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NETZWERK SELTENE ERKRANKUNGEN BADEN-WÜRTTEMBERG KOMPETENZZENTRUM

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Non-severe CID und CVID

Immundefekte von „severe“ bis „common“

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ZSE-B-Zentren an der Klinik für Kinder- und Jugendmedizin im A-Zentrum für seltene Erkrankgunen des Universitätklinikum Ulm: Zentrum für seltene Skeletterkrankungen (ZSSK) & Zentrum für seltene Störungen der Hämatopoese und Immundefekte ZSHID)

Indexpatientin Marie – Erkrankungsbeginn im Alter von 18 Monaten

- 18 Monate: **Autoimmunthrombozytopenie** – insgesamt > 9 Rückfälle
- „aus dem Auge“ im Alter von 5-10 Jahren
- 10 Jahre: prolongierte Fieberepisode mit Polyarthritis, Erythema nodosum, **Hypogammaglobulinämie** → sJIA? CVID?

  → Beginn regelmäßiger Immunglobulinsubstitution
- Seither wiederholte bakterielle (Haut-) Infektionen bei **Autoimmunneutropenie**n

  → G-CSF „on demand“
- 27 Jahre: **Bronchiektasien** nach wiederholten Infektionen der oberen Luftwege und 3 Pneumonien (2x Chlamydien)

Jüngerer Bruder von Marie – Erkrankungsbeginn nach Geburt

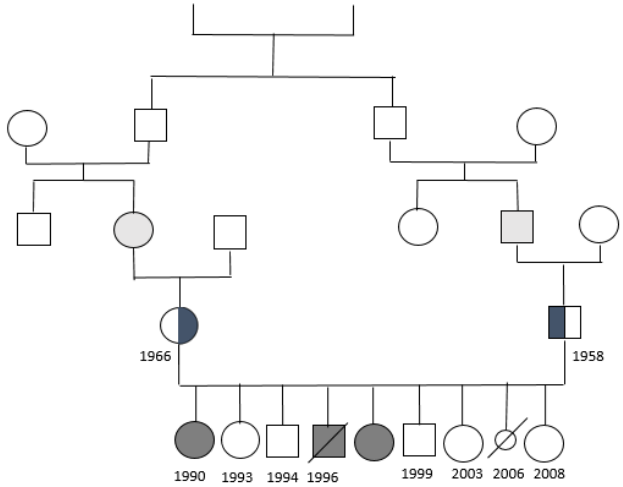
- Kongenitale **Thrombozytopenie** und **Hepatopathie**
- Im Alter von 3 Woche: **ITP** → Splenektomie
- V.a. **HLH** bei mehreren erfüllten Kriterien
- In Alter von 3 Monaten: **systemische CMV-Infektion**
- **Exitus letalis vor geplanter Stammzelltransplantation**

Jüngere Schwester von Marie – Erkrankungsbeginn im Altern von 10 Jahren (?)

- Keine Krankenhausvorstellungen trotz wiederholter Infektionen der oberen Luftwege
- Im Alter von 10 Jahren**: Morbus Hodgkin und Hypogammaglobulinämie**

→ Polychemotherapie und i.v. Immunglobulinsubstitution; auf Wunsch der Eltern vorzeitig beendet

- Derzeit aus den Augen, aber in Vollremission



Immunologie Marie
(ähnlich bei der jüngeren Schwester)

- Erniedrigte Gesamt-Immunglobuline
- T-Zellen numerisch und funktionell normal (wenn keine Im
- B-Zell-Subpopulationen:

Von allen B-Zellen (CD19+) sind:		absolut
IgM+/IgD+:	97 %	572 /µl
IgM-/IgD-	0,1 %	0 /µl
Transitionale B-Zellen		
IgM++/CD38++:	6,8 %	40 /µl
Naive B-Zellen		
IgD+/CD27-:	93 %	548 /µl
CD21-low B-Zellen		
CD21-low/CD38-low:	7,0 %	41 /µl
Plasmablasten		
IgM Plasmablasten (CD20-/IgM+/CD27+):	0,1 %	0 /µl
Class-switched Plasmablasten (CD20-/IgM-/CD27+):	0 %	0 /µl

Memory B-Zellen		absolut
CD27+ B-Zellen:	4,8 %	28 /µl
1. non-switched memory:		
IgM+/CD20+/CD27+:	4,5 %	26 /µl
IgM only (IgM+/IgD-/CD27+):	0,8 %	4 /µl
MZ-like (IgM+/IgD+/CD27+):	3,7 %	21 /µl
2. class-switched memory:		
IgM-/CD20+/CD27+:	0 %	0 /µl
IgA+:	0 %	0 /µl
IgG+:	0 %	0 /µl
3. atypical memory:		
IgM-/CD27-:		
Sonstige		
IgD only (IgM-/IgD+)	0 %	0 /µl

Funktionelle Tests und Molekulargenetik Marie

Name	Date of sample	Plasma spot ADA2 activity mU/g protein
Patient	27 Apr 2017	1.2
Control	27 Apr 2017	72.0

Previous Dried Plasma spots tested for ADA2 deficiency

Source of Samples	ADA2 activity mU/g plasma protein
ADA2 Deficient (N=38)	4.5 ± 4.4 (0.04 – 17.2)
ADA2 carriers (N=26)	53.6 ± 27.2 (27.2 – 108.7)
at risk not deficient (n=96)	263.1 ± 200.1 (34 – 1186)
Controls (N=36)	131.2 ± 50.2 (58 – 271)

Molekulargenetische Untersuchung (Labor Klaus Schwarz, Ulm) bestätigt die Diagnose: **homozygote Mutation im ADA2-Gen**

→ **Dediciency of Adenosine Deaminase 2 (DADA 2)**

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Klinische Manifestationen von DADA2: Marie, Bruder, Schwerster

IMMUNODEFICIENCY	IMMUNE DYSREGULATION	CNS	SKIN, vasculature	other	working diagnoses
recurrent URI recurrent UTI	ITP, AIHA, neutropenia	**TIA**, stroke Intracranial hemorrhage	**erythema nodosum**	**arthralgias, arthritis**	**systemic JIA**
recurrent viral infections (**herpes**)		cranial nerve palsy	livedo reticularis	**splenomegaly, HSM**	XLP-like disease ALPS-like disease
candidiasis	**MAS**	neurosensorial hearing loss	urticarial rash **eczema**	hypertension	**storage disease**
chronic lung disease	**hypogammaglobulemia**	polyneuropathy	aphtae	bowel perforation	CID, **CVID**
skin abscesses	**leucopenia, lymphopenia**		digital necrosis, ulcerations		cerebral vasculitis
	pancytopenia, SAA		aneurysms		cutaneous PAN
B-cell deficiency	AML, **lymphoma**			*ASYMPTOMATIC*	

Hämatopoetische Stammzelltransplantation (HSCT) bei DADA2
Bericht von Isabell Meyts, Leuven

- 14 Patienten mit ADA2 wurden transplantiert
- Mittleres Alter bei HSCT: 4 Jahre
- Follow up 11 Monate bis 9 Jahre
- Alle leben und gesund, keine weiteren vaskulären Ereignisse
- Auto-Immunphänophene traten post –HSCT in 4/10 Patienten auf

→ HSCT ist sicher und effektiv

→ Myeloisches Engraftement und vollständiger Chimärismus sind wichtig

CVID
(Common Variable Immunodeficiency)

- **Variables Immundefektsyndrom**

  (auch *Antikörpermangelsyndrom)*
- „Der am **häufigste**n zu einer symptomatischen Erkrankung führende angeborene (**primäre**) **Immundefekt** (1 pro 25.000)"
- **„Das Immunglobulin G im Serum ist immer erniedrigt,** in der Regel liegt es unter 3 g/l. Häufig sind die Immunglobuline A und M ebenfalls vermindert"
- „Es ... handelt sich beim variablen Immundefektsyndrom um **eine heterogene Gruppe unterschiedlicher Einzelkrankheiten** mit unterschiedlichen Ursachen, die bisher zum größten Teil nicht bekannt sind"

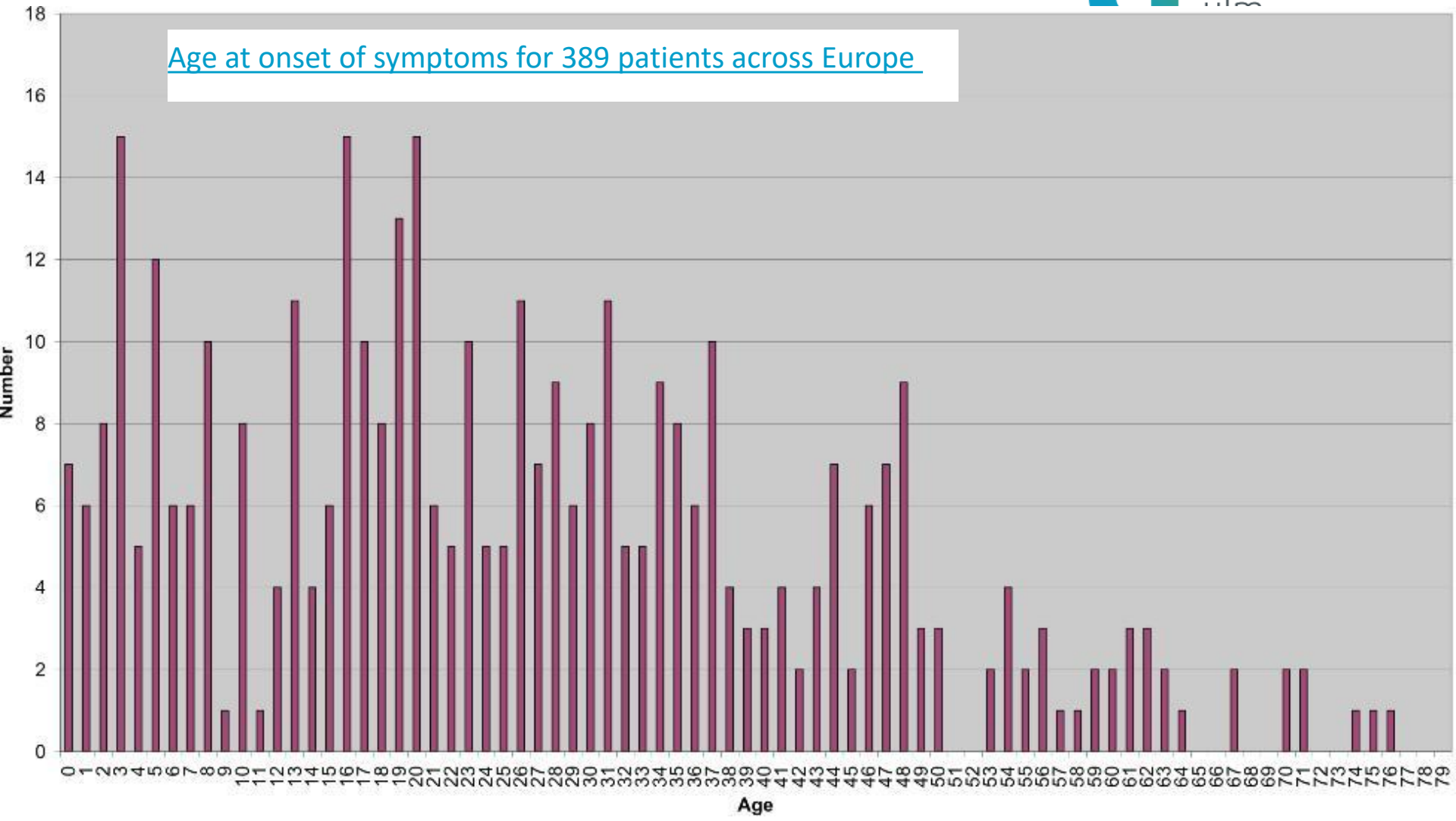
Klassifikation nach Warnatz et al., 2002

Gruppe	Immunologische Kennzeichen
Gruppe I :	CD27+ B-Zellen <0,4%
Ia	<20% CD21neg B-Zellen
Ib	>20% CD21neg B-Zellen
Gruppe II	CD27+ B-Zellen >0,4%

CD27 ist ein Marker für B-Gedächtniszellen, die eine Keimzentrumsreaktion durchlaufen haben.
CD21 kennzeichnet die Progression von unreifen über transitionale zu reifen B-Zellen

Hubert et al., http://www.immundefekt.de/hid.shtml

Combined variable immunodeficiency (CVID)



Chapel et al., Blood 2008

Combined variable immunodeficiency (CVID)

Autoimmunphänomene bei CVID (> 25%!)

Condition	%
Immune thrombocytopenia	34
Evans syndrome	12
Autoimmune haemolytic anaemia	10
Rheumatoid arthritis	7
Anti-IgA	5
Systemic lupus erythematosus	4
Alopecia	3
Diabetes mellitus	3
Inflammatory bowel disease	3
Pernicious anaemia	3
Myasthenia gravid	3
Neutropenia	3
Primary biliary cirrhosis	3
Immune urticaria	3
Anti-cardiolipin	2
Juvenile rheumatoid arthritis	2
Uveitis	2
Vasculitis	2
Lichen planus	1
Thyroiditis	1
Vitiligo	1

Cunningham-Rundles et al. Clin Exp Immunol 2011

Definition CVID und CID (Wikipedia)

CVID (Common Variable Immunodeficiency

- **Variables Immundefektsyndrom**

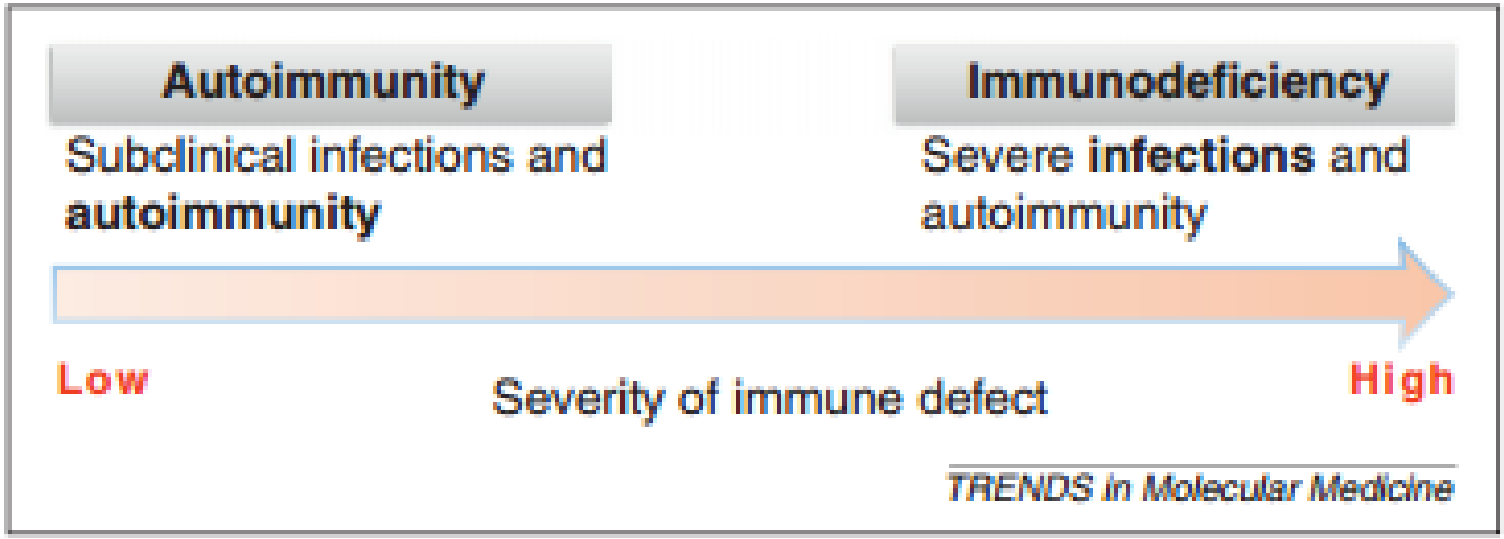
  (auch *Antikörpermangelsyndrom)*
- „Der am **häufigste**n zu einer symptomatischen Erkrankung führende angeborene (**primäre**) **Immundefekt** (1 pro 25.000)"
- **„Das Immunglobulin G im Serum ist immer erniedrigt,** in der Regel liegt es unter 3 g/l. Häufig sind die Immunglobuline A und M ebenfalls vermindert"
- „Es … handelt sich beim variablen Immundefektsyndrom um **eine heterogene Gruppe unterschiedlicher Einzelkrankheiten** mit unterschiedlichen Ursachen, die bisher zum größten Teil nicht bekannt sind"

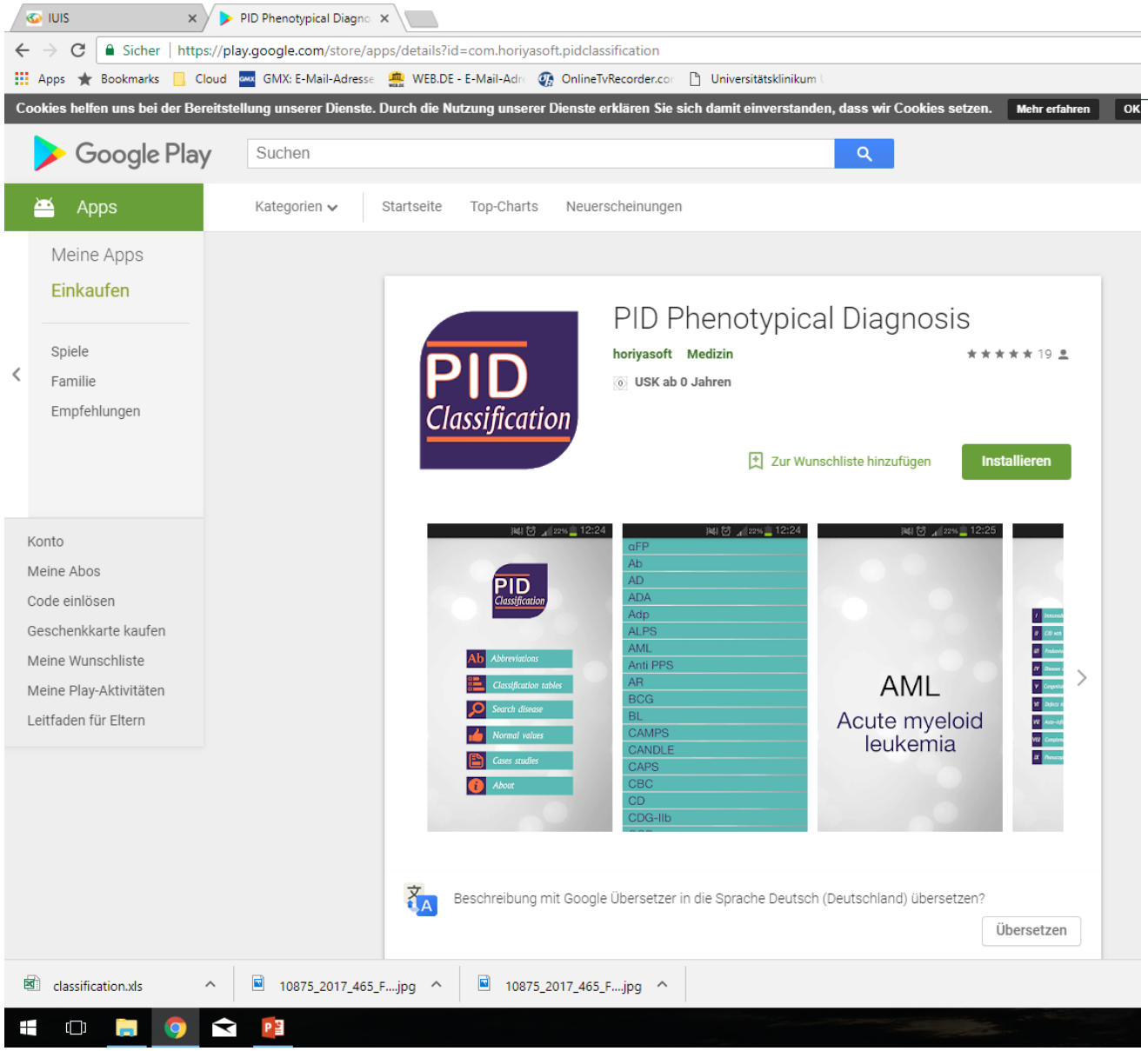
CID (Combined Immunodeficiency)

- Kombinierte Immundefekte…
- "are immunodeficiency disorders that involve multiple components of the immune system, **including both humoral and cell-mediated immunity"**

CVID (Common Variable Immunodeficiency

CID (Combined Immunodeficiency)

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PID Phenotypical Diagno
Sicher | https://play.google.com/store/apps/details?id=com.horiyasoft.pidclassification
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Konto
Meine Abos
Code einlösen
Geschenkkarte kaufen
Meine Wunschliste
Meine Play-Aktivitäten
Leitfaden für Eltern
PID Classification
PID Phenotypical Diagnosis
horiyasoft
Medizin
19
USK ab 0 Jahren
Zur Wunschliste hinzufügen
Installieren
Abbreviations
Classification tables
Search disease
Normal values
Cases studies
About
aFP
Ab
AD
ADA
Adp
ALPS
AML
Anti PPS
AR
BCG
BL
CAMPS
CANDLE
CAPS
CBC
CD
CDG-IIb
AML
Acute myeloid leukemia
Beschreibung mit Google Übersetzer in die Sprache Deutsch (Deutschland) übersetzen?
Übersetzen
classification.xls
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10875_2017_465_F....jpg

The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies (Bousfiha et al., J Clin Immunol 2018)

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I. Immunodeficiencies affecting cellular and humoral immunity.
(a) Severe combined immunodeficiencies SCID, defined by CD3 T cell lymphopenia*.

IIa. CID with associated or syndromic features

III. Predominantly Antibody deficiencies, a: Hypogammaglobulinemia

IV. Diseases of immune dysregulation.
a : Hemophagocytic Lymphohistiocytosis HLH & EBV susceptibility

V. Congenital defects of phagocyte number, function, or both. a : Neutropenia (without anti-PMN)

VI. Defects in Intrinsic and Innate immunity. a : Bacterial and Parasitic Infections

VIIa. Auto-inflammatory disorders

VIII. Complement deficiencies

IX. Phenocopies of PID

Associated with Somatic Mutations

Splenomegaly, lymphadenopathy, autoimmune cytopenias. Defective lymphocyte apoptosis.

ALPS-SFAS.
(somatic mutations in *TNFRSF6*)/ *ALPS-FAS* (ALPS type Im)

RALD. RAS-associated autoimmune leukoproliferative disease. (ALPS Like); ***N-RAS GOF, K-RAS GOF***
Sporadic; granulocytosis, monocytosis/ALPS-like

Cryopyrinopathy, (Muckle-Wells /CINCA/NOMID-like

Associated with Auto-Antibodies

Chronic mucocutaneous candidiasis (isolated or with APECED syndrome). AutoAb to IL-17 and/or IL-22.
Endocrinopathy, chronic mucocutaneous candidiasis /CMC.
Germline mutation in *AIRE*

Adult-onset immunodeficiency with susceptibility to mycobacteria. Auto-Ab to IFNg.
Mycobacterial, fungal, salmonella, VZV infections / MSMD or CID.

Recurrent skin infection. AutoAb to IL-6.
Staphylococcal infections / *STAT3 deficiency*

Ig but Poor

The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies (Bousfiha et al., J Clin Immunol 2018)

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III. Predominantly Antibody deficiencies, a: Hypogammaglobulinemia

Serum Immunoglobulin Assays : IgG, IgA, IgM, IgE

IgG, IgA and/or IgM ↓ ↓

Exclude second causes: drugs [Hx], myeloma [bone marrow], lymphoma. Ig loss (not hypo-IgM) in urine, gastro-intestinal or skin.

→ B Lymphocyte (CD19+) enumeration (CMF)

B absent

Severe bacterial infection. All Ig isotypes decreased.

X-Linked Agammaglobulinemia. *BTK*
Some patients have detectable Ig. ProBc: Nl

AR : **μ heavy chain Def. *IGHM***
Igα def. *CD79A*, Igβ def. *CD79B*
BLNK def. *BLNK*, λ5 def. *IGLL1*
ProBc: Nl

PI3KR1 def. *PIK3R1*. ProBc: Decreased

AD
E47 transcription factor def. *TCF3*.

B >1 %

Commun Variable Immunodeficiency Phenotype

CVID with no gene defect specified.
Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease

AD. Severe bacterial infections; EBV susceptibility.
PIK3CD mutation (GOF). *PIK3CD GOF*. Decreased pro-Bc.
PIK3R1 deficiency (LOF). *PIK3CD*. Pro-Bc present and low memory Bc.

PTEN Deficiency (LOF). *PTEN*. *AD*. Lymphoproliferation, Autoimmunity.

CD81 deficiency. *CD81*. Recurrent infections, may have glomerulonephritis.

TACI deficiency. *TNFRSF13B* (*TACI*). AD or AR . Variable clinical expression

BAFF receptor deficiency. *TNFRSF13C* (*BAFF-R*). Variable clinical expression. Low IgG and IgM.

TWEAK deficiency. *TWEAK* (*TNFSF12*). *AD*. Pneumonia, bacterial infections, warts, thrombocytopenia. Neutropenia. Low IgM and A, lack of anti-pneumococcal antibody.

Mannosyl-oligosaccharide glucosidase deficiency (MOGS). *MOGS* (*GCS1*). Bacterial and viral infections, severe neurologic disease, also known as congenital disorder of glycosylation type IIb (CDG-IIb). Severe hypogammagl.

TTC37 deficiency. *TTC37* . Recurrent bacterial and viral infections, Abnormal hair findings: trichorrhexis nodosa. Poor antibody response to pneumococcal vaccine.

IRF2BP2 deficiency. *IRF2BP2*. Recurrent infections, possible autoimmunity and inflammatory disease. Hypogammaglobulenia, absent IgA.

CD19 deficiency. *CD19*. Recurrent infections, may have glomerulonephritis.

CD20 deficiency. *CD20*. Recurrent infections. Low IgG, Nl or elevated IgM and IgA.

CD21 deficiency. Recurrent infections. Low IgG, impaired anti-pneumococcal response.

TRNT1 deficiency. *TRNT1*. Congenital sideroblastic anemia, deafness, developmental delay. B cell deficiency and hypogammagl.

NFKB1 deficiency. *NFKB1*. AD. Recurrent sinopulmonary infections, COPD, EBV proliferation, autoimmunity, autoinflammation. Ig normal or low, Bc low or normal, low memory Bc.

NFKB2 deficiency. *NFKB2*. AD. Recurrent sinopulmonary infections, alopecia and endocrinopathies (ie, central adrenal insufficiency). Low Bc.

IKAROS deficiency. *IKZF1*. AD. Recurrent sinopulmonary infections. Low or normal Bc potentially reducing levels with age.

ATP6AP1 deficiency. *ATP6AP1*. XL. Hepatopathy, leukopenia, low copper. Leukopenia and hypogammagl.

The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies (Bousfiha et al., J Clin Immunol 2018)

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VIIb. Auto-inflammatory disorders

Sterile inflammation (skin / bone / joints)

Predominant on the bone / joints

Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia and hyper-calprotectinemia. *PSTPIP1* (*C2BP1*). AD

DA: 5 days **FA:** Fixed interval : 4-6 weeks

Sterile pyogenic arthritis, Pyoderma gangrenosum, inflammatory skin rash, Myositis. Acute-phase response during attacks

Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome). ***LPIN2.*** AR

DA : Few days **FA** : 1-3 / month

Chronic recurrent multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia, cutaneous inflammatory disorders

DIRA (Deficiency of the Interleukin 1 Receptor Antagonist). ***IL1RN.*** AR
Continuous inflammation.
Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis.

Cherubism. *SH3BP2.*
AR.
Bone degeneration in jaws

Predominant on the skin

Blau syndrome. *NOD2* (CARD15). AD.
Continuous inflammation.

Uveitis, Granulomatous synovitis, Camptodactyly, Rash, Cranial neuropathies, 30% develop Crohn colitis. Sustained modest acute-phase response.

CAMPS. *CARD14.* AD. Psoriasis.

DITRA. (Deficiency of IL-36 receptor antagonist). ***IL-36RN.*** AR .

Life-threatening, multisystemic inflammatory disease characterized by episodic widespread, pustular psoriasis, malaise, and leukocytosis.

ADAM17 deficiency. *ADAM17*. AR.

Early-onset pustular dermatitis, short and broken hair, paronychia, frequent cutaneous bacterial infections, and Early onset diarrhea , high IL-1 and IL-6 production. Lack of TNF-α was considered partly responsible for their increased susceptibility to infection and development of cardiomyopathy.

SLC29A3 mutation. *SLC29A3* . AR.

Hyperpigmentation hypertrichosis, Rosai-Dorfman like histiocytosis-lymphadenopathy plus H syndrome

Otulipenia/ORAS. *OTULIN*. AR.
Arthralgia, Fever, diarrhea , dermatitis.
Lipodystrophy, myalgia, Neutrophilia

AP1S3 deficiency. *AP1S3*. AR.
Pustular psoriasis

Type 1 Interferonopathies

Progressive encephalopathy, ICC, Cerebral atrophy, HSM, leukodystrophy , Thrombocytopenia, Elevated hepatic transaminases . Chronic cerebrospinal fluid (CSF) lymphocytosis

Aicardi-Goutieres syndrome.
TREX1 AR-AD (+SLE, FCL), ***RNASEH2A, RNASEH2B*** (+SP), ***RNASEH2C, SAMHD1*** (+ Skin vascularitis, mouth ulcers, arthropathy, FCL), ***ADAR1*** (+BSN, SP), ***IFIH1* GOF** AD (+ SLE, SP, SMS)

Spondyloenchondro-dysplasia with immune dysregulation (SPENCD). *ACP5.*

Possibly recurrent bacterial and viral infections, SLE-like auto-immunity (Sjögren's syndrome, hypothyroidism, inflammatory myositis, Raynaud's disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, short stature, SP, ICC.

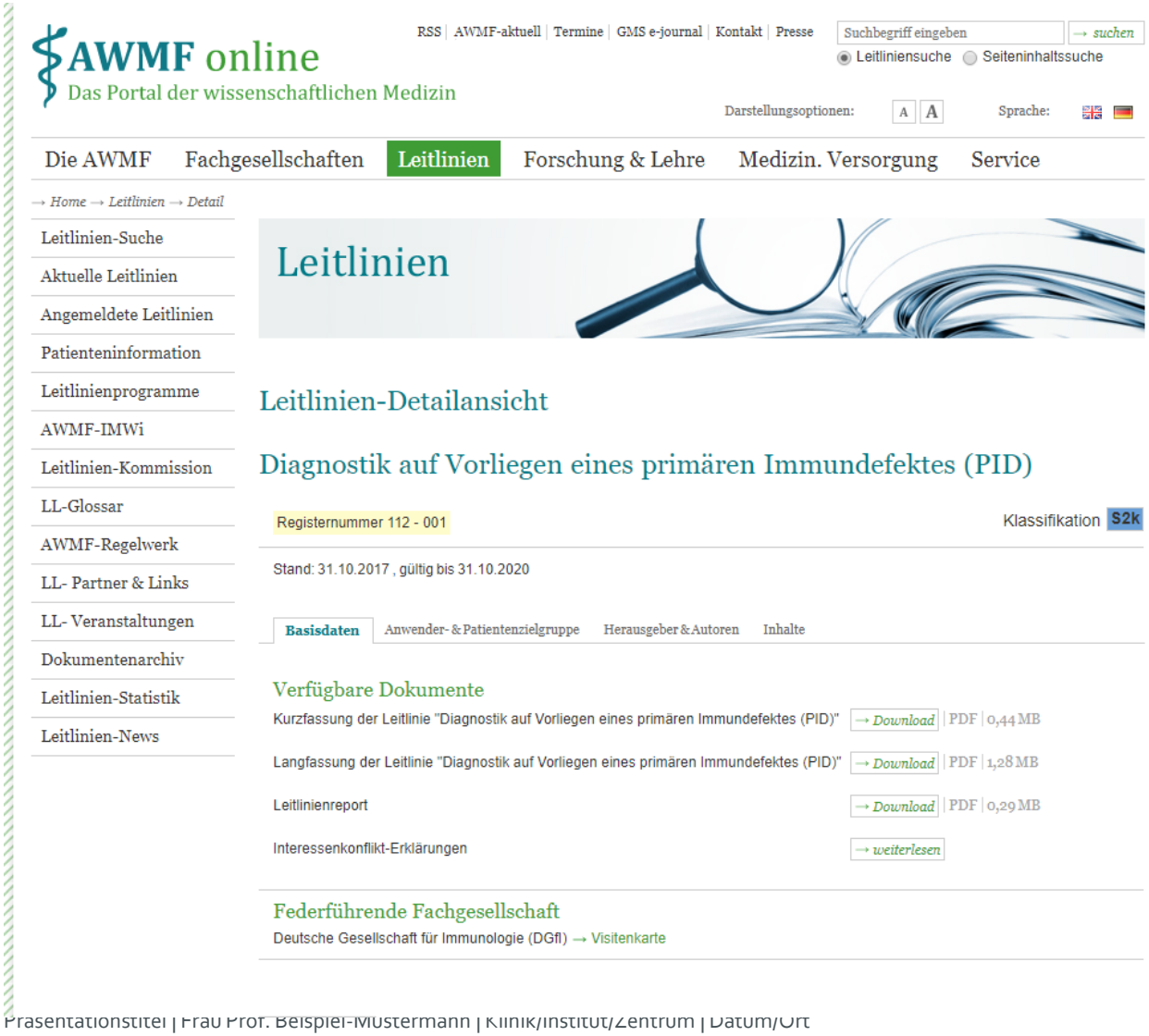
STING-associated vasculopathy, infantile-onset. *TMEM173*. Early-onset inflammatory disease, Skin vasculopathy, inflammatory lung disease, systemic autoinflammation and ICC, FCL

ADA2 deficiency. *CECR1.* Polyarteritis nodosa, childhood-onset, early-onset recurrent ischemic stroke and fever, Livedo racemosa, low IgM, Hypogammagl, Lymphopenia

XL reticulate pigmentary disorder. *POLA1*. Hyper-pigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies

USP18 def . *USP18.* TORCH like syndrome.

AWMF-Leitlinie



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- Leitlinien-Statistik
- Leitlinien-News

Leitlinien

Leitlinien-Detailansicht

Diagnostik auf Vorliegen eines primären Immundefektes (PID)

Registernummer 112 - 001 Klassifikation S2k

Stand: 31.10.2017 , gültig bis 31.10.2020

Basisdaten | Anwender- & Patientenzielgruppe | Herausgeber & Autoren | Inhalte

Verfügbare Dokumente

Kurzfassung der Leitlinie "Diagnostik auf Vorliegen eines primären Immundefektes (PID)"	→ Download	PDF | 0,44 MB
Langfassung der Leitlinie "Diagnostik auf Vorliegen eines primären Immundefektes (PID)"	→ Download	PDF | 1,28 MB
Leitlinienreport	→ Download	PDF | 0,29 MB
Interessenkonflikt-Erklärungen	→ weiterlesen	

Federführende Fachgesellschaft
Deutsche Gesellschaft für Immunologie (DGfI) → Visitenkarte

Kernaussage 1: Pathologische Infektanfälligkeit, charakterisiert durch **E**rreger, **L**okalisation, **V**erlauf, **I**ntensität und **S**umme (**ELVIS**), ist ein Leitsymptom für primäre Immundefekte.

E Erreger (z.B. Pneumocystis jir., CMV, BCG …)

L Lokalisation (Leberabszess, Hirnabszess …)

V Verlauf (kein Therapieansprechen)

I Intensität (Pneumonie, Meningitis, Sepsis …)

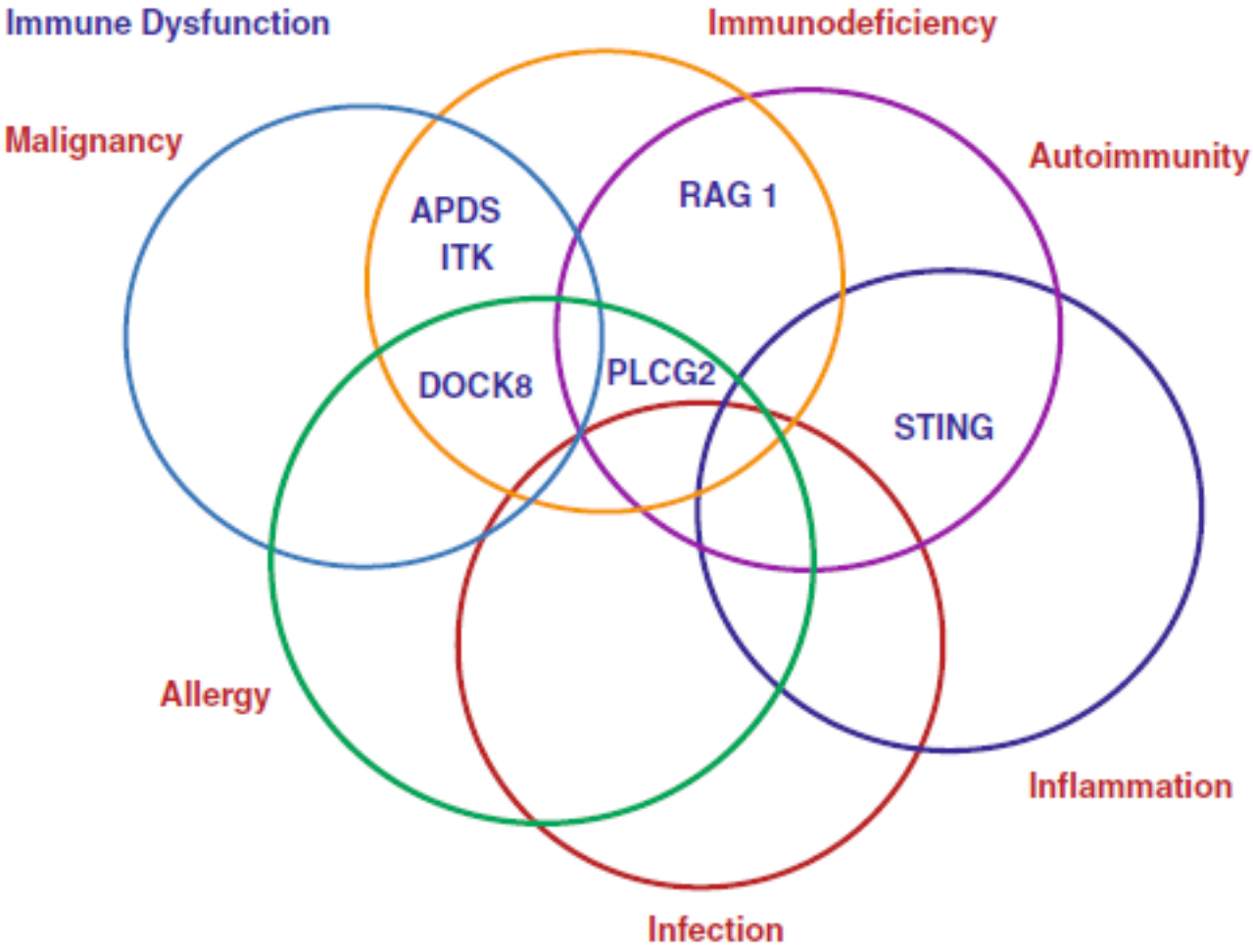
S Summe der Infektionen

Kernaussage 2: Trotz fehlender Infektanfälligkeit kann ein primärer Immundefekt vorliegen.

G	Granulome (mit und ohne Erregeridentifikation)
A	Autoimmunität
R	Rezidivierendes …
F	Fieber ohne Erregernachweis
I	(Fiebersyndrome, FHL, zyklische Neutropenie…)
E	Ekzematöse Erkrankungen
L	Lymphoproliferation (ALPS, XLP …)
D	chronische Darmentzündung (CGD, NEMO, XLP…)

ImmunDYSfunktion als Ursache für die Pathogenese von Symptomen

Überlappungen und Zusammenhänge



Mahlaoui et al, 2017
Grafik nach A. Cant 2017

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Immune dysregulation in Primary Immune Deficiency

- autoimmune cytopenias: IgA deficiency, XLA, WAS, **CID**
- vasculitis: WAS, CVID, **CID**
- granuloma: CGD, CVID, **CID**
- inflammatory bowel disease: CGD, CVID, **CID**
- severe atopy, eczema: IgA deficiency, **CID**
- lymphoproliferation: WAS, XLP, ALPS, **CID**

Kernaussage 3: Primäre Immundefekte können sich auch erst im Jugendlichen- oder Erwachsenenalter manifestieren.

PID – Abklärungs-Algorithmus

- **Anamnese**
- **Klinik**
- **Basisimmunologie**
- **Erweiterte Immunologie**
- **Molekulare Diagnostik**

- Differential-Blutbild
- Immunglobuline*
  - IgG, IgA, IgM, IgE
  - Impfantwort (Tetanus, Diphterie, HIB, Pneumokokken)
  - Isohämagglutinine

* Altersnormen beachten

PID – Abklärungs-Algorithmus

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- **Anamnese**
- **Klinik**
- **Basisimmunologie**
- **Erweiterte Immunologie**
- **Molekulare Diagnostik**

- Lymphozytensubpopulationen*
  (T-/B-/NK-, naive T-, aktivierte T-, doppelt negative T- Zellen etc.)
- KM-Phänotypisierung
- T-Zellfunktion in vitro
- NK-Zellfunktion in vitro
- Phagozytäre Funktionen in vitro
- Enzymatische Tests / CH50
- Ausschluß materno-fötale Transfusion
- (Immun-)Histologie

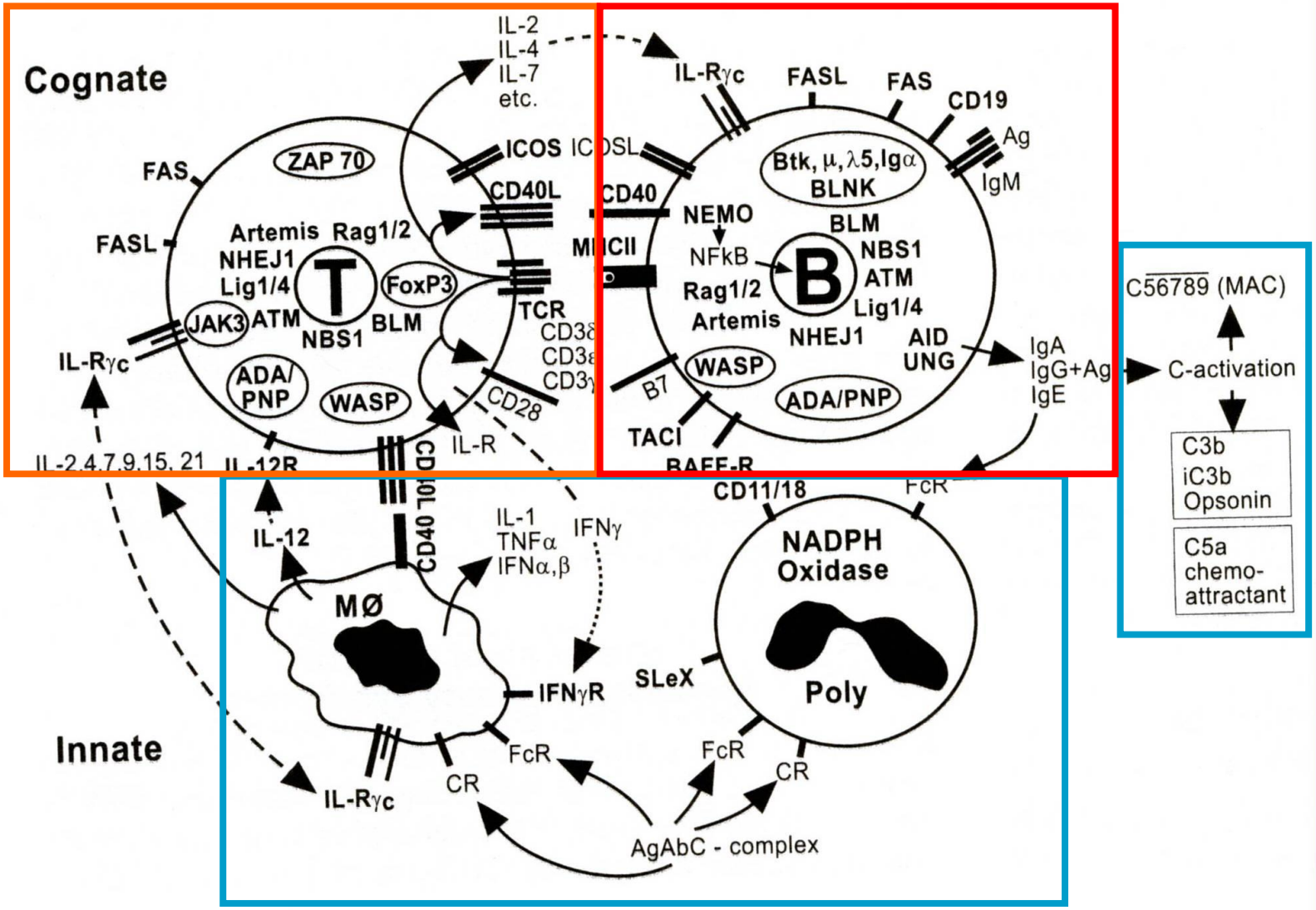
* Alle Zellzahlen als absolute Zahlen erfassen, Altersnormen beachten

PID – Abklärungs-Algorithmus

- **Anamnese**
- **Klinik**
- **Basisimmunologie**
- **Erweiterte Immunologie**
- **Molekulare Diagnostik**

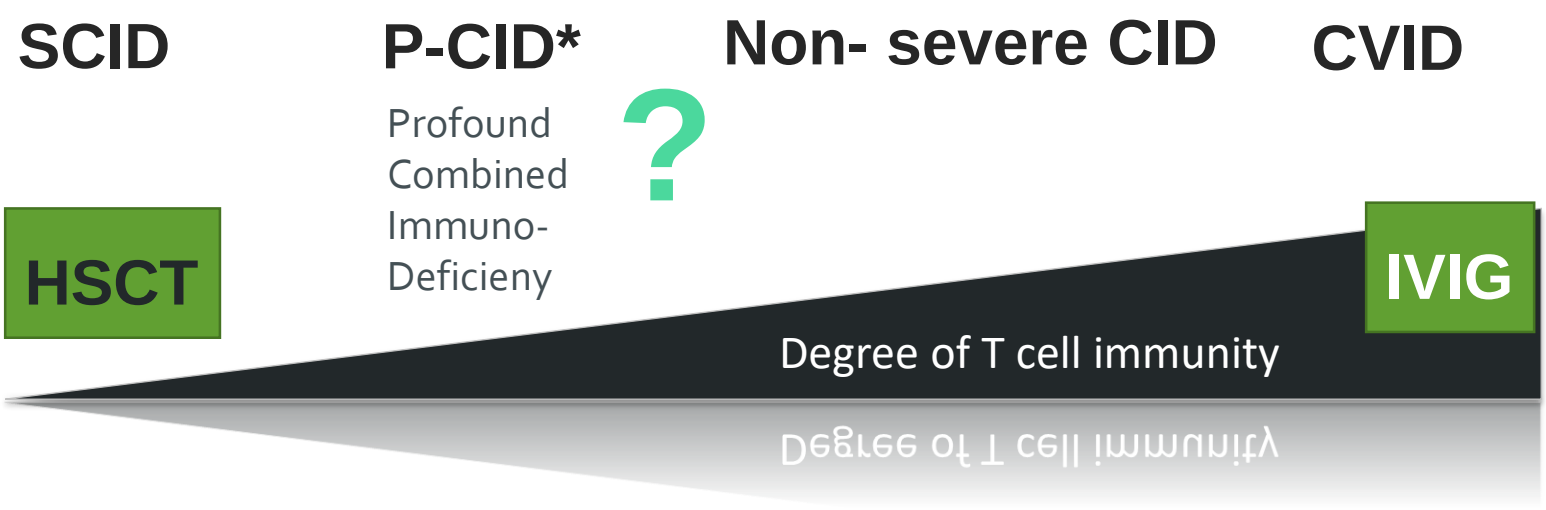
- DNA Analytik des/r Kandidatengen(e)s
- RNA Analyse
- Protein Analyse
- Spezifische Funktionsanalysen
- Moderne genetische Diagnostik (Exom-Sequencing, Array-Assays)

PID – Synpsis


Cognate
IL-2
IL-4
IL-7
etc.
ICOS
ICOSL
CD40L
CD40
MHCII
TCR
CD3δ
CD3ε
CD3γ
CD28
IL-R
ZAP 70
FAS
FASL
Artemis
Rag1/2
NHEJ1
Lig1/4
T
FoxP3
JAK3
ATM
BLM
NBS1
IL-Rγc
ADA/
PNP
WASP
IL-2,4,7,9,15, 21
IL-12R
IL-12
IL-Rγc
IL-Rγc
FASL
FAS
CD19
Ag
IgM
Btk, μ, λ5, Igα
BLNK
NEMO
NFkB
B
BLM
NBS1
ATM
Lig1/4
Rag1/2
Artemis
NHEJ1
AID
UNG
IgA
IgG+Ag
IgE
B7
WASP
ADA/PNP
TACI
BAFF-R
C56789 (MAC)
C-activation
C3b
iC3b
Opsonin
C5a
chemo-
attractant
CD40L
IL-1
TNFα
IFNα,β
IFNγ
MØ
IFNγR
CD11/18
FcR
NADPH
Oxidase
SLeX
Poly
FcR
CR
FcR
CR
Innate
IL-Rγc
AgAbC - complex

Combined Immundeficiencies (CID)

Non-SCID T-cell disorders



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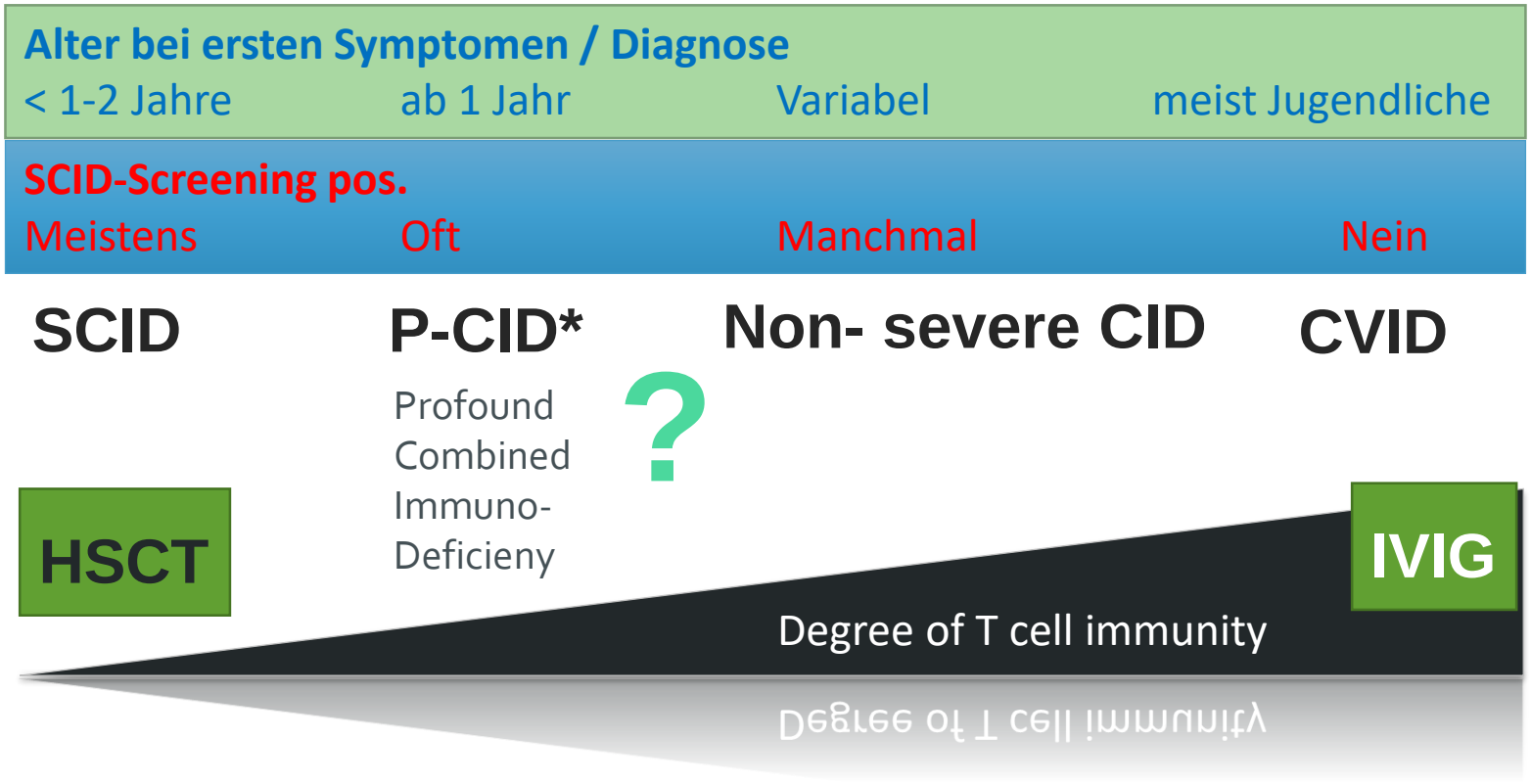
Combined Immundeficiencies (CID)



P-CID Study

Profound Combined Immunodeficiency (P-CID) Study overview and update 2018

Carsten Speckmann and Stephan Ehl on behalf of the PCID-study group:

Alessandro Aiuti, Michael Albert, Waleed Al-Herz, Luis Allende, Tadej Avcin, Horst v. Bernuth, Caterina Cancrini, Andrew Cant, Alain Fischer, Sebastian Fuchs, Sujal Ghosh, Bobby Gaspar, Andrew Gennery, Luis Gonzalez-Granado, Sophie Hambleton, Fabian Hauck, Manfred Hoenig, Despina Moshous, Tim Niehues, Capucine Picard, Jana Pachlopnik-Schmid, Janine Reichenbach, Nikolaus Rieber, Chaim Roifman, Ansgar Schulz, Klaus Schwarz, Markus Seidel, Pere Soler, Polina Stepensky, Brigitte Strahm, Thomas Vraetz, Jolan Walter, Beata Wolska, Austen Worth.

SCID

Profound CID (P-CID)

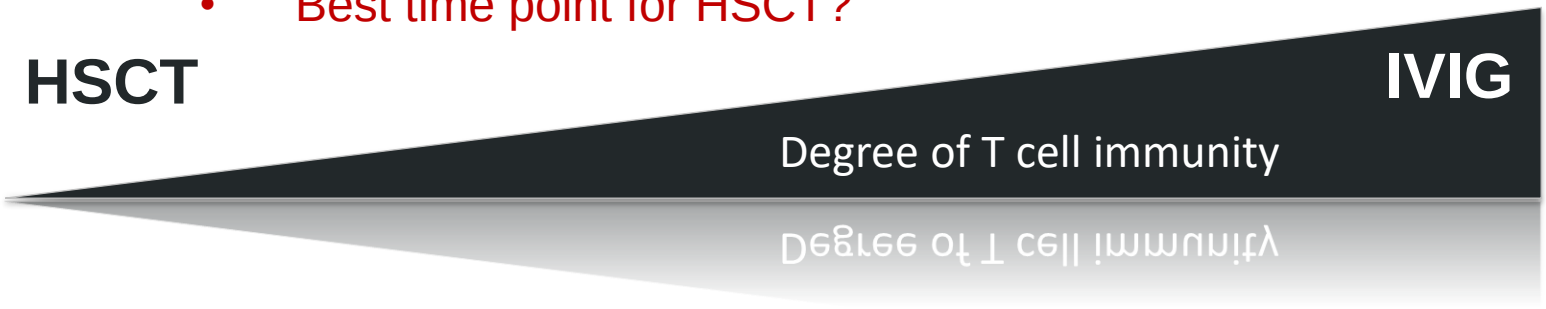
- Natural history of patients with T-cell deficiency (1-16y)
- Clinical evolution +/- HSCT?
- Predictive outcome parameters?

  (prospective “matched pair analysis”)
- Best time point for HSCT?

CVID

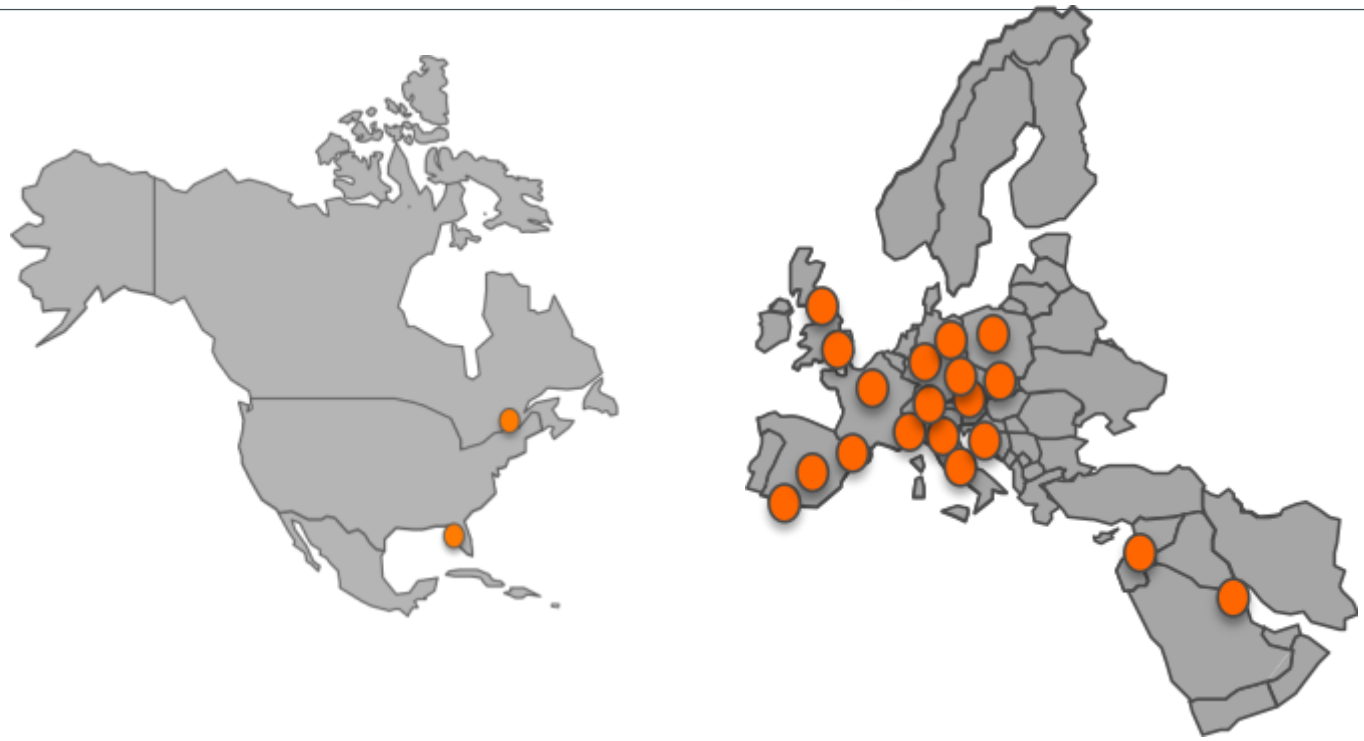
HSCT

IVIG



27 participating centers (Europe, Middle East, North America):

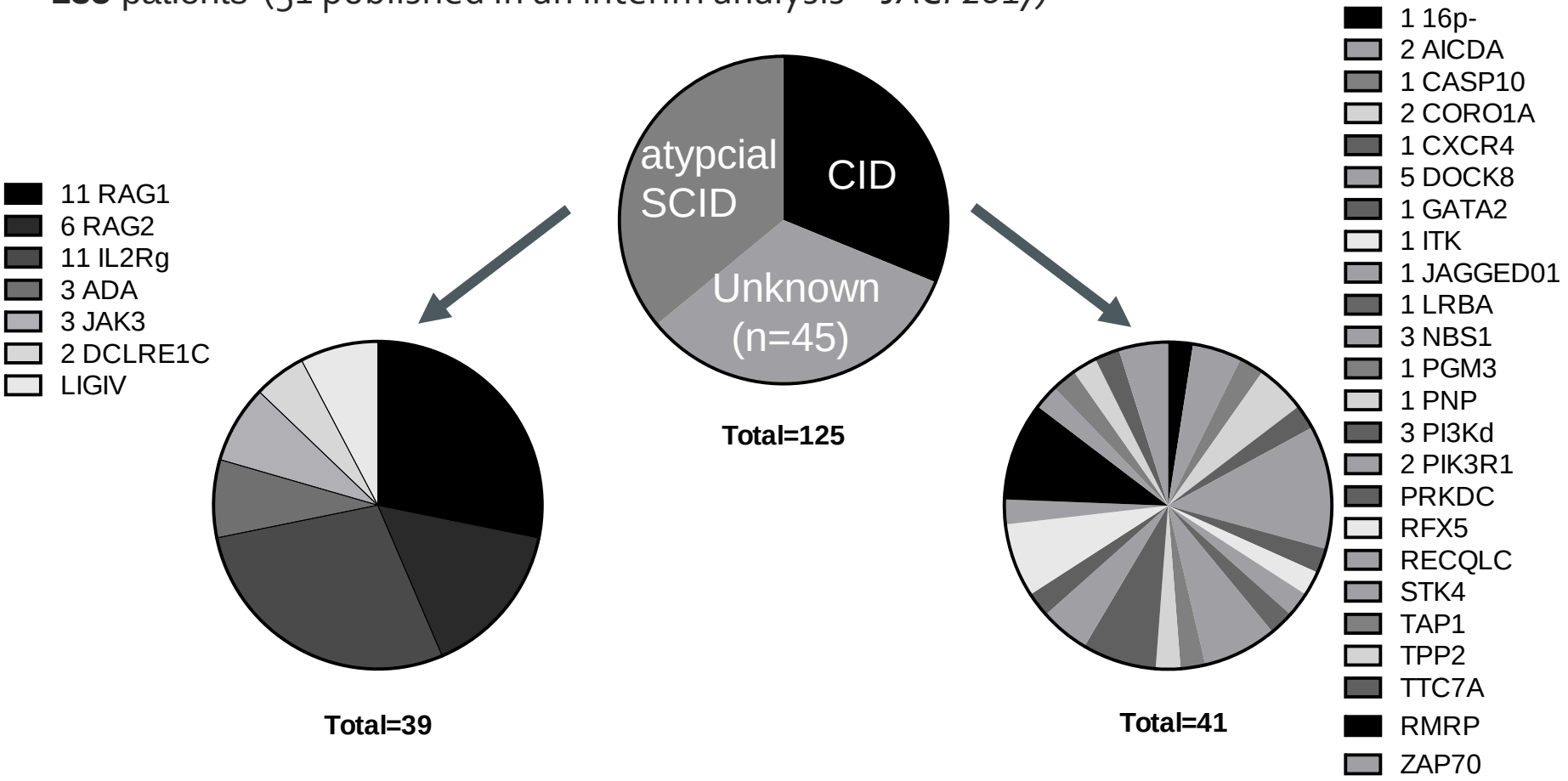
-Barcelona
-Berlin
-Florence
-Freiburg
-Graz
-Hannover
-Jerusalem
-Krefeld
-Kuwait
-Leiden
-London
-Ljubljana
-Madrid
-Milano
-Munich
-Newcastle
-Paris
-Rome
-Sevilla
-St. Petersburg, FL
-Toronto
-Turino
-Tübingen
-Ulm
-Warsaw
-Würzburg
-Zürich



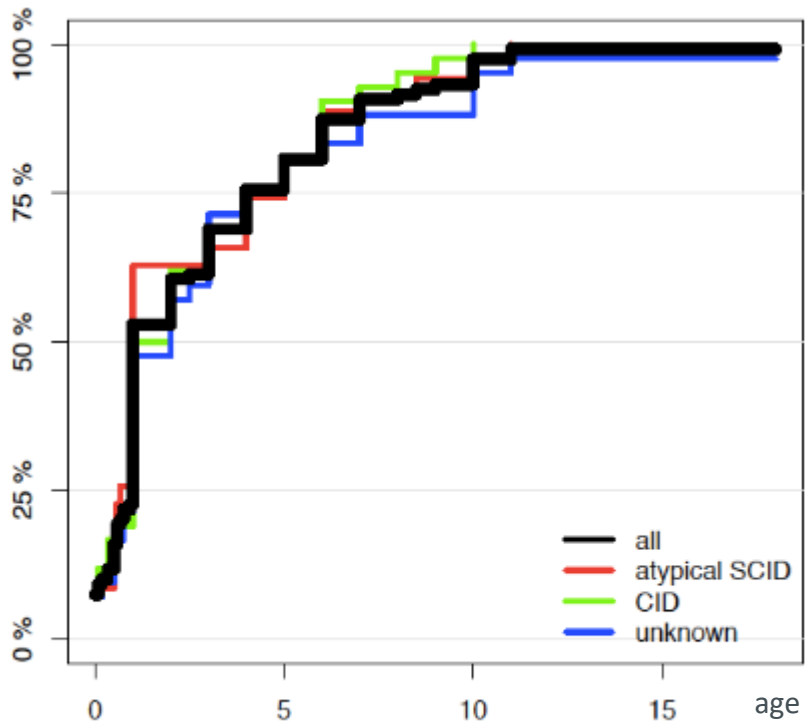
P-CID Genetics

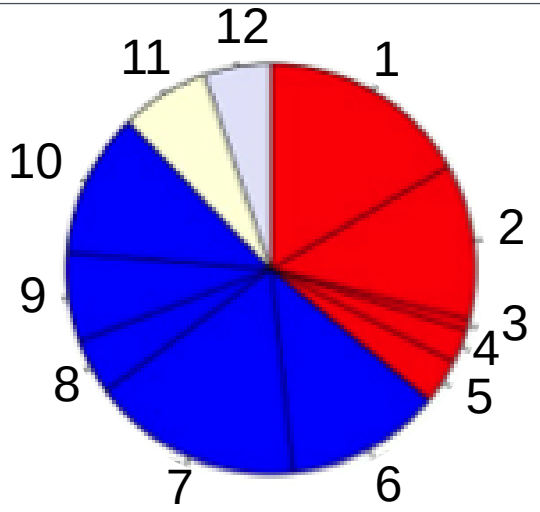
Recruitment Status (February 2017)

- **135** patients (51 published in an interim analysis – *JACI 2017)*



P-CID Age and type of clinical manifestation (n= 119)





immune dysregulation

infection

1 **Invasive bacterial infections**
2 **Severe acute viral infections**
3 **Persistent viral infections**
4 **Opportunistic infections**
5 **Other infections**

6 **Autoimmune disease**
7 **Skin disease**
8 **Gastrointestinal disease**
9 **Lymphoproliferation**
10 **Autoimmune cytopenia**

11 **Other ID related organ complications**
12 **Chronic lung disease**

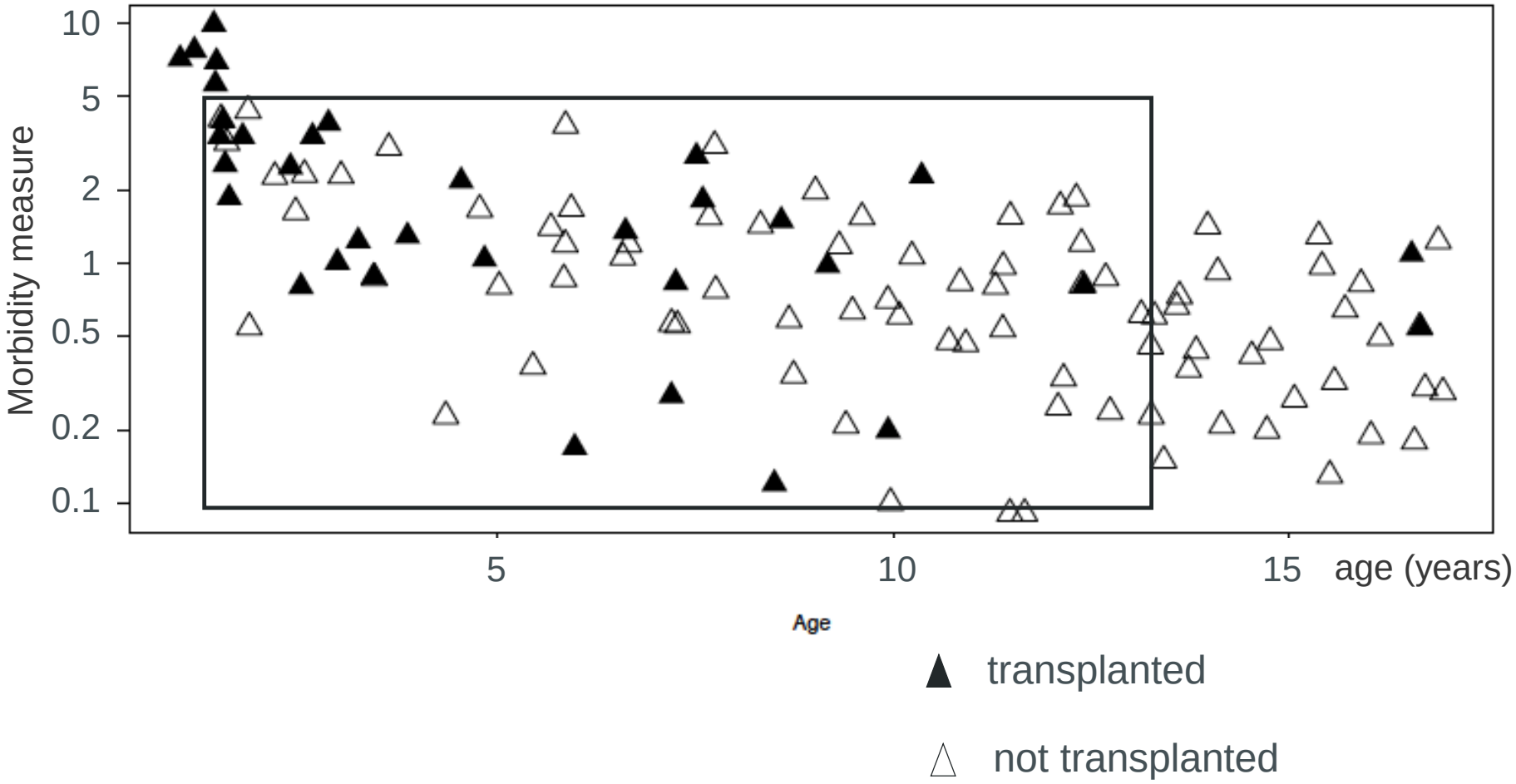
How can we assess severity of disease?

Morbidity Assessment of the cohort (n= 119)

1) **Invasive infections** / year
2) **Viral or opportunistic infections** / year
3) **Autoimmune events** / year
4) Onset of **chronic lung disease** features / year
5) **Complications** due to AI **cytopenias** / year

The number of events in category 1-5 is summed and divided by the age

Morbidity Assessment of the cohort (n= 119)



Mortality HSCT and non-HSCT groups

(n = 19/118, Email survey - July 2017)

9/48 died in the HSCT group (3x atypical SCID, 2x CID, 4x unknown)

4x infection (i.e. viral)
2x multiple organ dysfunction
1x respiratory failure
2x NA

(66% of patients with end organ problems / 37% active infections at HSCT)

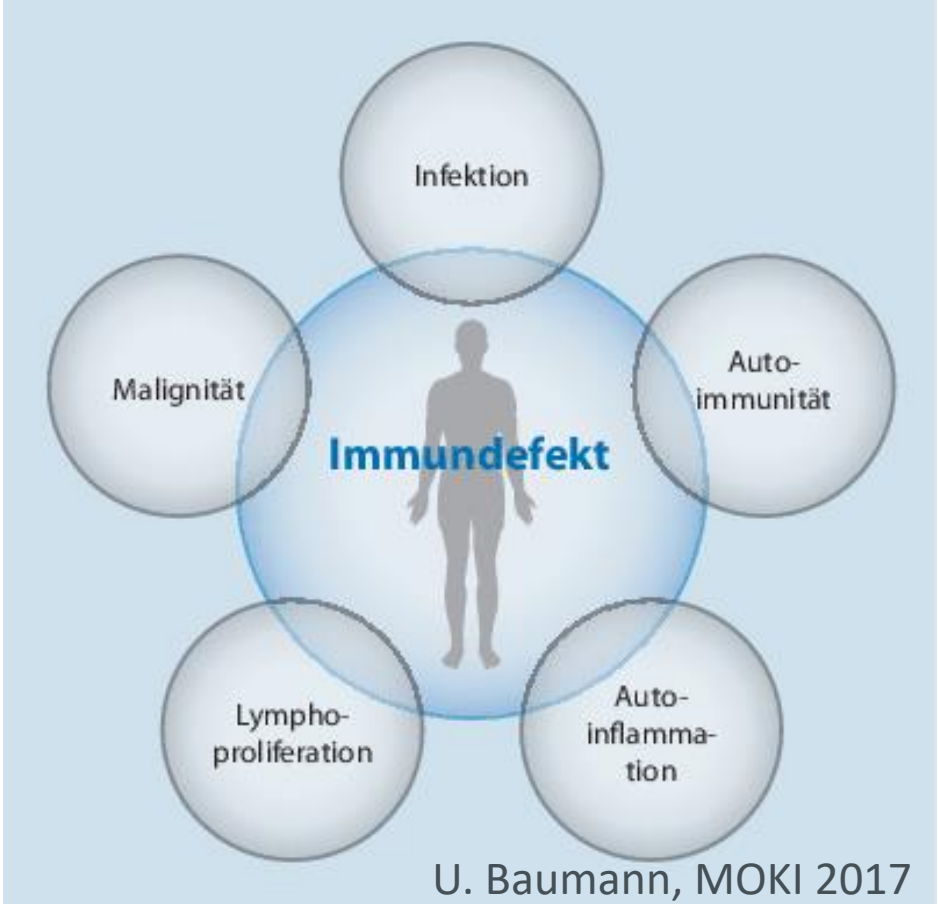
10/70 died in the non-HSCT group (3x atypical SCID, 6x CID, 1x unknown)

4x infection (i.e. viral)
1x B-cell LPD (EBV) ,
2x interstitial lung disease
2x liver disease,
1x multiple organ dysfunction (after chemotherapy for lymphoma)

Summary and Outlook

- The PCID-study is the first prospective outcome study on patients with non-SCID T cell deficiencies
- Autoimmunity is a clinical hallmark of P-CID
- The mortality of P-CID (+/- HSCT) is high
- The cohort structure allows for a prospective matched pair analysis
- This study will provide data to facilitate HSCT decisions on indication and time point of HSCT in P-CID patients

Merke: ein Immundefekt manifestiert sich nicht immer und nicht nur durch Infektanfälligkeit!



Danke!

ansgar.schulz@uniklinik-ulm.de

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The P-CID study

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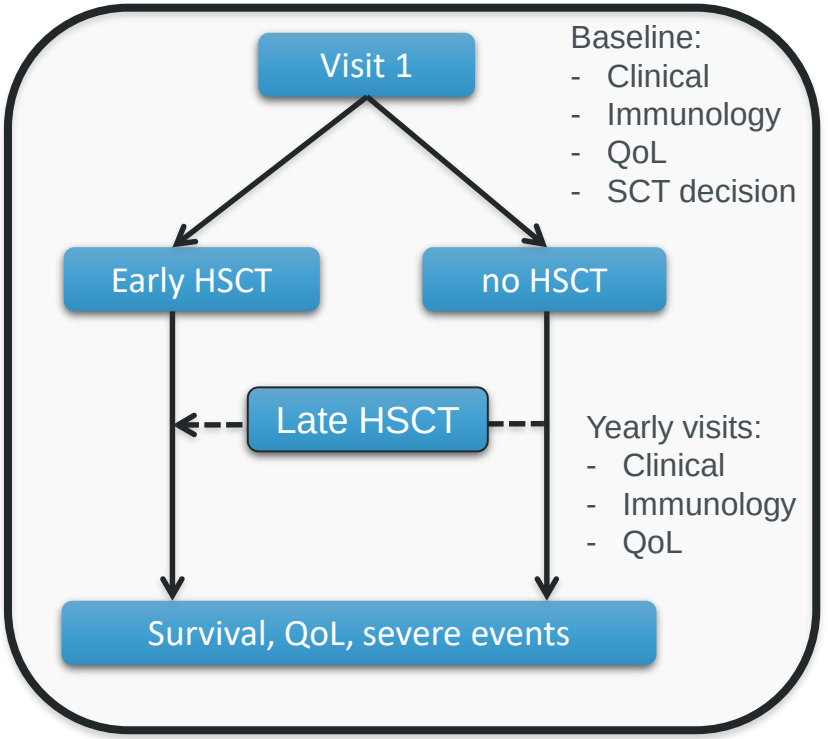
Inclusion criteria

- **Lab evidence of T cell deficiency (2/4):**

- Reduced T cell numbers ($CD4$ ***or*** $CD8$)
- Reduced naïve T cells
- Reduced PHA or anti-$CD3$ response
- Increased γ/δ T cells

- ***and*** **Clinical evidence of T cell deficiency**

- major infection ***or***
- major immune dysregulation ***or***
- virally induced malignancy



Recruitment: 2011 - 2018 (7y)
End of study: 2024 (min. f/u 5y/pt)
Targeted pt #: min. 160

available at www.sciencedirect.com

Clinical Immunology

www.elsevier.com/locate/yclim

2011

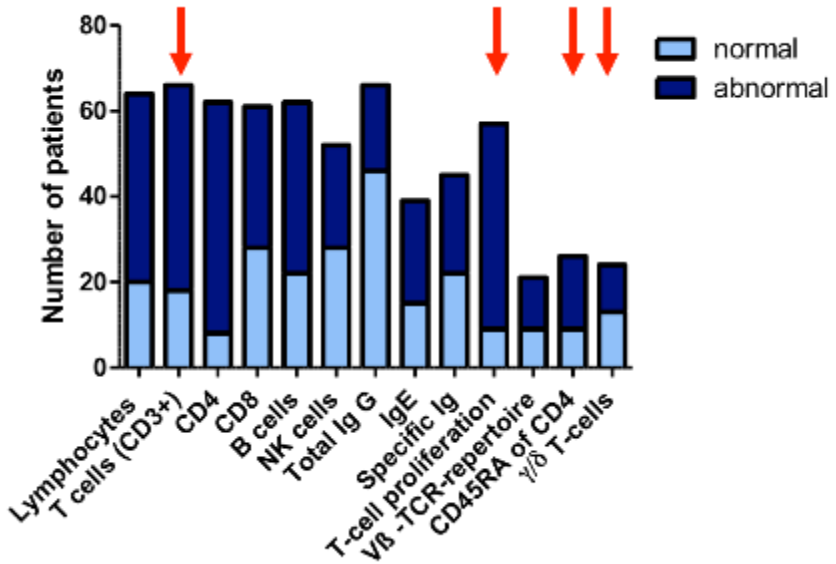
Clinical and immunological manifestations of patients with atypical severe combined immunodeficiency

Kerstin Felgentreff [a, b, 1], Ruy Perez-Becker [c, 1], Carsten Speckmann [a, 1], Klaus Schwarz [a, d], Krzysztof Kalwak [e], Gasper Markelj [f], Tadej Avcin [f], Waseem Qasim [g], E.G. Davies [g], Tim Niehues [c], Stephan Ehl [a, b, *]

- Identification of 70 patients with hypomorphic mutations in SCID-causing genes

A combination of 2/4 lab criteria identifies most patients with „atypical“ SCID:

- T cell numbers ↓
- Naive CD4 T cells ↓
– γδ T cells ↑
- T cell proliferation ↓



Combined variable immunodeficiency (CVID)

Bryant et al. (1990) klassifizierten die CVID Patienten anhand der Zahl der peripheren B-Zellen:
Typ I mit normaler Anzahl peripherer B-Zellen,
Typ II mit reduzierter Anzahl peripherer B-Zellen
Typ III dem Auftreten von **Granulomen**

Klassifikation nach Bryant et al., 1990

Gruppe	Immunglobulinsekretion in vitro
Gruppe A	keine Sekretion von IgM und IgG
Gruppe B	lediglich Sekretion von IgM
Gruppe C	Sekretion von IgM und IgG

Gruppen A und B decken sich mit der Warnatz Gruppe I; die Gruppe Bryant C mit Warnatz Gruppe II. Die klinischen Phänomene Splenomegalie und autoimmune Zytopenien sind mit Gruppe Ia assoziiert

Klassifikation nach Warnatz et al., 2002

Gruppe	Immunologische Kennzeichen
Gruppe I :	CD27+ B-Zellen <0,4%
Ia	<20% CD21neg B-Zellen
Ib	>20% CD21neg B-Zellen
Gruppe II	CD27+ B-Zellen >0,4%

CD27 ist ein Marker für B-Gedächtniszellen, die eine Keimzentrumsreaktion durchlaufen haben.
CD21 kennzeichnet die Progression von unreifen über transitionale zu reifen B-Zellen

Hubert et al., http://www.immundefekt.de/hid.shtml

Monogenetic defects that can present with antibody deficiency associated with autoimmunity

Gene product (gene)	Function	B-cell defects	T-cell defects	Autoimmune (inflammatory) symptoms	Other characteristics	Age of onset	References
Thymic selection and regulatory T cells							
'Leaky' RAG 1 and 2; (*RAG1* and *RAG2*)	BCR/TCR rearrangement	From defective TI Ab responses and selective IgG (subclasses) deficiency to agammaglobulinemia and absence of B cells	From severe deficiency of naive CD4 T cells, progressive T lymphopenia to absence of T cells	AIE, erythroderma, AIHA, AIN, ILD	NK cells normal to absent, eosinophilia. LAD, Sm, erythroderma, GD, leukocytoclastic vasculitis, T-cell lymphoma	Usually birth, up to 30y	[14▪,15▪,16,17▪]
CTLA4 (*CTLA4*)	Transmits inhibitory signals to T cells	Progressive loss of Ig, B cells, increase of CD21low B cells	Dysregulation of Tregs, hyperactivation of effector T cells	Lymphocytic organ infiltration (intestines, lung, brain), psoriasis, AIE, AIT, AIHA, ITP, arthritis, ILD	Sm, LAD	Child–adult	[18▪▪,19▪▪,20]
LRBA (*LRBA*)	Controls lysosomal turnover of CTLA4 in T cells	Low IgG, IgA, disturbed B-cell development, activation, plasmablast formation, Ig secretion and proliferation	Decreased T-cell proliferation, disturbed Treg, skewing toward memory T cells, follicular Treg, and Th cells, increased apoptosis	AIE, AIHA, ITP, AIT myasthenia gravis. IPEX-like disease, ILD	EBV-induced LP, bronchiectasis nephrotic syndrome, GHD, cerebral granuloma, asthma	Usually < 4y	[21▪▪,22,23▪▪,24,25]
Signaling pathways							
Itk (*ITK*)	Tyrosine kinase downstream of TCR, critical role during thymic $CD4^+/CD8^+$	Normal B cells, specific Ab responses low, progressive hypogamma	Low $CD4^+$, high $CD8^+$ T cells	AIHA, ITP, AIT, nephritis	Decreased iNKT cells EBV-associated LP, LAD, Hm, Sm, Hodgkin's lymphoma, pulmonary nodules	3–13 years	[26–28]
	specific npaired	T-cell lymphopenia, defects in chemotaxis, activation, cytokine production	AIHA, AIE, IgA nephropathy, arthritis	High IgE, eczema, thrombocytopenia, neutropenia, malignancy risk	Circa 2 years	[29]
	:2, creased lls, ponses	Increased T-cell apoptosis, reduced cytokine production	AIHA, AIT, immune complex GN, ILD	Hm, Sm, LP, GHD, warts, cirrhosis-associated diffuse hepatocellular dysplasia, mastocytoma	Birth–4 years, one patient at 22 years	[30▪,31]
	gM	reduced naïve and impaired T-cell proliferation, up to normal T cells (in [32])	AIE, ILD	Reduced NK cells, LAD, neutropenia, erythema nodosum	Birth–infancy, one patient 13 years	[32,33]
	Ab low Ig ells, naïve B	Skewing toward CD4, normal Tregs, impaired T-cell activation and proliferation	AIE, ILD	Eczema-like rash	Birth–infancy	[34,35▪,36▪]
	B-cell memory	Impaired T-cell maturation, low memory T cells, absence of Tregs	AIE	Secondary diffuse leukoencephalopathy	6 months	[37▪]
	ocked at	T-cell defects, impaired ICOS upregulation	No AID described (but HSCT at early age)	Defective BAFFR expression	13 months	[38,39]
	high enia, ory B urvival,	Perturbed memory and Tfh cells	AIE	Decreased NK cells	1 year	[40▪]
	nma	Unknown	AIE, AIT, ITP, AIHA, AIN, ILD, alopecia	PG, NRH, Hm, Sm, lung fibrosis, marginal zone non-Hodgkin's lymphoma	2–65 years	[41▪]
	, and duction paired itation d absent	Reduced terminal differentiation of T cells (incl. Tfh cells), increased CD4/CD8 ratio	Alopecia, ITP, inflammatory condition of CNS	Decreased NK cells or NK toxicity, central adrenal insufficiency	5 months to 7 years	[42▪–44▪]
	reduced y B cells	Normal calcium fluxes	AIT, cold urticarial, vitiligo, arthritis	ANA positive, low NK cells, atopy, GD	1–65 years	[45]
	tients, ss of y B $CD21^{low}$		Juvenile-onset SLE; GN, arthritis, alopecia, AIHA, CNS vasculitis, AIT, skin involvement, relapsing polychondritis	LAD	1 year	[46–48]
	al B-cell t	Increased DNTs, decreased Th17 and Treg cells	Multiorgan AI: IDDM, ITP, AIHA, AINAIE, ILD, livedo-like exfoliating dermatitis, uveitis	Decreased NK cells and DCs, increased eosinophils. LP, mycobacterial disease, LGL, allergies, vasculopathy	Birth–17 years	[49,50▪▪,51▪▪]
STAT1 GOF	Role in induction IL-17 producing Th17 cells	Progressive lymphopenia and hypogamma, loss of memory B cells	Normal no. of Tregs, FOXP3 expression and suppressive function	IDDM, AIT, AIHA, ITP, AIE,	GHD	Infancy–toddler	[52]
TACI (*TNFRSF13B*) CVID	Ligation to APRIL and BAFF, TD and TI CSR, plasma blast differentiation	IgG and IgA decreased Impaired B-cell differentiation	Varies from normal no. and function to reduced naive CD4 T cells, disturbed Tfh	AIHA, ITP, ILD, AIE	LAD, GD	All ages	[53,54,55▪,56]
Lymphocyte homeostasis							
Fas (*TNFRSF6*) ALPS-FAS Fas ligand (*TNFSF6*) ALPS-FASLG Caspase-10 (*MHC4*) ALPS-CASP10	Interaction of Fas with *Fas ligand* allows formation of a signaling complex that includes FADD, *caspase-8*, and *caspase-10*. Autoproteolytic processing of the caspases leads to apoptosis	Usually high, sometimes low Ig, defective apoptosis	Increased DNTs, defective apoptosis	ITP, AIHA, AIN, ILD, uveitis, GN, hepatitis	Elevated sFASL, IL-10/IL-18 or B12, eosinophilia, monocytosis, LAD, Sm, Hm, other LP, malignancy risk	Usually childhood, also adults	[57]

CURRENT OPINION IN ALLERGY AND CLINICAL IMMUNOLOGY

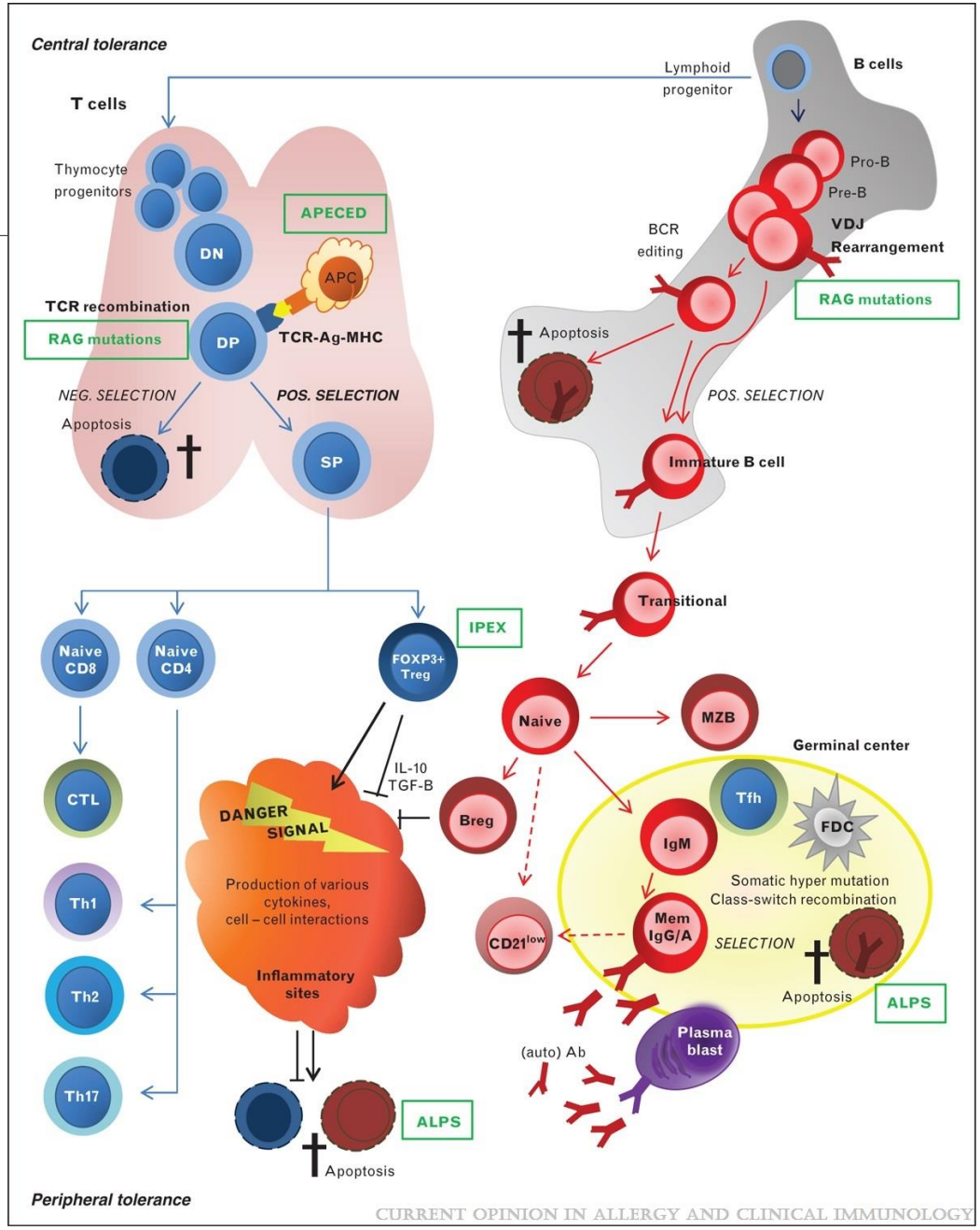
KEY POINTS

- Autoimmune manifestations affect over 30% of patients with common variable immunodeficiency.
- New monogenic defects elucidate immunopathological mechanisms causing the coincidence of immunodeficiency and autoimmunity.
- Improved understanding of disease-causing genetic defects and the immunopathology of the different autoimmune manifestations will improve treatment.

CURRENT OPINION IN ALLERGY AND CLINICAL IMMUNOLOGY

van de Ven, Annick A.J.M.; Warnatz, Klaus
Current Opinion in Allergy and Clinical Immunology15(6):514-524, December 2015.

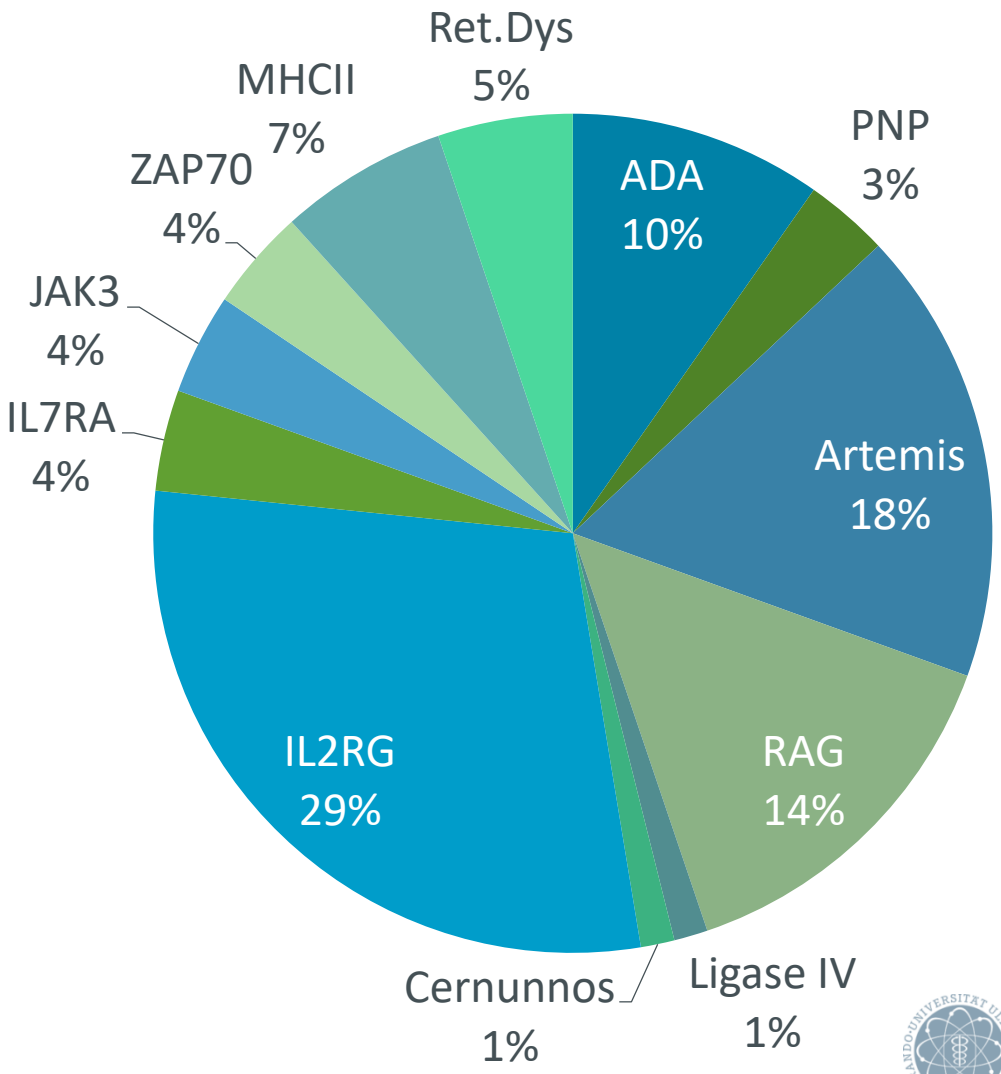
The autoimmune conundrum in common variable immunodeficiency disorders



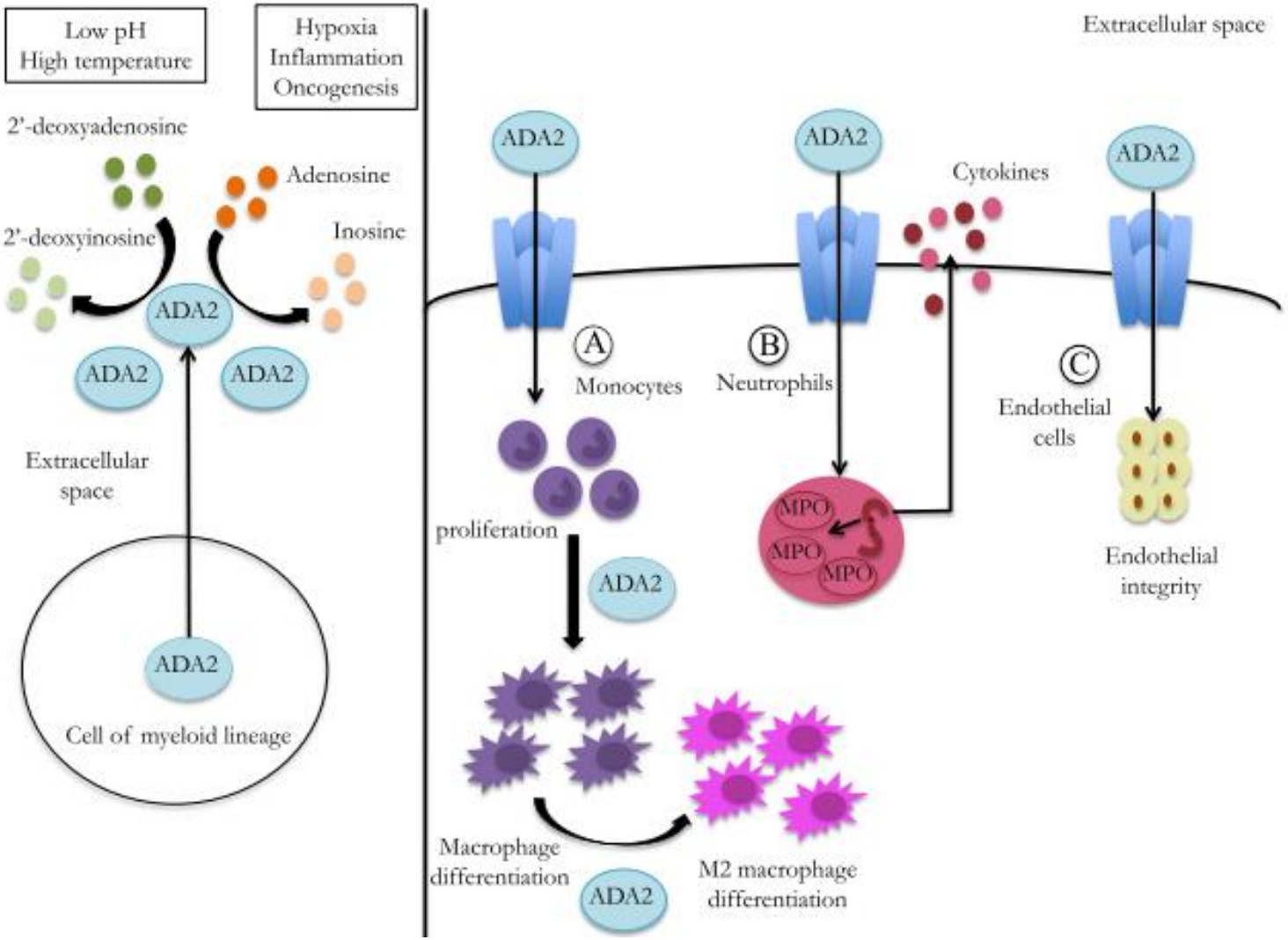
van de Ven, Annick A.J.M.; Warnatz, Klaus
Current Opinion in Allergy and Clinical Immunology15(6):514-524, December 2015.

Verteilung

HSCT wegen CID ín Ulm



Deficiency of ADA2: Pathomechanismus



The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies (Bousfiha et al., J Clin Immunol 2018)

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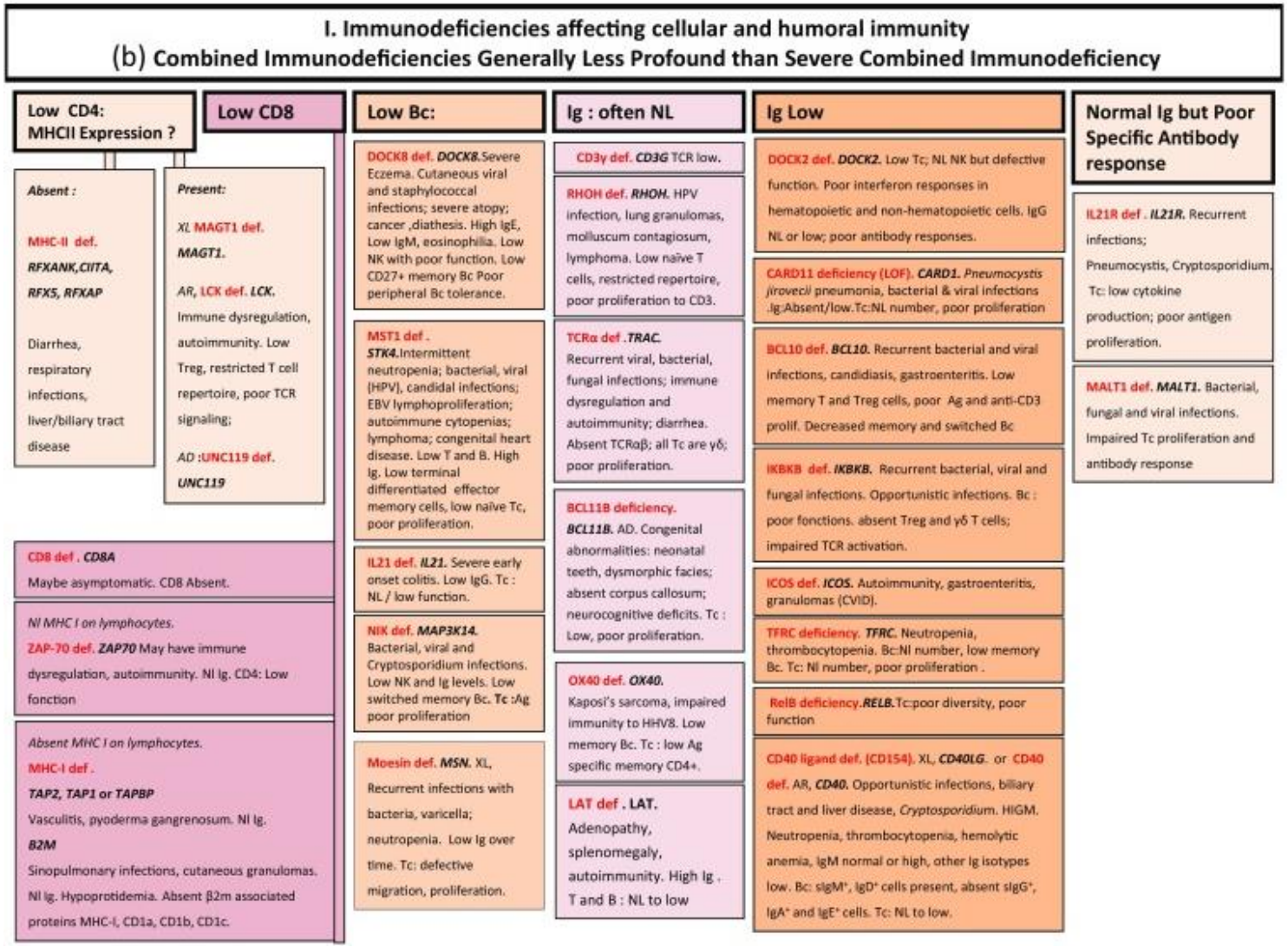

The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies (Bousfiha et al., J Clin Immunol 2018)

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IIa. CID with associated or syndromic features

Congenital thrombocytopenia

XL: **Wiskott Aldrich Sd .** ***WAS (LOF).*** **XL thrombocytopenia** is a mild form of WAS. Recurrent bacterial and viral infections; bloody diarrhea; eczema; lymphoma; autoimmune disease; IgA nephropathy; vasculitis. Small platelets; Decreased IgM. Low antibody to polysaccharides; often increased IgA and IgE. Nl Bc. Tc: Progressive decrease in numbers; Low Tc responses to anti-CD3.

AR: **WIP deficiency.** ***WIPF1,*** Recurrent bacterial and viral infections; eczema; bloody diarrhea . WAS protein absent. +/- small platelets; increased IgE. Bc : Nl to low. Tc: Reduced; defective lymphocyte responses to anti-CD3.

AR: **ARPC1B deficiency.** ***ARPC1B.*** Recurrent invasive infections, colitis, vasculitis. Mild thrombocytopenia, normal sized platelets; autoantibodies (ANA, ANCA); eosinophilia; defective Arp2/3, filament branching. High IgA and IgE.

DNA Repair Defects other than those listed in Table1: Karyotype

Ataxia telangiectasia. ***ATM:*** Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased α-fetoprotein; increased radiosensitivity, chromosomal instability and translocations. Often decreased IgA, IgE and IgG subclasses; increased IgM; antibodies variably decreased. Tc : Progressive decrease, abnormal proliferation to Mitogens.

Nijmegen breakage sd. ***NBS1.*** Microcephaly; bird-like face; lymphomas; solid tumors; increased radiosensitivity; chromosomal instability. Often decreased IgA, IgE and IgG subclasses;increased IgM; antibodies variably decreased. Bc: Variably reduced. Tc: progressive decrease.

Bloom sd. ***BLM.*** Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability. Low Ig.

PMS2 def. ***PMS2.*** Café-au-lait spots ; lymphoma, colorectal carcinoma, brain tumors. HIGM and abnormal antibody responses. Reduced Bc, switched and non-switched.

Immunodeficiency with centromeric instability and facial anomalies. **ICF1.** ***DNMT3B;*** **ICF2:***ZBTB24;* **ICF3:***CDCA7;* **ICF4:***HELLS.* Facial dysmorphism; macroglossia; bacterial/opportunistic infections; malabsorption; malignancies. Cytopenias; multiradial configurations of chromosomes 1,9,16; no DNA breaks. Ig: Hypogammaglobulinemia; Tc and Bc: decreased or Nl.

MCM4 def. ***MCM4.*** Viral infections:EBV,HSV,VZV.Short stature.Bc lymphoma; Adrenal failure; NKc low number and function.

RNF168 def. ***RNF168.*** Short stature; mild defect of motor control to ataxia; normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity (= Riddle Sd). Low IgG or IgA.

POLE1 (Polymerase ε subunit 1) deficiency . ***POLE1.*** Recurrent respiratory infections; meningitis; facial dysmorphism, livido, short stature (FILS syndrome). Low IgM, lack of antibody to PPS. Low memory Bc. Decreased Tc proliferation.

POLE2 (Polymerase ε subunit 2) deficiency. ***POLE2.*** Recurrent infection, systemic BCG infections, autoimmunity (type 1 diabetes, hypothyroidism), facial dysmorphism; Low Ig; Very low Bc. Lymphopenia, lack of TRECS, absent proliferation of antigens.

NSMCE3 deficiency. ***NSMCE3.*** Severe lung disease (possibly viral); thymic hypoplasia, Chromosomal breakage; radiation sensitivity. Ig: Decreased Ab responses to PPS, normal IgG, IgA, elevated IgM. Tc : Number decreased, poor response to mitogens and antigens.

ERCC6L2 (Hebo deficiency). ***ERCC6L2.*** Facial dysmorphism; microcephaly, bone marrow failure. Low Bc, Nl Ig. Lymphopenia.

Ligase I deficiency . ***LIGI*** Recurrent respiratory infections; growth retardation; sun sensitivity; lymphoma; radiation sensitivity. Low IgA and IgG. Reduced antibody responses. Lymphopenia, decreased mitogen response.

GINS1 def. ***GINS1.*** IUGR. Neutropenia, NK cells very low. Tc: and Bc low or normal. High IgA, Low IgG and IgM.

Immuno-osseous dysplasias

Cartilage Hair Hypoplasia. ***RMRP.*** Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine. Ig: Normal or reduced. Tc: Varies from severely decreased (SCID) to normal; impaired lymphocyte proliferation.

Schimke sd. ***SMARCAL1*** Short stature, spondylo-epiphyseal dysplasia, IUGR; nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure. Tc: Decreased.

MYSM1 deficiency. ***MYSM1.*** Short stature, congenital bone marrow failure, myelodysplasia, Skeletal anomalies; cataracts; developmental delay. Affects granulocytes. Bc: immature. Tc: lymphopenia, reduced naïve Tc. Hypogammaglobulinemia.

MOPD1 Deficiency. ***RNU4ATAC.*** Recurrent bacterial infections, lymphadenopathy, Spondyloepiphyseal dysplasia, IUGR, retinal dystrophy, facial dysmorphism; +/- microcephaly. Ig: NL specific antibodies variably decreased.

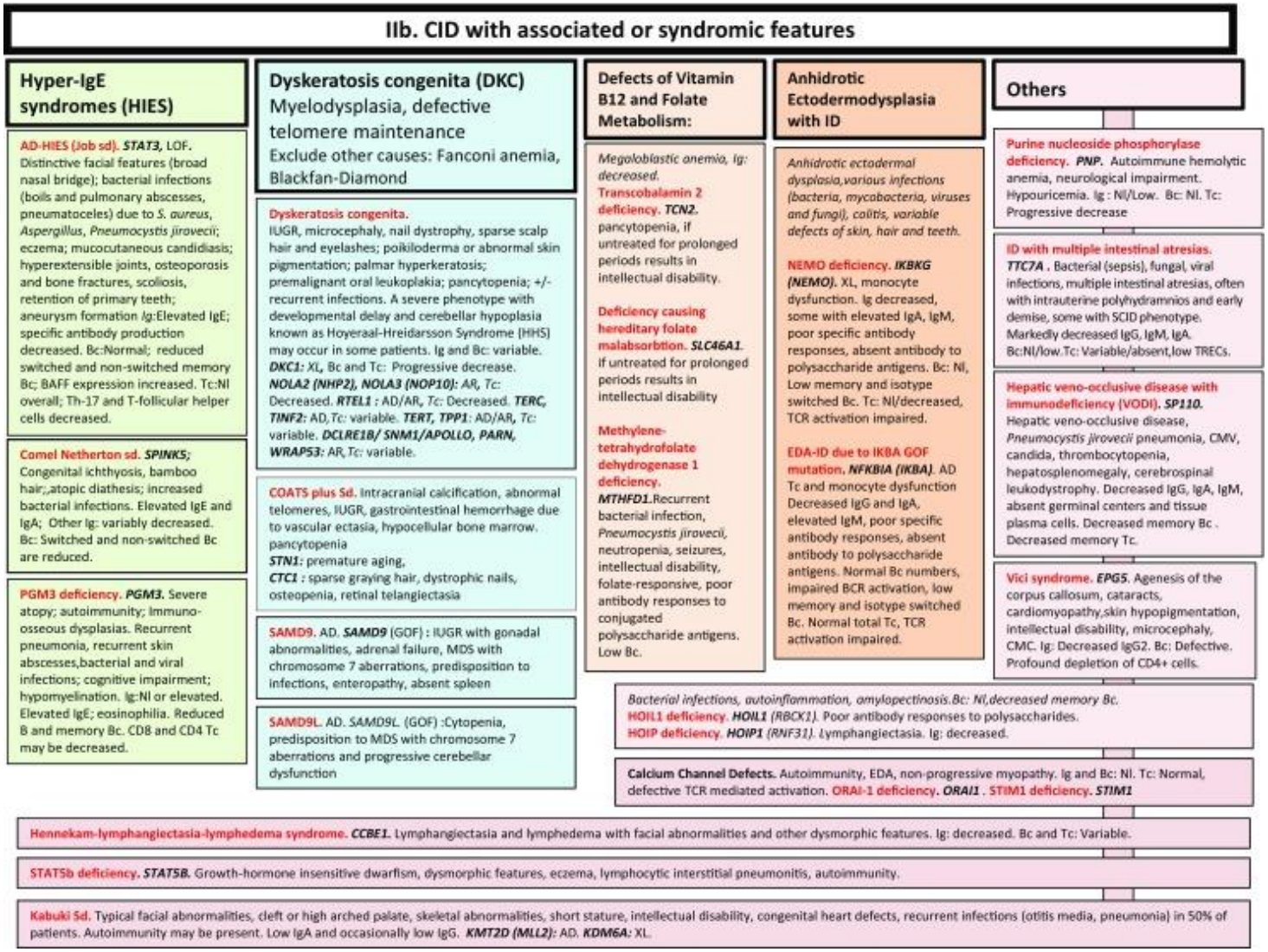
EXTL3 Deficiency. ***EXTL3.*** Platyspondyly, kyphosis, variable skeletal dysplasias, development delay Ig: variably decreased. Tc: reduced.

Thymic Defects with Additional Congenital Anomalies

AD. Hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism, intellectual disability . Ig : Normal or decreased. Tc: Decreased or Nl :
DiGeorge/velocardiofacial Sd. Chr22q11.2 deletion Sd. 22q11.2DS.
TBX1 deficiency . *TBX1* + Renal disease, deafness.
Chromosome 10p13-p14 deletion Syndrome. ***10p13-p14DS.***

AD. CHARGE sd. *CHD7, SEMA3E.* Coloboma, heart anomaly, choanal atresia, intellectual disability, genital and ear anomalies; CNS malformation; some are SCID-like and have low TRECs. Ig: Normal or decreased. Tc: Decreased or normal; response to PHA may be decreased

The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies (Bousfiha et al., J Clin Immunol 2018)



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III. Predominantly Antibody deficiencies. b: Other Antibody deficiencies

Serum Immunoglobulin Assays : IgG, IgA, IgM, IgE

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

AID deficiency. *AICDA.*
Bacterial infections, enlarged lymph nodes and germinal centers.

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

INO80. *INO80 .*
Severe bacterial infections.

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

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

Selective IgA deficiency. *Unknown.*
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. 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.
May be asymptomatic. One or more IgG and/or IgA subclasses as well as IgE may be absent.

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

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

High Bc numbers due to constitutive NF-κB activation

CARD11 GOF .
CARD11. AD. BENTA syndrome

Splenomegaly,
lymphadenopathy,
poor vaccine responses.

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IV. Diseases of immune dysregulation.
a : Hemophagocytic Lymphohistiocytosis HLH & EBV susceptibility

Hemophagocytic Lymphohistiocytosis (HLH)

Hypopigmentation:
Partial albinism . Decreased NK and CTL activities(cytotoxicity and/or degranulation). Bc and Tc: NI

Chediak Higashi sd. *LYST*
Recurrent infections, fever, (H)SM, bleeding tendency, progressive neurological dysfunction. Giant lysosomes (WBC), neutropenia, cytopenias, Specific hair shaft anomaly.

Griscelli sd type 2. *RAB27a.*
Fever, (H)SM, cytopenias; Specific hair shaft anomaly.

Hermansky Pudlak sd type 2. *AP3B1.*
Recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia; Specific hair shaft anomaly.

Hermansky-Pudlak sd, type 10. *AP3D1.*
Oculocutaneous albinism, severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay .

Familial Hemophagocytic Lymphohistiocytosis Syndromes: Fever, (H)SM, cytopenias,
NI Bc. Increased activated Tc.
Decreased to absent NK and CTL activities cytotoxicity.

Perforin deficiency (FHL2).*PRF1.*

UNC13D / Munc13-4 deficiency (FHL3). *UNC13D.*

Syntaxin 11 deficiency (FHL4). *STX11.*

STXBP2 / Munc18-2 deficiency (FHL5) *STXBP2.*
Enteropathy

Susceptibility to EBV

RASGRP1 deficiency. *RASGRP1.*
Recurrent pneumonia, herpes virus infections, EBV associated lymphoma. Increased IgA. Bc and Tc: Poor activation, proliferation, motility

CD70 deficiency. *CD70 (TNFSF7).*
Hodgkin's lymphoma. Reduced IgM, IgG, IgA (75%) and reduced Ag-specific Ab responses (50%). Bc:poor antibody and memory responses. Tc:low Treg, poor activation and function

CTPS1 deficiency. *CTPS1.*
Recurrent/chronic bacterial and viral infections (EBV, VZV), EBV lympho-proliferation, Bc non-Hodgkin lymphoma. Tc: poor proliferation to Ag

RLTPR (CARMIL2) deficiency. RLTPR. Recurrent bacterial, fungal and mycobacterial infections, viral warts, molluscum and EBV lymphoproliferative and other malignancy, atopy. Ig NI to low, poor T dependent antibody response. NI Bc. Tc: low Treg, high CD4, poor function.

ITK deficiency. *ITK* . EBV associated Bc lymphoproliferation, lymphoma, NI or low IgG. Tc: Progressive decrease

MAGT1 deficiency (XMEN). *MAGT1.XL.* EBV infection, lymphoma, viral infections, respiratory and GI infections. Low CD4 Low recent thymic emigrant cells, poor proliferation to CD3

PRKCD deficiency. *PRKCD.* Recurrent infections, EBV chronic infection, lymphoproliferation, SLE-like autoimmunity (nephrotic and antiphospholipid Sd). Low IgG. Low memory Bc high CD5 Bc

EBV associated HLH

XL, **XLP1. *SH2DIA.***
Clinical and immunologic features triggered by EBV infection: lymphoproliferation, Lymphoma. Hypogamma globulinemia,
Absent iNKT cells. Impaired NK cell and CTL cytotoxic activity . Reduced Memory B cells . SAP deficiency (CMF).

XL, **XLP2. *XIAP.***
Splenomegaly, lymphoproliferation, Colitis, IBD, hepatitis. Hypogamma-globulinemia, Low iNKT cells. Increased T cells susceptibility to apoptosis to CD95 and enhanced activation-induced cell death (AICD). Normal NK and CTL cytotoxic activity. XIAP def (CMF)

AR, **CD27 deficiency . *CD27 (TNFRSF7).***
Features triggered by EBV infection, aplastic anemia, low iNKTc lymphoma. Low Ig

FAAP24 deficiency. *FAAP24.*
EBV-driven lymphoproliferative disease. Failure to kill autologous EBV transformed Bc.

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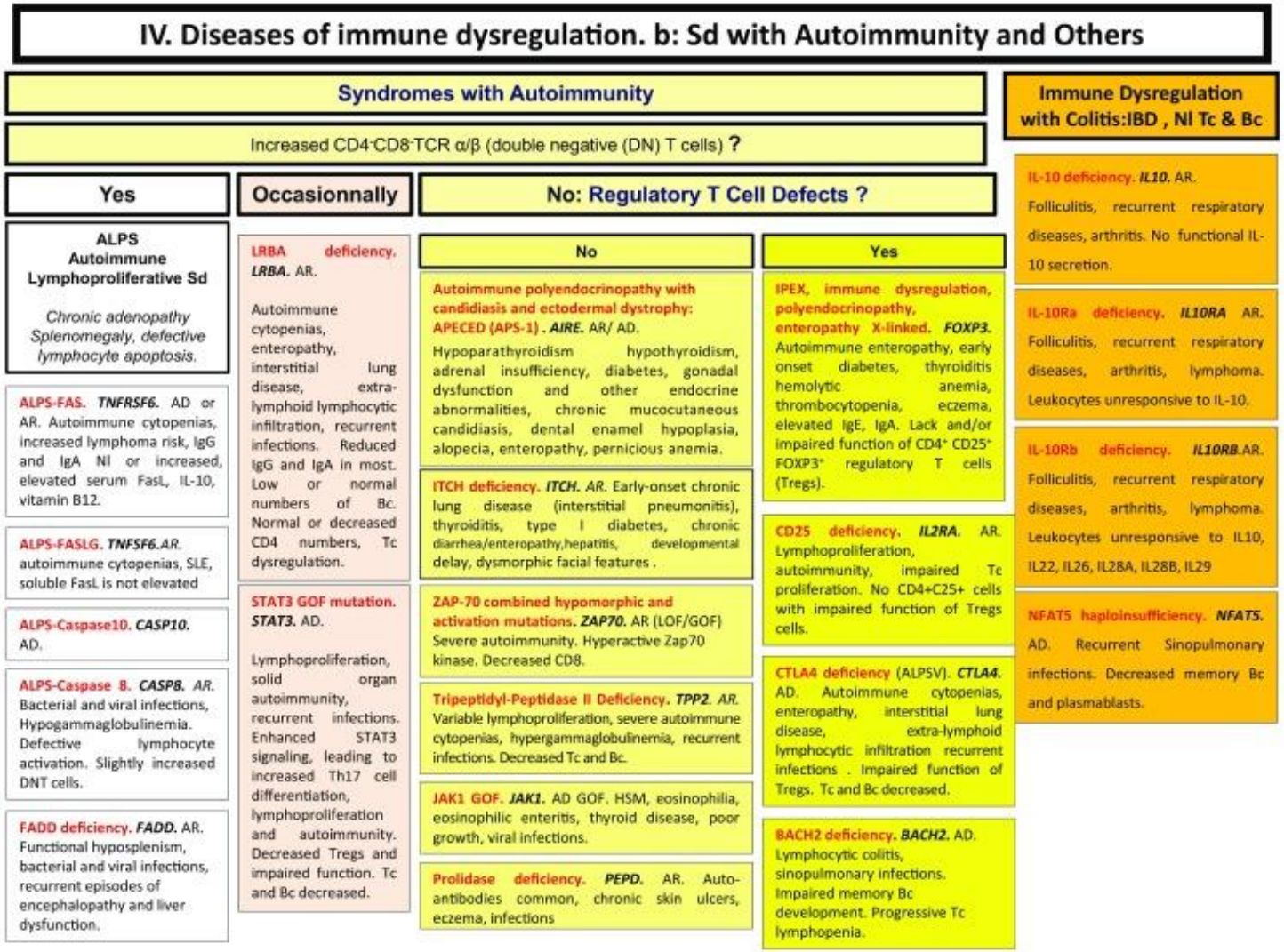

The genetic basis of CID (non-SCID)

- **„atypical“ SCID**

- ADA
- RAG1
- RAG2
- Artemis
- cg-chain
- IL-7RA
- CD45
- CD3 g,d,e,z
- IkBkB
- ORAI1
- ...

„bona fide“ CID

- Coronin A
- PNP
- ZAP70
- Itk
- STIM1
- WAS
- DOCK8
- MHCII
- CARD11
- MALT1
- BCL10
- TPP2
- ...

Radiosensitive disorders

- Ligase IV
- Cernunnos
- DNA PKcs
- NBS
- AT
- ...

Syndromic

- CHH
- Schimke
- ICF
- 22q11
- PGM3
- ...

„sometimes“ CID

- STAT1 GOF
- STAT3 GOF
- PIK3CD
- PIK3R1
- CTLA4
- LRBA
- NEMO
- IkBalpha
- IPEX
- CD25
- ....