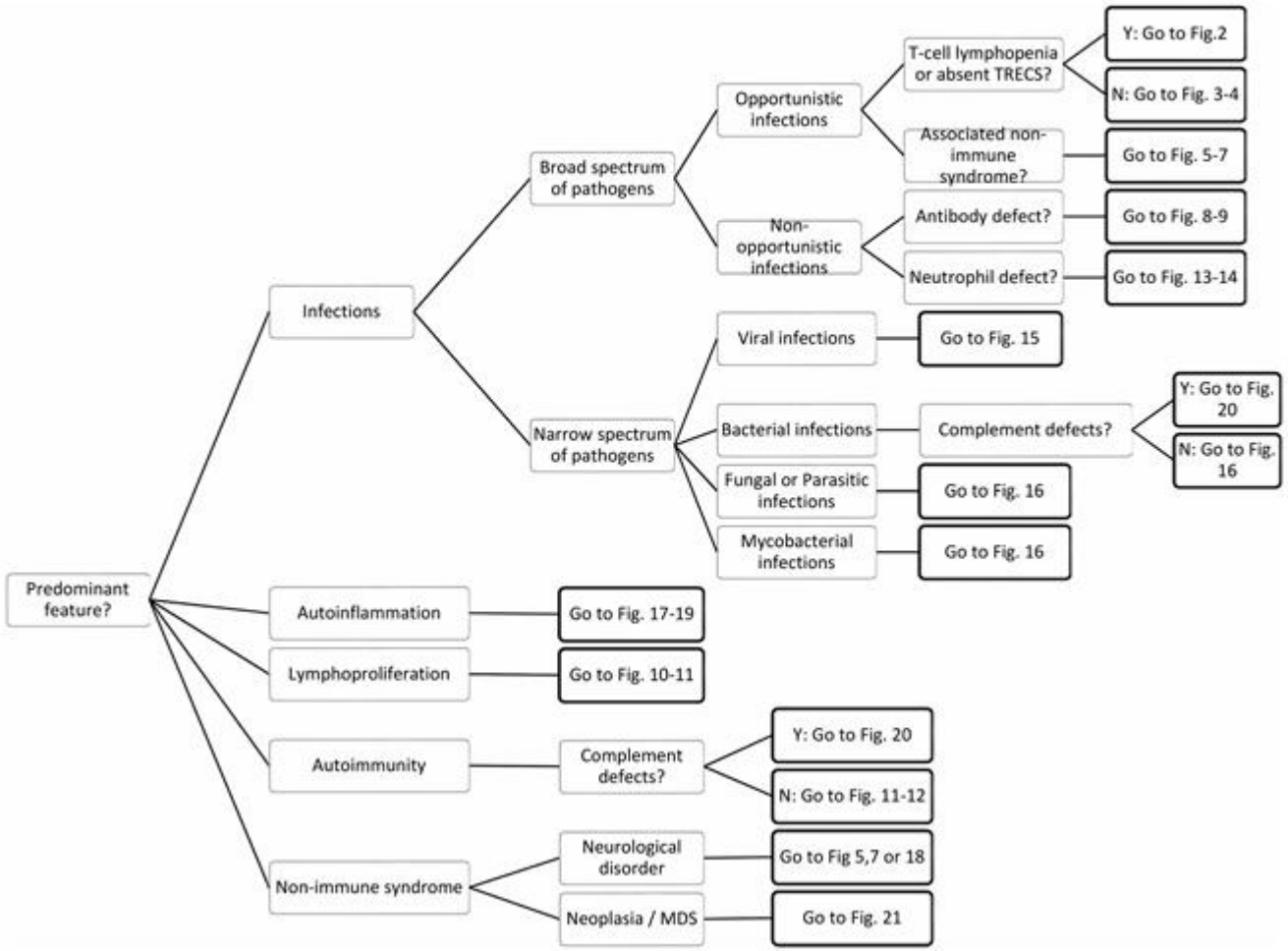
The 2024 update of IUIS phenotypic classification of human inborn errors of immunity

Ahmed Aziz Bousfiha[1,2], Leïla Jeddane[3], Abderrahmane Moundir[1], M. Cecilia Poli[4,5], Ivona Aksentijevich[6], Charlotte Cunningham-Rundles[7], Sophie Hambleton[8], Christoph Klein[9], Tomohiro Morio[10], Capucine Picard[11], Anne Puel[12,13,14], Nima Rezaei[15], Mikko R.J. Seppänen[16], Raz Somech[17], Helen C. Su[18], Kathleen E. Sullivan[19], Troy R. Torgerson[20], Stuart G. Tangye[21,22], and Isabelle Meyts[23]

Here, we report the 2024 update of the phenotypic classification by the International Union of Immunological Societies (IUIS) expert committee (EC) on inborn errors of immunity (IEI), which accompanies and complements the 2024 genotypic classification. The aim of this classification is to help diagnosis for clinicians at the bedside and focuses on clinical features and basic laboratory phenotypes of specific IEI. In this update, 559 IEI are described, including 67 novel monogenic defects and 2 new phenocopies. This phenotypic classification is presented in the form of decision trees when possible, with essential clinical or immunological phenotype entries.

Ahmed Aziz Bousfiha, Leïla Jeddane, Abderrahmane Moundir, M. Cecilia Poli, Ivona Aksentijevich, Charlotte Cunningham-Rundles, Sophie Hambleton, Christoph Klein, Tomohiro Morio, Capucine Picard, Anne Puel, Nima Rezaei, Mikko R.J. Seppänen, Raz Somech, Helen C. Su, Kathleen E. Sullivan, Troy R. Torgerson, Stuart G. Tangye, Isabelle Meyts; The 2024 update of IUIS phenotypic classification of human inborn errors of immunity. *J Hum Immun* 5 May 2025; 1 (1): e20250002. doi: https://doi.org/10.70962/jhi.20250002

Decision tree orienting through IEI classification categories



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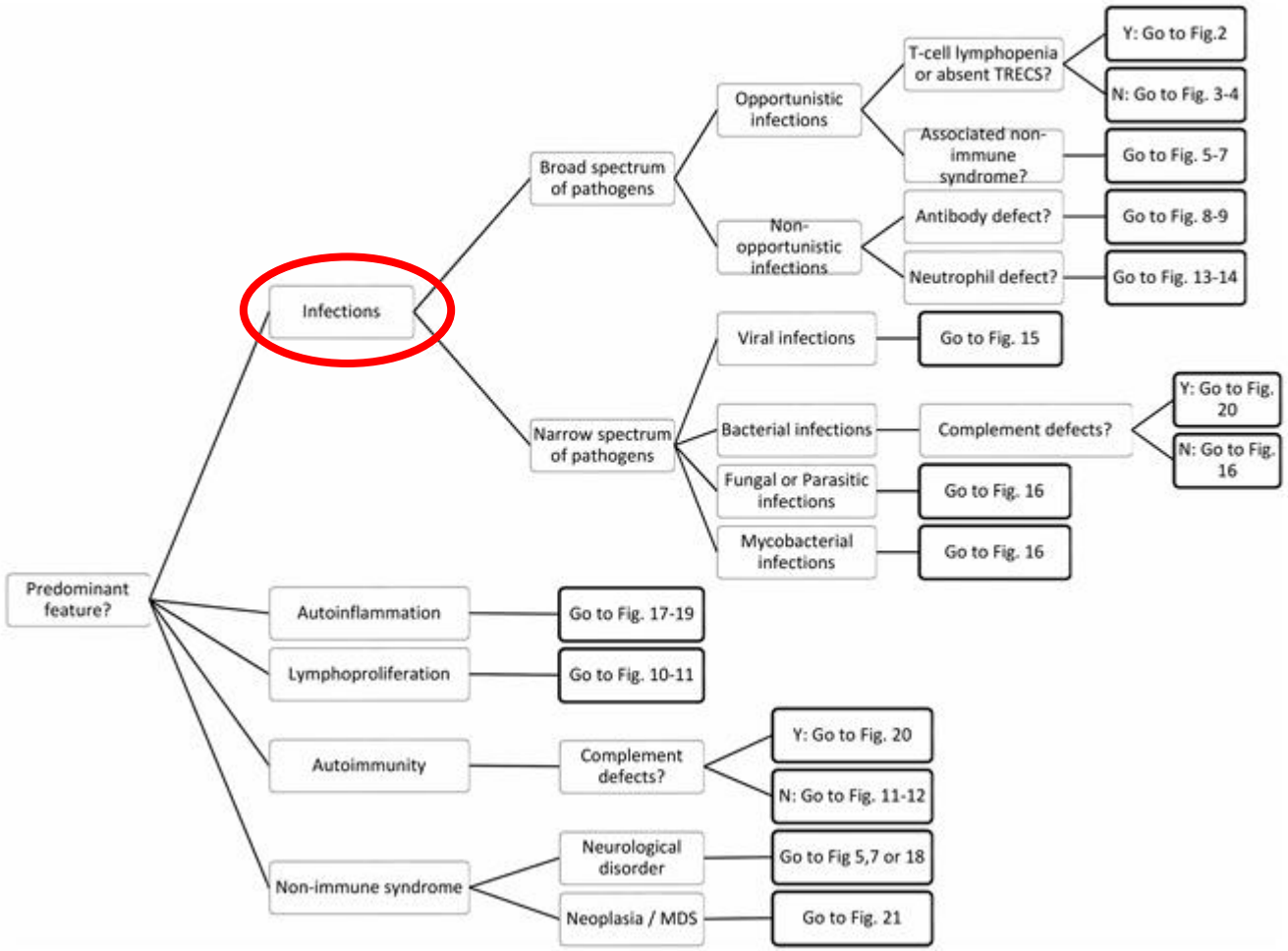

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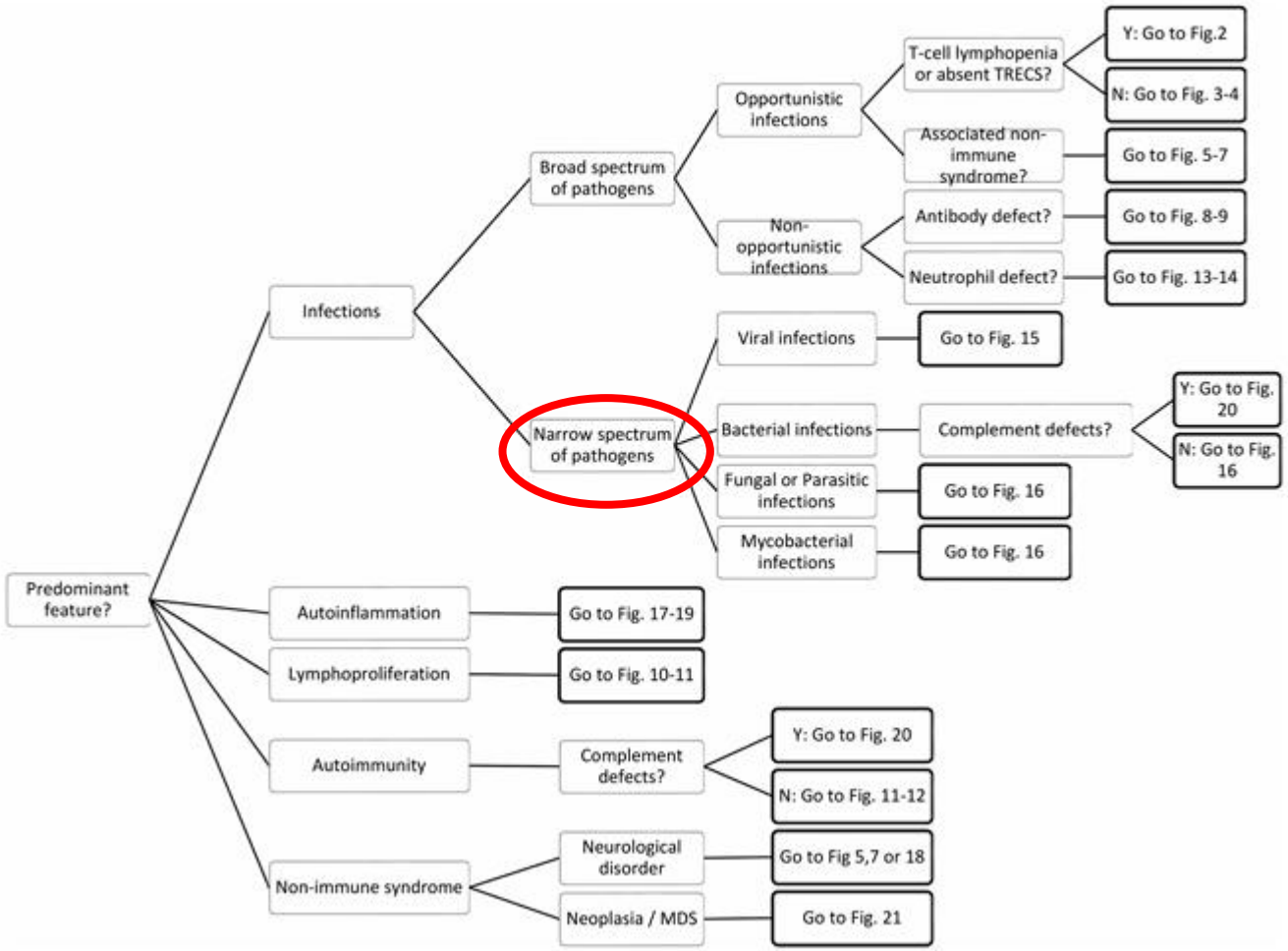

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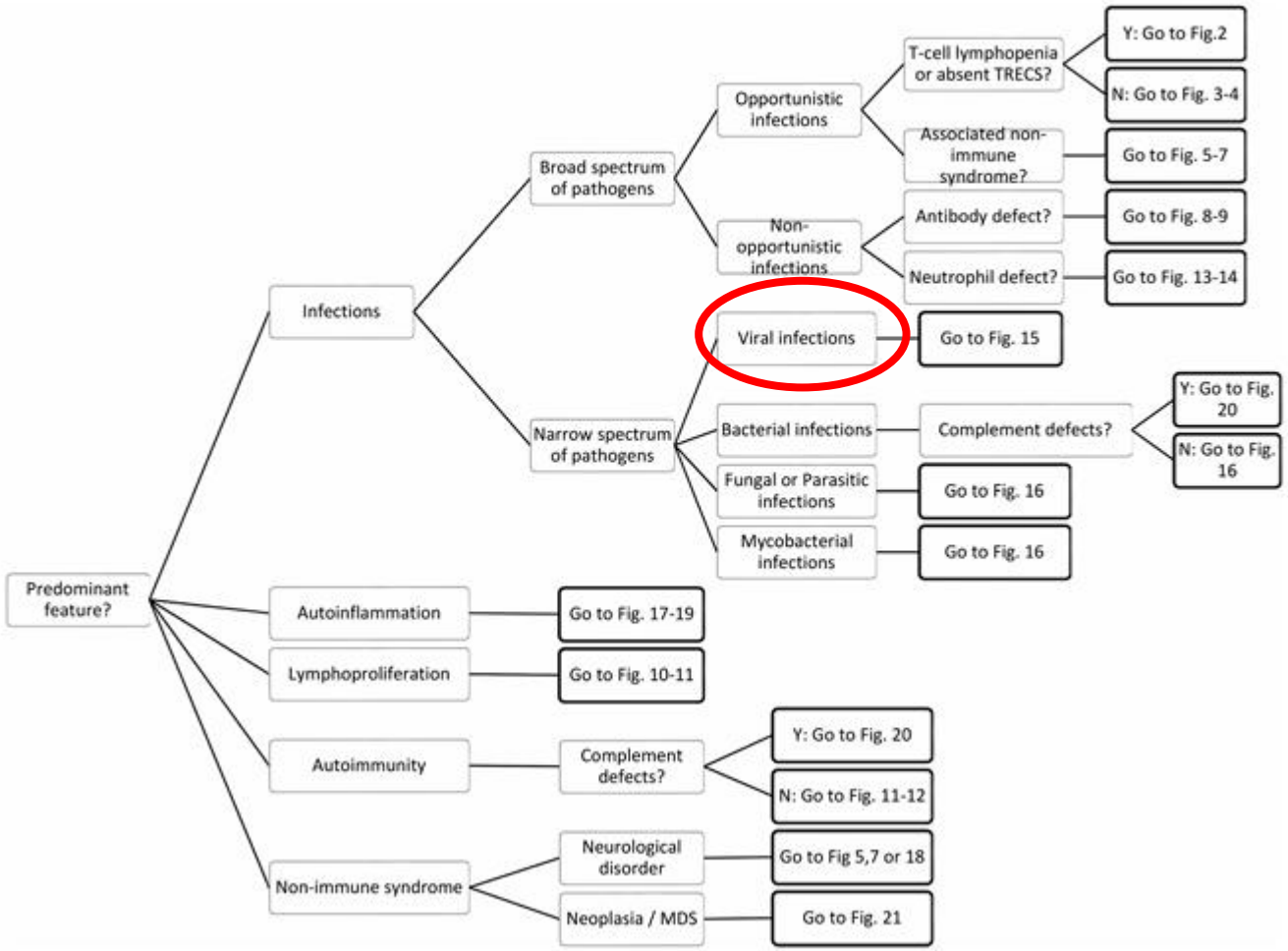

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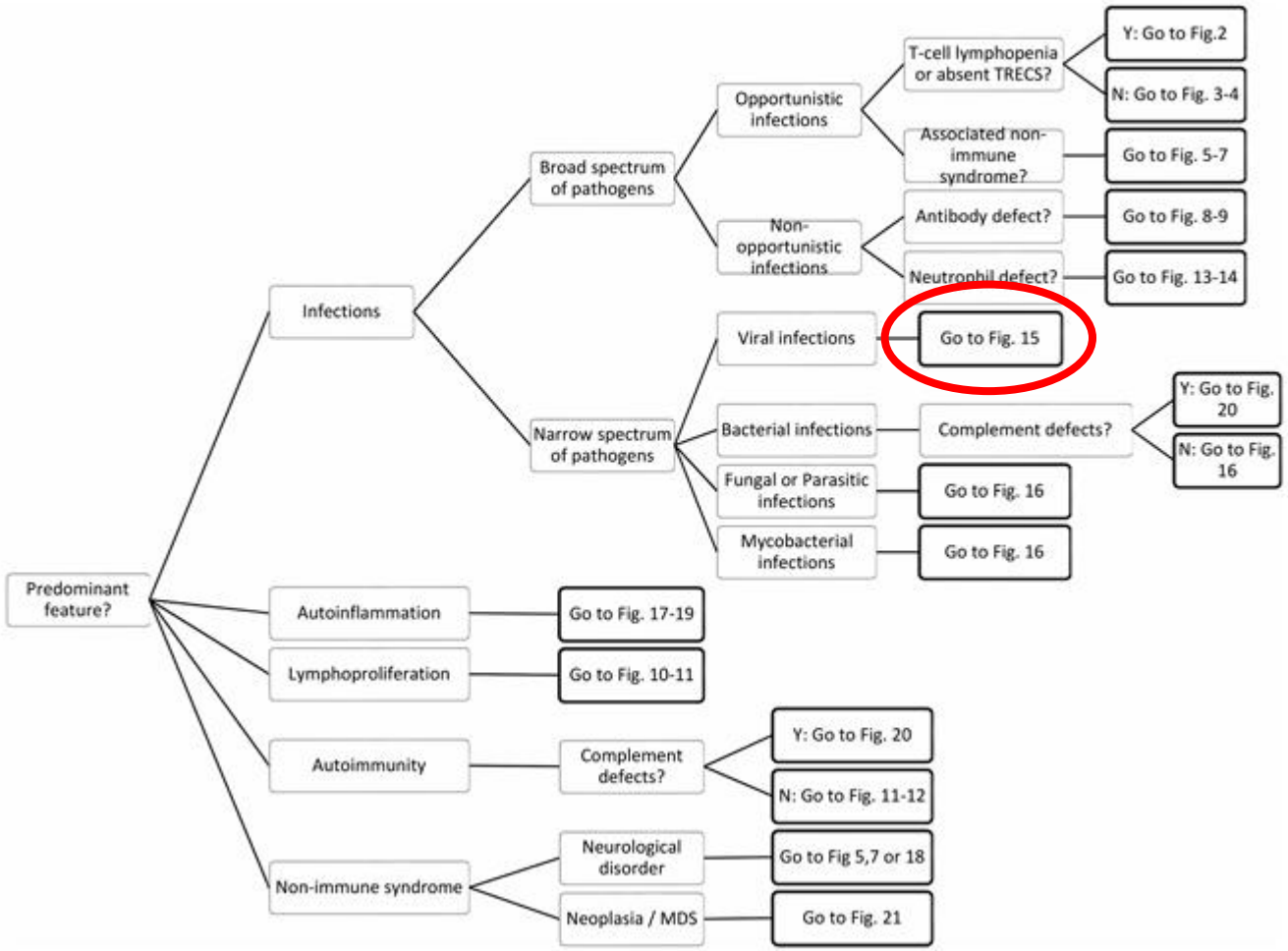

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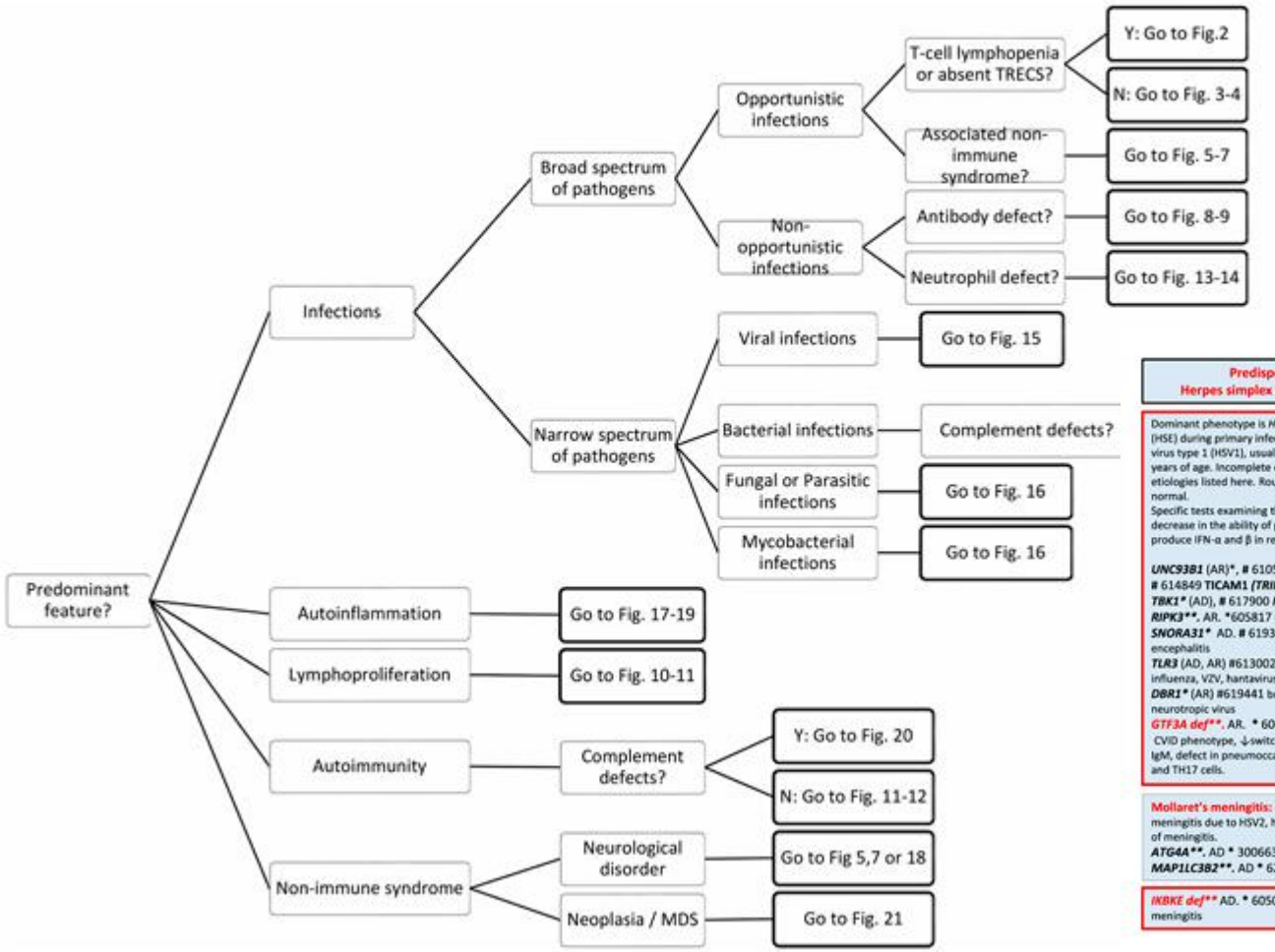


Predisposition to Herpes simplex virus Encephalitis

Dominant 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)*, # 610551 **TRAF3**** (AD), # 614849 **TICAM1** ***(TRIF)**** (AR, AD), #614850 ***TBK1**** (AD), # 617900 ***IRF3**** (AD) # 616532 ***RIPK3****, AR. *605817 Recurrent HSE
SNORA31* AD. # 619396 Forebrain HSV-1 encephalitis
TLR3 (AD, AR) #613002 + severe pulmonary influenza, VZV, hantavirus, RSV.
DBR1* (AR) #619441 brainstem infections by neurotropic virus
GTF3A def*. AR. * 600860
CVID phenotype, ↓switched memory Bc, absent IgM, defect in pneumoccal antibody response ↓ TFH and TH17 cells.

Mollaret's meningitis: recurrent lymphocytic meningitis due to HSV2, history of multiple episodes of meningitis.
ATG4A*, AD * 300663
MAP1LC3B2*. AD * 620673

IKBKE def* AD. * 605048 Recurrent HSV-2 meningitis

Predisposition to HPV

Epidermodysplasia verruciformis
HPV (group B1) infections (disseminated flat warts) and high risk of skin cancer
EVER1 def. ***TMC6*** AR. # 226400
EVER2 def*. ***TMC8*** AR. # 618231
CIB1 def*. ***CIB1*** AR. # 618267

WHIM (Warts, Hypogammaglobulinemia, infections, myelokathexis) sd.
CXCR4 AD GOF. # 193670
Warts (chronic HPV infection), recurrent infections, neutropenia, ↓Bc, ↓Ig.

RHOH def**. ***RHOH*** AR. # 618307
HPV infection, lung granulomas, molluscum contagiosum, lymphoma.

Predisposition to Viral Infection

STAT1 def*. ***STAT1*** AR LOF. #613796 Mycobacterial infection. Severe disease.

STAT2 def*. ***STAT2*** AR. # 616636
Adverse multisystemic reaction to vaccination, atypical Kawasaki disease, HLH

MDA5 def (LOF)*. ***IFIH1*** AR. # 619773
Rhinovirus, RSV and other RNA viruses

IFNAR1 def. ***IFNAR1*** AR. # 619935
IFNAR2 def*. ***IFNAR2*** AR. #616669
Severe adverse reactions to live attenuated vaccines (HLH-like, encephalopathy, acute respiratory distress and multiorgan failure), Severe SARS-CoV-2 infection

RNA poymerase III def*. ***POLR3A****. *614258
POLR3C*. *617454 ***POLR3F****. # 619872 AD.
Severe VZV infection or reactivation.

IRF7 def.** ***IRF7*** AR. # 616345
Severe influenza disease.

IRF9 def*. ***IRF9*** AR. # 618648
Adverse effects to live attenuated vaccines, septic shock. Lymphopenia and ↓Ig.

IL-18BP def.** ***IL18BP***. AR. # 618549
Fulminant viral hepatitis

IRF8 def. ***IRF8*** AR. #226990 Recurrent viral infections and susceptibility to mycobacteria. ↓NKc, monocytes and DC

ZNFX1 def. ***ZNFX1***. AR. #619644
Severe infections by viruses, mycobacteria; early-onset severe inflammation affecting liver, brain, kidneys, lungs, HSM, HLH, lymphadenopathy, multiorgan failure

Severe COVID19. ***TLR7*** XL. #301051 ***TLR3*** AD, ***UNC93B1*** AD, ***TICAM1*** AD, ***TBK1*** AD, ***IRF3*** AD, ***IRF7*** AR/AD, ***IFNAR1*** AR/AD ***and IFNAR2*** AD
Severe respiratory insufficiency in response to COVID-19 infection

CD16 def*. ***FCGR3A*** AR. # 615707
Severe herpes viral infections (VZV, EBV, and HPV). Impaired NKc function.

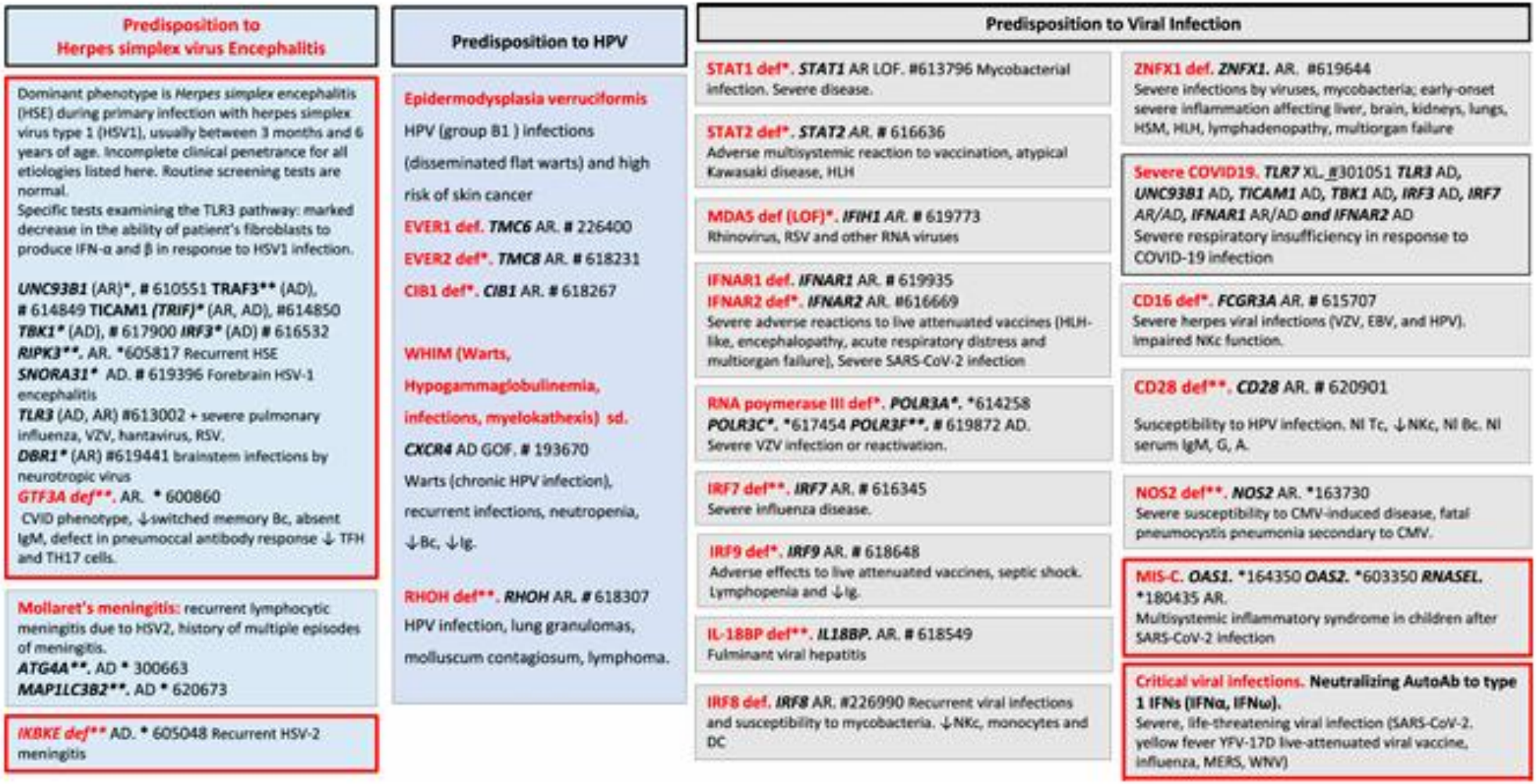
CD28 def.** ***CD28*** AR. # 620901
Susceptibility to HPV infection. Nl Tc, ↓NKc, Nl Bc. Nl serum IgM, G, A.

NOS2 def.** ***NOS2*** AR. *163730
Severe susceptibility to CMV-induced disease, fatal pneumocystis pneumonia secondary to CMV.

MIS-C. ***OAS1***. *164350 ***OAS2***. *603350 ***RNASEL***. *180435 AR.
Multisystemic inflammatory syndrome in children after SARS-CoV-2 infection

Critical viral infections. Neutralizing AutoAb to type 1 IFNs (IFNα, IFNω).
Severe, life-threatening viral infection (SARS-CoV-2, yellow fever YFV-17D live-attenuated viral vaccine, influenza, MERS, WNV)

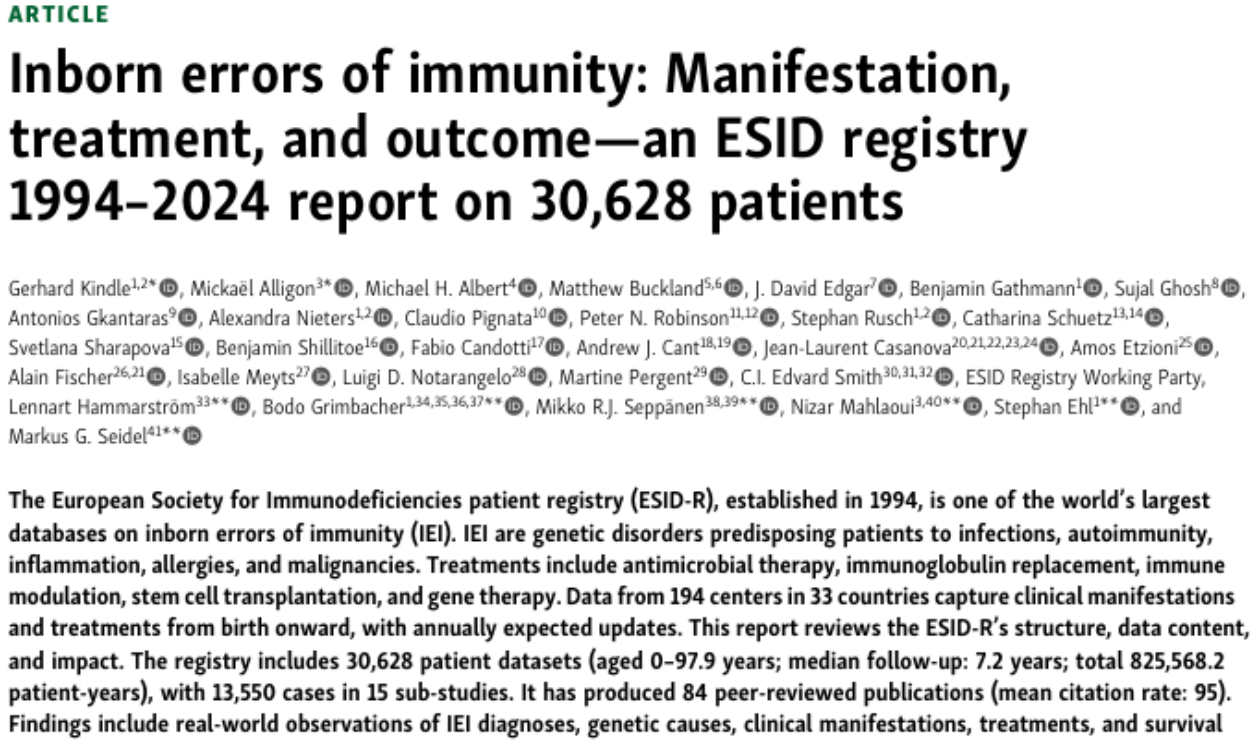
Decision tree orienting through IEI classification categories



Inborn Errors of Immunity: Manifestation, Treatment, and Outcome—ESID Registry Report

Analys av data från **30,628 patienter i ESID-registret** för att:

- kartlägga kliniska manifestationer
- kartlägga behandling
- kartlägga överlevnad



ARTICLE

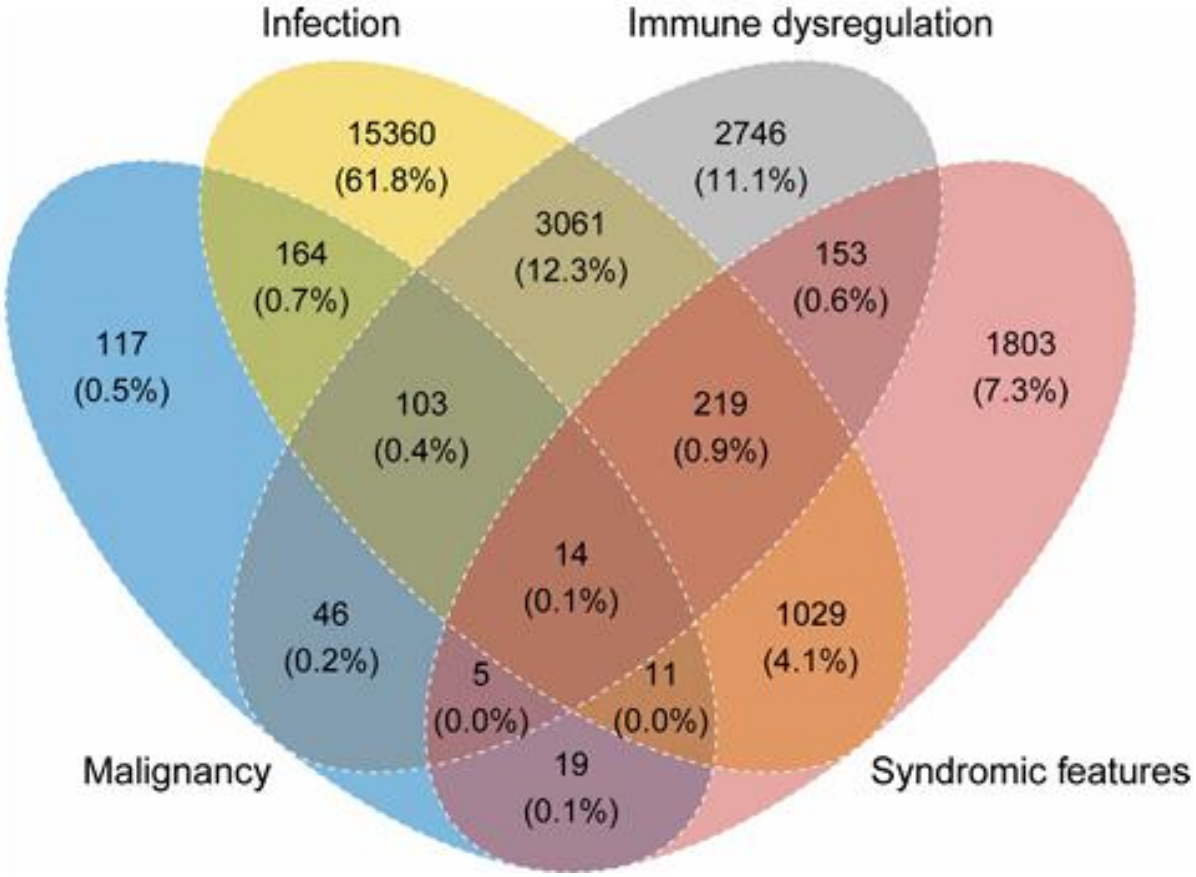
Inborn errors of immunity: Manifestation, treatment, and outcome—an ESID registry 1994–2024 report on 30,628 patients

Gerhard Kindle[1,2*], Mickaël Alligon[3*], Michael H. Albert[4], Matthew Buckland[5,6], J. David Edgar[7], Benjamin Gathmann[1], Sujal Ghosh[8], Antonios Gkantaras[9], Alexandra Nieters[1,2], Claudio Pignata[10], Peter N. Robinson[11,12], Stephan Rusch[1,2], Catharina Schuetz[13,14], Svetlana Sharapova[15], Benjamin Shillitoe[16], Fabio Candotti[17], Andrew J. Cant[18,19], Jean-Laurent Casanova[20,21,22,23,24], Amos Etzioni[25], Alain Fischer[26,21], Isabelle Meyts[27], Luigi D. Notarangelo[28], Martine Pergent[29], C.I. Edvard Smith[30,31,32], ESID Registry Working Party, Lennart Hammarström[33**], Bodo Grimbacher[1,34,35,36,37**], Mikko R.J. Seppänen[38,39**], Nizar Mahlaoui[3,40**], Stephan Ehl[1**], and Markus G. Seidel[41**]

The European Society for Immunodeficiencies patient registry (ESID-R), established in 1994, is one of the world's largest databases on inborn errors of immunity (IEI). IEI are genetic disorders predisposing patients to infections, autoimmunity, inflammation, allergies, and malignancies. Treatments include antimicrobial therapy, immunoglobulin replacement, immune modulation, stem cell transplantation, and gene therapy. Data from 194 centers in 33 countries capture clinical manifestations and treatments from birth onward, with annually expected updates. This report reviews the ESID-R's structure, data content, and impact. The registry includes 30,628 patient datasets (aged 0–97.9 years; median follow-up: 7.2 years; total 825,568.2 patient-years), with 13,550 cases in 15 sub-studies. It has produced 84 peer-reviewed publications (mean citation rate: 95). Findings include real-world observations of IEI diagnoses, genetic causes, clinical manifestations, treatments, and survival

Kindle G, Alligon M, Albert MH, Buckland M, Edgar JD, Gathmann B, Ghosh S, Gkantaras A, Nieters A, Pignata C, Robinson P, Rusch S, Schuetz C, Sharapova S, Shillitoe B, Candotti F, Cant AJ, Casanova JL, Etzioni A, Fischer A, Meyts I, Notarangelo LD, Pergent M, Smith CIE; ESID Registry Working Party; Hammarström L, Grimbacher B, Seppänen M, Mahlaoui N, Ehl S, Seidel MG. Inborn errors of immunity: manifestation, treatment, and outcome - an ESID registry 1994-2024 report on 30,628 patients. medRxiv [Preprint]. 2025 Apr 16:2025.02.20.25322586. doi: 10.1101/2025.02.20.25322586. PMID: 40568655; PMCID: PMC12191083.

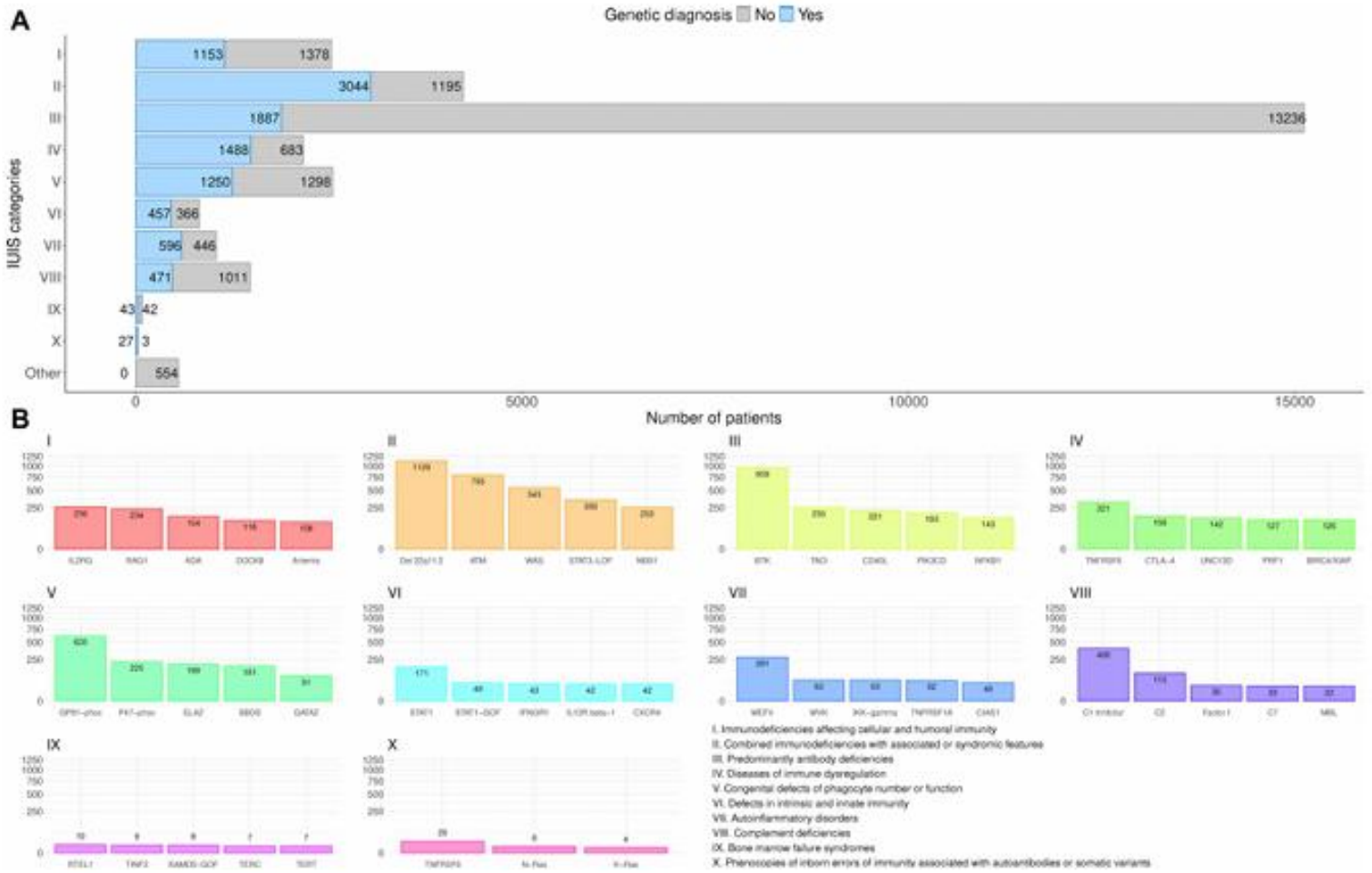
Kliniska manifestationer vid diagnos



Vanligast isolerade symptom:

1. *Infektioner* — *61,8% (80,3% alla inkluderade)*
2. *Immundysreglering* — *11,1%*
3. *Symptom associerade med syndrom* — *7,3%*

Genetiska diagnoser

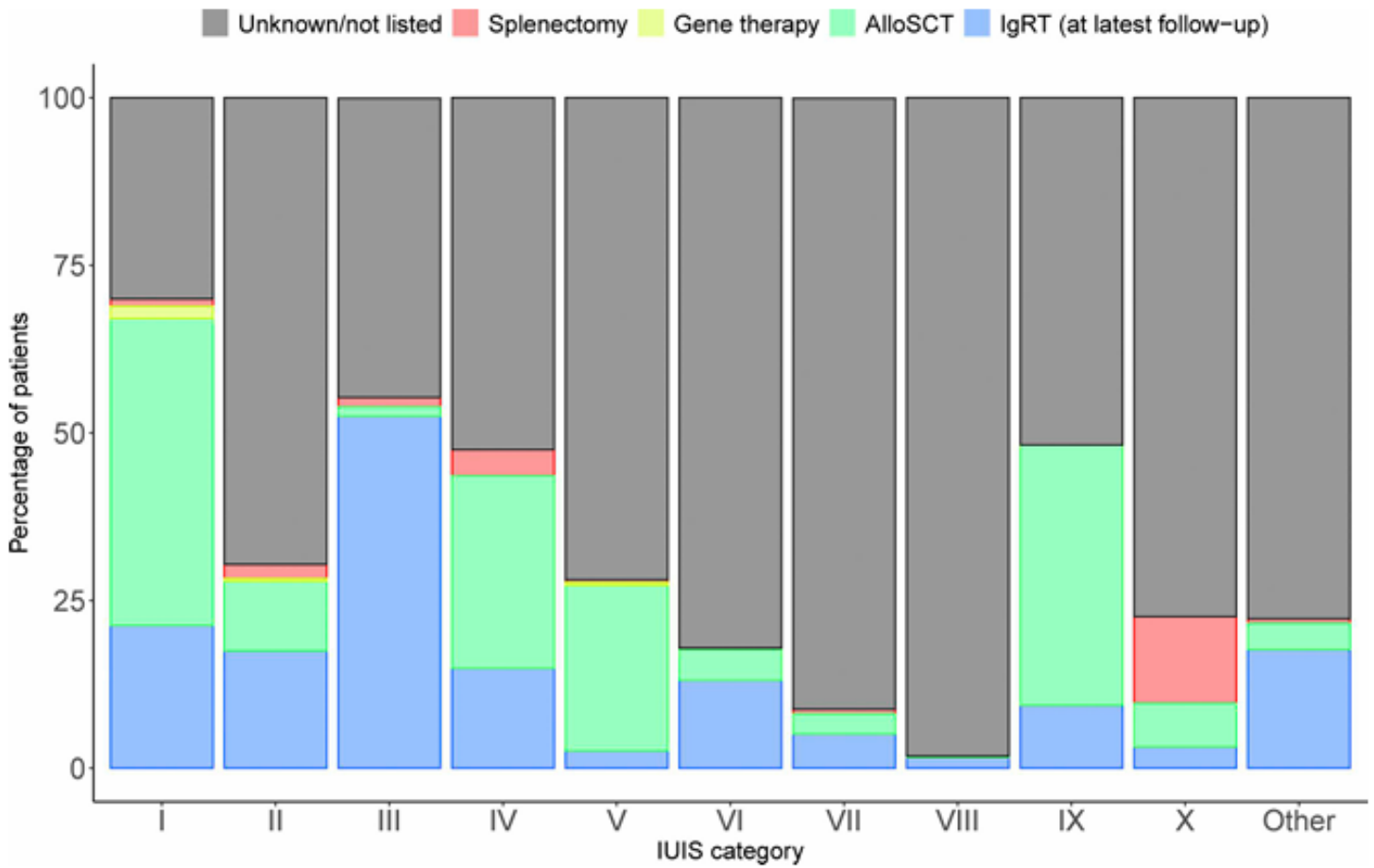


Största andel av patienter med SCID och CID
Liten andel av antikroppsdefekterna (CVID)

Behandling

Största andel av patienter med SCID, antikroppsdefekter, immundysreglering och benmärgssvikt hade/haft någon form av behandling

Komplementdefekterna hade ett litet behov av behandling

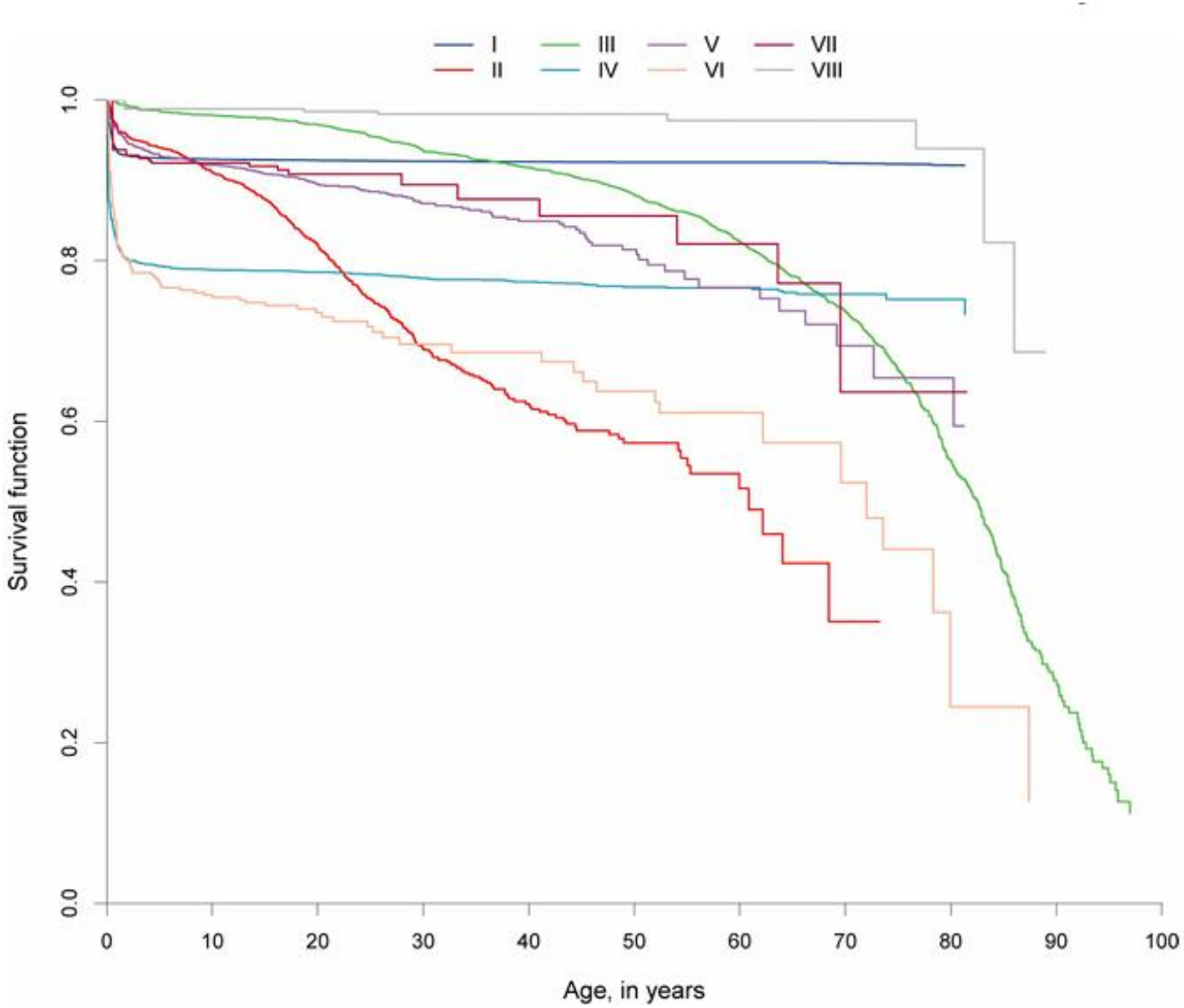


Överlevnad

Överlevnad SCID!

Sorgebarn:
CID (röd)
Defekter i det medfödda försvaret (intrinzic+innate)(aprikos)

Antikroppsbrister (grön)

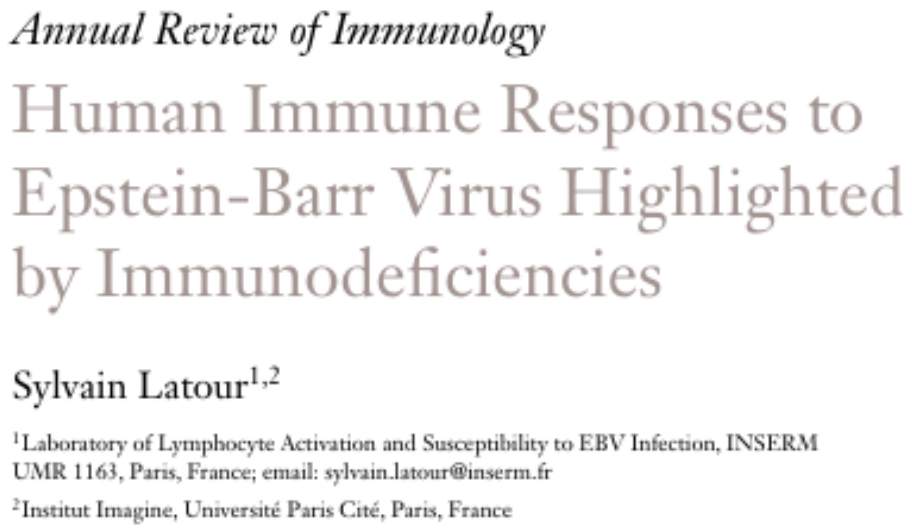


Human Immune Responses to Epstein-Barr Virus Highlighted by Immunodeficiencies

Review:

Inborn errors of immunity (IEI) som biologisk modell för att förstå hur immunsystemet bekämpar Epstein-Barr-virus (EBV)

Artikeln fokuserar på genetiska immunbrister som antingen predisponerar för eller skyddar mot EBV-infektion


Annual Review of Immunology

Human Immune Responses to Epstein-Barr Virus Highlighted by Immunodeficiencies

Sylvain Latour[1,2]

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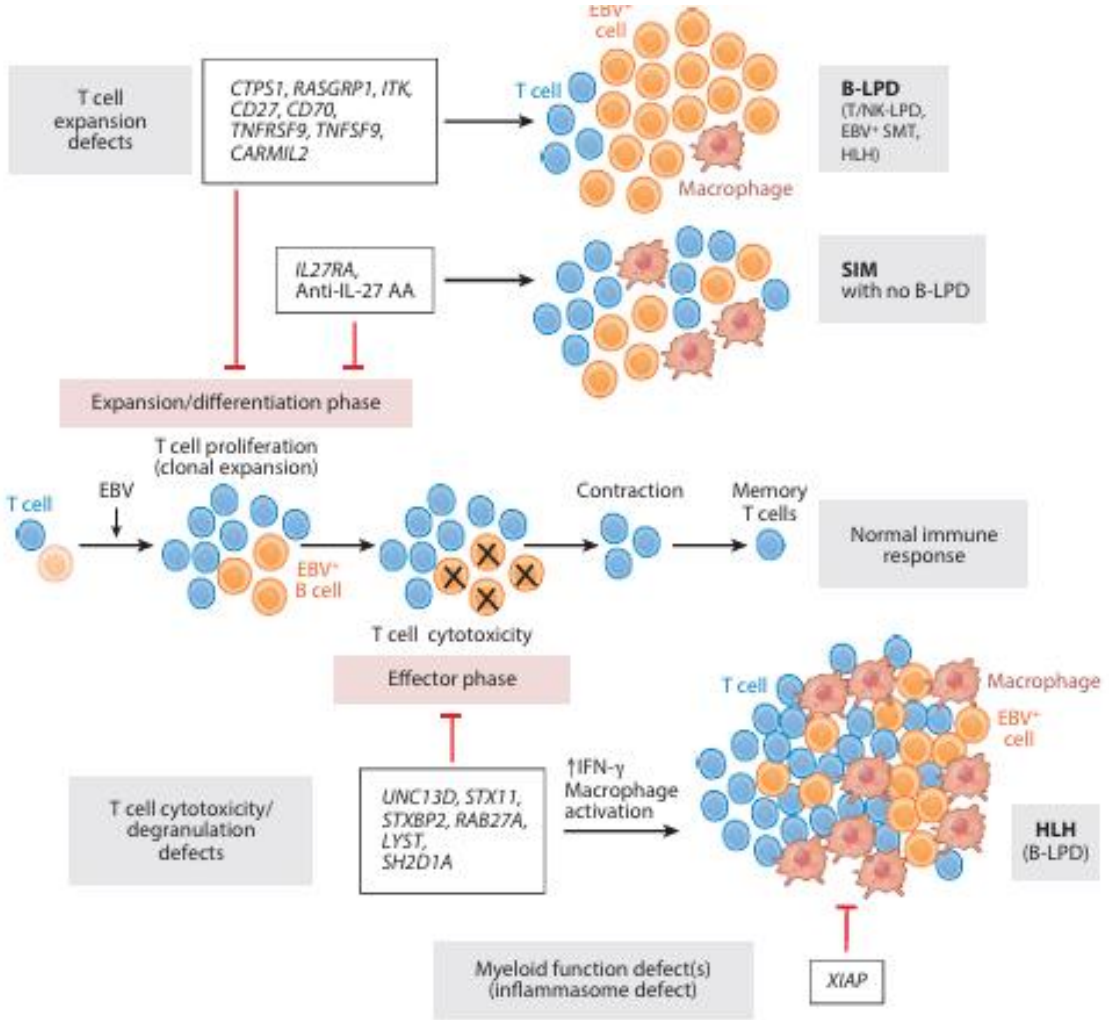
[2]Institut Imagine, Université Paris Cité, Paris, France

Latour S. Human Immune Responses to Epstein-Barr Virus Highlighted by Immunodeficiencies. Annu Rev Immunol. 2025 Apr;43(1):723-749. doi: 10.1146/annurev-immunol-082323-035455. PMID: 40279309.

Normalt och patologiskt immunsvar mot EBV



Cytotoxiska defekter → HLH och svår infektion

Immunbrister som påverkar T-cellernas cytoxicitet

Gen	**Sjukdom**	**Effekt**
PRF1, *UNC13D*, *STXBP2*	Familjär HLH	Defekt cytolytisk granulexocytos → okontrollerad EBV-reaktion
SHD1A, XIAP	XLP, XLP-2	Dysreglerad apoptos och ökad risk för HLH, lymfom
STX11, *RAB27A*	Griscelli syndrom typ 2	Svår EBV-inducerad HLH

T cells expansion och differentiering

Funktion	Gen	Sjukdom	Effekt
Costimulatoriska signaler	*CD27*, *CD70*	CD27/CD70-brist	Otillräcklig T-cellshjälp → EBV-driven B-cellsexpansion
Costimulatoriska signaler	*TNFRSF9*, *TNFSF9*	CD137/CD137L-brist	Försämrad T-cellsexpansion → ökad risk för EBV-lymfom
Signalerar nedströms om TCR	*CTPS1*	CTPS1-brist	Defekt T-cellproliferation → svår EBV-infektion och lymfoproliferation
IL27-signalväg	*IL27RA*	IL27RA-defekt	Svår EBV-infektion, men inga andra symptom

Human Immune Responses to Epstein-Barr Virus Highlighted by Immunodeficiencies

Sammanfattning:

- Immunbrist som inte predisponerar för EBV-infektion visar att den medfödda (innate) och den humorala immuniteten är mindre viktig vid en EBV-infektion
- Immunbrist som predisponerar för EBV-infektion visar att immunförsvarets centrala mekanism för att bekämpa och kontrollera EBV är det T-cellsmedierade immunförsvaret ($CD8^+$ T-celler)
- Genetiska defekter som påverkar T-cellssignalering, co-stimulering eller cytotoxisk funktion leder till ökad risk för hemofagocytos och lymfoproliferation

Investigating pulmonary and non-infectious complications in common variable immunodeficiency disorders: a UK national multi-centre study

- Retrospektiv, tvärsnittsstudie (UKPIN-registret, Storbritannien) av förekomst av icke-infektiösa komplikationer, särskilt lungrelaterade, hos patienter med CVID i Storbritannien
- Jämförde 129 patienter med interstitiell lungsjukdom (CVID-ILD) med dem som har extra-pulmonella komplikationer (CVID-EP)


Investigating pulmonary and non-infectious complications in common variable immunodeficiency disorders: a UK national multi-centre study

Heba M. Bintalib[1,2,3*], Sofia Grigoriadou[4], Smita Y. Patel[5], Leman Mutlu[6], Kavitha Sooriyakumar[7], Prashantha Vaitla[8], Elizabeth McDermott[8], Elizabeth Drewe[8], Cathal Steele[9], Manisha Ahuja[10], Tomaz Garcez[11], Mark Gompels[12], Alexandros Grammatikos[12], Archana Herwadkar[13], Rehana Ayub[14], Neil Halliday[15,16], Siobhan O. Burns[17,18], John R. Hurst[1†] and Sarah Goddard[19†]

Bintalib HM, Grigoriadou S, Patel SY, Mutlu L, Sooriyakumar K, Vaitla P, McDermott E, Drewe E, Steele C, Ahuja M, Garcez T, Gompels M, Grammatikos A, Herwadkar A, Ayub R, Halliday N, Burns SO, Hurst JR, Goddard S. Investigating pulmonary and non-infectious complications in common variable immunodeficiency disorders: a UK national multi-centre study. Front Immunol. 2024 Sep 10;15:1451813. doi: 10.3389/fimmu.2024.1451813. PMID: 39318627; PMCID: PMC11420000.

Investigating pulmonary and non-infectious complications in common variable immunodeficiency disorders: a UK national multi-centre study

- Bronkiektasier förekom hos 64 % av patienterna och var associerade med försämrad lungfunktion
- CVID-ILD identifierades hos 62 % av kohorten och var den mest framträdande komplikationen
- Lymfadenopati och frånvaro av gastrointestinala sjukdomar var starka prediktorer för ILD
- Leversjukdom fanns hos nästan hälften av CVID-ILD-patienterna, men ingen signifikant skillnad mellan grupperna
- CVID-ILD-patienter fick oftare immunsuppressiv behandling t ex rituximab och MMF

γδ T Cells and Inborn Errors of Immunity

Review:

- Hur påverkar *immunbrist* utveckling, funktion och homeostas av γδ T-celler?
- Fokuserar på immunbrister där γδ T-celler är selektivt påverkade

REVIEW OPEN ACCESS

Highlights - Reviews

γδ T Cells and Inborn Errors of Immunity

Sagar[1] | Stephan Ehl[2,3]

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Received: 10 October 2024 | **Revised:** 11 June 2025 | **Accepted:** 11 June 2025

Keywords: γδ T cells | inborn errors of immunity | primary immunodeficiency | human | mouse

ABSTRACT

Gamma delta (γδ) T cells are pivotal in diverse immune responses, encompassing defense against infections, cancer surveillance, and tissue repair. Inborn errors of immunity (IEI) are rare genetic conditions disrupting human immune system development and function, with some impacting γδ T cells. In this review, we focus on IEI leading to a relative increase or decrease of γδ T cells compared to αβ T cells. We discuss how these disorders provide unique insights, in particular concerning the importance of signaling pathways for human αβ versus γδ T cell development, function, and homeostasis. Wherever suitable, we also include data from respective mouse models of IEIs that corroborate patient observations but also illustrate relevant species differences. This comparative approach identifies gaps in knowledge and defines areas for future research. Overall, this review underscores the relevance of IEIs in elucidating the development and function of human γδ T cells with potential implications for diagnosing and treating patients with immune disorders.

Sagar, Ehl S. γδ T Cells and Inborn Errors of Immunity. Eur J Immunol. 2025 Jun;55(6):e51457. doi: 10.1002/eji.202451457. PMID: 40556329; PMCID: PMC12188109.

γδ T Cells and Inborn Errors of Immunity

Skillnader mellan γδ T-celler och αβ T-celler:

- γδ T-celler känner igen antigen direkt, utan behov av MHC-presentation
- γδ T-celler har en bredare målrepertoar och kan rikta sig mot icke-peptid-molekyler och stressinducerade antigen
- γδ T-celler teagerar snabbt utan att behöva genomgå klonal expansion
- γδ T-celler fungerar som en bro mellan det medfödda (innate) och det adaptiva immunförsvaret
- γδ T-celler kan utveckla svar som liknar immunologiskt minne

REVIEW OPEN ACCESS

Highlights - Reviews

γδ T Cells and Inborn Errors of Immunity

Sagar[1] | Stephan Ehl[2,3]

[1]Department of Medicine II (Gastroenterology, Hepatology, Endocrinology, and Infectious Diseases), Faculty of Medicine, Freiburg University Medical Center, University of Freiburg, Freiburg, Germany | [2]Institute for Immunodeficiency, Center for Chronic Immunodeficiency, Faculty of Medicine, Medical Center-University of Freiburg, University of Freiburg, Freiburg, Germany | [3]CIBSS - Cente for Integrative Biological Signalling Studies, University of Freiburg, Freiburg, Germany

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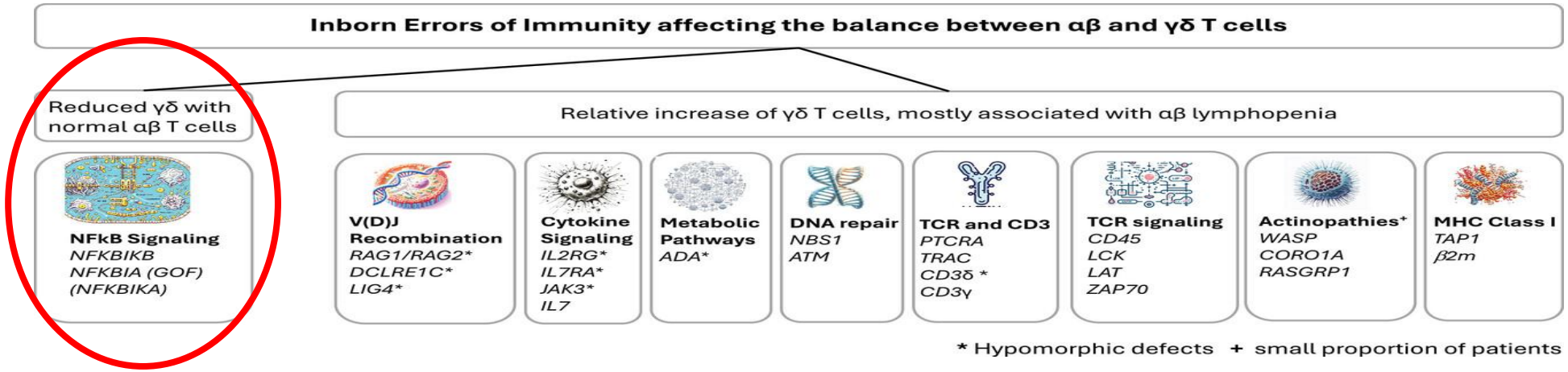
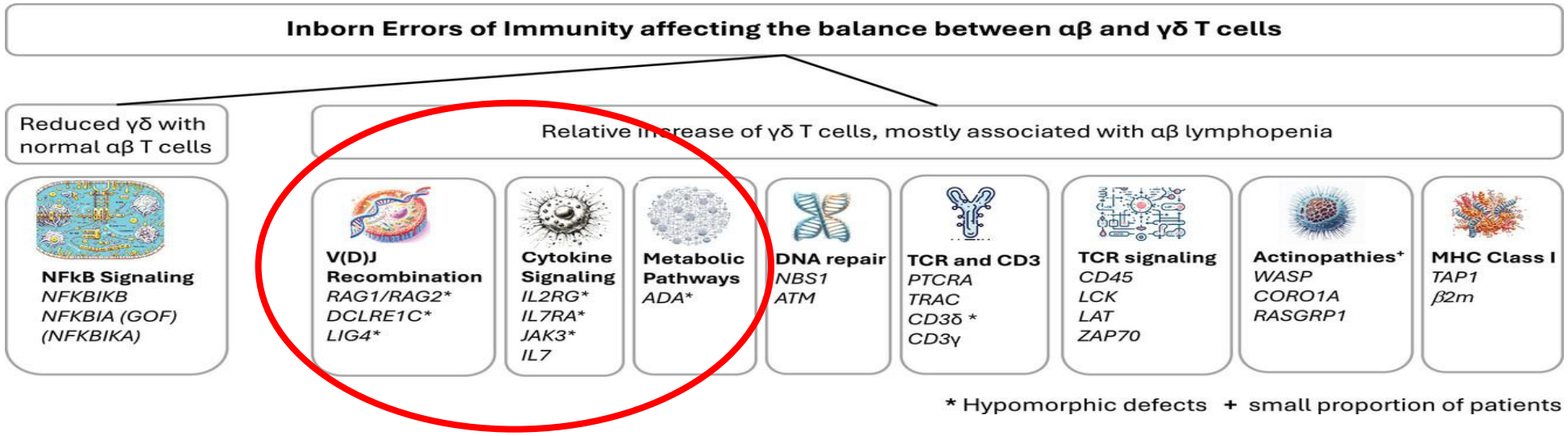
Immunbrist som leder till minskat antal γδ T-celler

- Mutationer i gener som påverkar NF-κB-signalering **(t.e**x. *NFKBIA*, *NFKBIB*) resulterar i kraftigt reducerade γδ T-celler, medan αβ T-celler ofta är bevarade
- Detta tyder på att γδ T-celler är särskilt beroende av stabil NF-κB-aktivering under sin utveckling



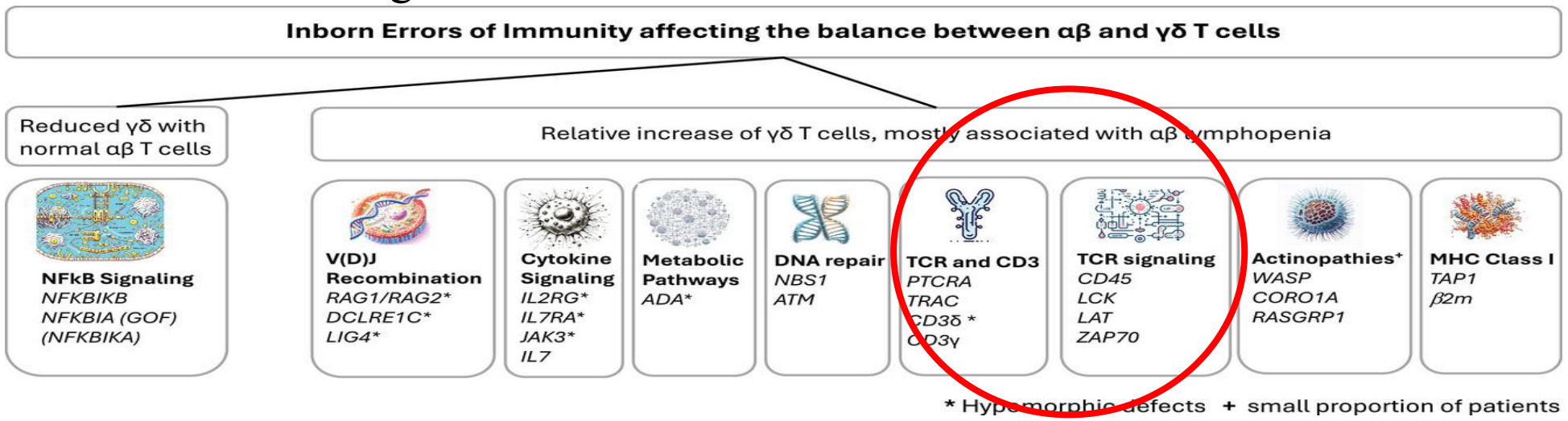
Immunbrister med ökad γδ T-cellsexpansion

- Vid vissa former av atypisk SCID (t.ex. hypomorfa mutationer i *RAG1/2*, *IL7R*, *JAK3*) ses en kompensatorisk expansion av γδ T-celler.
- γδ T-celler verkar mindre beroende av V(D)J-rekombination och IL-7-signalering än αβ T-celler.



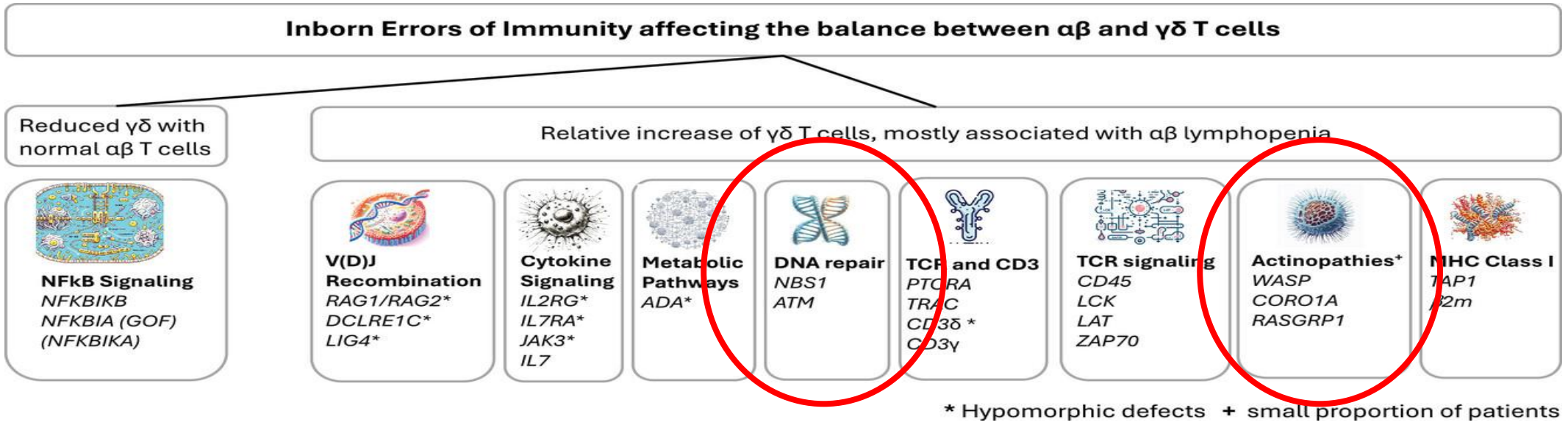
TCR-signalering och γδ T-cellers motståndskraft

- Mutationer i gener som påverkar TCR signalering (*PTCRA*, *TRAC*, *CD3D*, *ZAP70*, *LAT*, *LCK* m.fl) ⟹ αβ T-celler kraftigt reducerade, men γδ T-celler är ofta bevarade eller till och med expanderade
- Jämfört med αβ T-celler ter sig γδ T-celler kontrollerade via alternativa vägar och beroende av andra signaler



DNA-reparationsdefekter och immunbrist som påverkar actin

- Sjukdomar som *Nijmegen breakage syndrome* och *ataxia telangiectasia* visar γδ T-cell-dominans
- Immunbrist som påverkar cytoskelett (t.ex. *WASP*, *Coronin-1A*) påverkar αβ T-celler mer än γδ T-celler



MHC klass I-brist

- Patienter med *TAP1* eller *β2-mikroglobulin*-mutationer har låga $CD8^+$ αβ T-celler (normala $CD4^+$ αβ T-celler) men ökad $CD8^+$ γδ T-cellspopulation
- Bekräftar att γδ T-celler är MHC-oberoende, vilket gör dem funktionella även vid antigenpresentationsdefekter