Immundefektusok molekuláris alapjai

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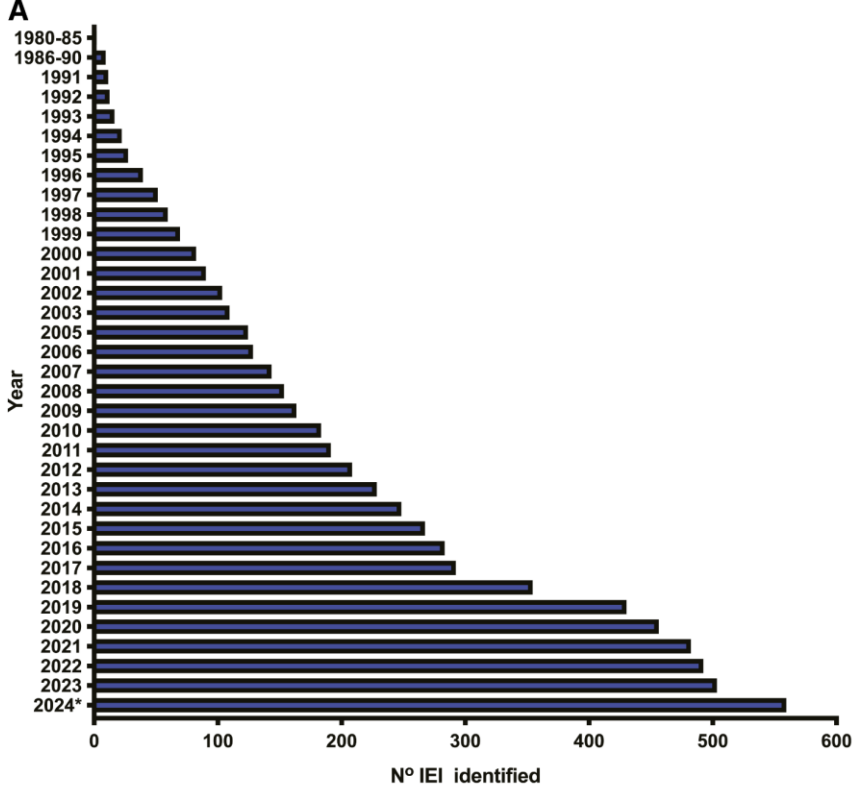

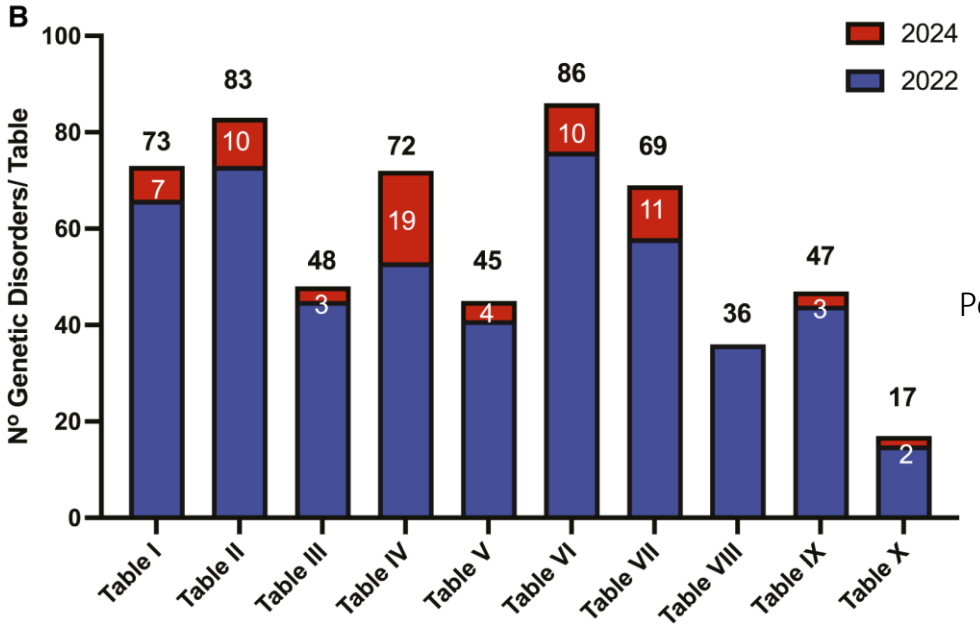

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IUIS* felosztás 2019-2024

IUIS kategóriák	Genetikai defektusok száma (2019/2022/2024)
I. A sejtes és a humorális immunitást érintő PID (kombinált immundeficienciák)	58/66/73
II. Immunhiányok egyéb eltérésekkel vagy szindrómákkal társulva	62/69/83
III. Elsősorban antitesthiány szindrómák	39/45/48
IV. Immun-dysregulációs kórképek	45/52/72
V. Fagocita defektusok	41/42/45
VI. Természetes vagy veleszületett immunitás zavarai	64/74/86
VII. Autoinflammatórikus szindrómák	41/56/69
VIII. Komplement defektusok	36
IX. Csontvelő-elégtelenségek	44/47
X. PID fenokópiák	15/17
Összesen:	445/499/559

2022 óta 69 új defektus

*International Union of Immunological Societies

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

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

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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.

Figure 2. Immunodeficiencies affecting cellular and humoral immunity
Severe combined immunodeficiencies (SCID), defined by CD3 T cell lymphopenia. Low TRECS ᵞ

CD19 NI: SCID T- B+

SCID T-B+NK+

IL7Rα. ***IL7R*** AR.
608971

No γ/δ T cells:
CD3δ*. ***CD3D*** AR
615617
CD3ε*. ***CD3E*** AR
615615
CD3ζ**. ***CD3Z*** AR
610163

NI γ/δ T cells:
CD45*
PTPRC AR
619924

LAT def*. ***LAT*** AR.
602354
Typical SCID or CID. High Ig.

Coronin-1A def*. ***CORO1A*** AR. # 615401
Detectable thymus

PAX1 def*. ***PAX1*** AR (LOF)
615560
Omenn's-like syndrome. Tc deficiency not corrected by HSCT despite donor chimerism. NI IgM, ↓ IgA, NI to ↑ IgE.

LCP2/SLP76 def**. ***SLP76*** AR (LOF)
619374
Autoimmunity, ↑ IgM, ↓ IgA.

Winged helix def*. ***FOXN1***. AR
601705
Congenital thymic aplasia.

ITPKB def**. ***ITPKB*** AR *147522
Panleukopenia, anemia, thrombocytopenia. NI IgM, IgA; ↓ IgG.

SCID T-B+NK-

γc def. ***IL2RG***
XL, **CD 132 def**
300400

JAK-3 def. ***JAK3***
AR, **CD 132+**
600802

CD19 ↓: SCID T-B-

SCID T-B-NK+

Microcephaly ?

Yes	No
Radiation sensitivity - *With facial dysmorphism:* DNA ligase IV def. ***LIG4*** AR # 606593 CERNUNNOS /XLF def*. ***NHEJ1*** AR. # 611291 - *Without facial dysmorphism:* DNA PKcs def*. ***PRKDC*** AR # 615966 Variable Ig levels	RAG 1/2 def (***RAG1/ RAG2***) AR # 601457 NUDCD3 def. ***NUDCD3*** AR. Abnormal VDJ recombination + Radiation sensitivity DCLRE1C def ***DCLRE1C*** AR ***(ARTEMIS).*** # 602450

SCID T-B-NK-

ADA def. ***ADA*** AR
102700
Chondrosternal dysplasia, cognitive defects, sensorineural deafness, multicentric dermatofibrosarcoma protuberans. Progressive disease.

Reticular dysgenesis. ***AK2*** AR
267500
Neutropenia, deafness.

Activated Rac2 defect*. ***RAC2,*** AD GOF. # 618986
Lymphoproliferation, neutropenia.

Figure 3. Immunodeficiencies affecting cellular and humoral immunity
Combined immunodeficiencies: Generally less profound than SCID

Low CD4 cells, Normal CD8: MHC class II Expression ?

Absent

MHC-II def. *RFXANK, CIITA, RFX5, RFXAP.* AR #209920, 620815, 620816, 620817
Nl to low Ig

Present

LCK def. *LCK.* *AR* # 615758
Immune dysregulation, auto-immunity. ↓Treg, ↑IgM.

ITK deficiency. *ITK* AR. # 613011 *EBV* associated immune dysregulation. Nl to low Ig

Polymerase δ def*. AR.
POLD1 #620836 or ***POLD2*** ** #600815. Short stature, intellectual disability. ↓ Bc, ↓ Ig.

STK4 def. *STK4* AR. # 614868 Autoimmune cytopenias, warts, EBV lymphoproliferation, lymphoma, congenital heart disease. Progressive loss of naïve Tc, ↑ T_{EM} and T_{EMRA} cells, poor proliferation. ↓: memory Bc, IgM & Ab responses. ↑IgG, IgA, IgE.

Thymoma with hypogammaglobulinemia (Good syndrome). **AutoAb to various cytokines.**
Invasive bacterial, viral or opportunistic infections, autoimmunity, PRCA, lichen planus, cytopenia, colitis, chronic diarrhea. No B cells, ↑ CD8 Tc.

Low CD8 cells, Normal CD4

CD8 def*. *CD8A* AR. # # 608957
May be asymptomatic

Nl MHC class I on lymphocytes.
ZAP-70 def. *ZAP70* AR (LOF/GOF). **#** 269840
Nl Ig. CD4: Poor fonction
***Combined hypomorphic and activating mutations*: #** 617006 Severe autoimmunity. Nl or decreased CD4 and Bc. Low IgM, IgG Nl or low.

Absent MHC class I on lymphocytes.
Nl Ig
MHC-I def.
TAP2, TAP1* or *TAPBP
. AR. #604571, 620813, 620814. Vasculitis, pyoderma gangrenosum.
B2M* AR. #241600 Cutaneous granulomas. Hypoprotidemia.

Low B cells, Hypogammaglobulinemia

IRF4 multimorphic (IRF4 R95T). *IRF4.* AD-neomorph. *601900
Nl Tc, ↓memory CD8+, ↓Tfh and Th17

IKAROS def.* (CD154). *IKZF1.* AD DN. *603023 Early CID onset. No memory Tc and Bc.

PRIM1 def*. *PRIM1.* AR
620005 Microcephaly, Short stature, Facial dysmorphism and bilateral cryptorchidism. Lipodystrophy. Hepatic fibrosis.↑ type I interferon signature

Moesin def.* *MSN.* XL. # 300988
Neutropenia. ↓ Ig over time. Tc: defective migration, proliferation. Tc lymphopenia improving with time.

IL21 def. *IL21* AR.
615767 Severe early onset colitis. Tc: NL / low function. Poor specific antibody responses;↑ IgE

IKBKA def. *IKKα*** AR (also known as *IKK1* or *CHUK*) * 600664
Absent secondary lymphoid tissues, skeletal abnormalities. ↓ NK function. Nl Tc

SASH3 def*. *SASH3* XL. #301082
Immune dysregulation, refractory autoimmune cytopenias/neutropenia.. ↓Tc, ↓Bc, ↓ NK. ↓specific Ab responses.

C-REL def. *REL.***
619652 Defective innate immunity. Low Ig. Tc: decreased memory CD4, poor proliferation.

MAN2B2 def. *MAN2B2*** AR. #618899
Vasculitis, arthritis, neuro-developmental delay; congenital disorder of glycosylation. Nl or low Ig

NIK def. *MAP3K14***
AR. **#** 604655.↓: NK **Tc:**Ag poor proliferation

Omenn Sd (hypomorphic mutations in RAG and other related SCID defects) # 603554
Erythroderma, Alopecia, Adp, HSM, Eo ↑, IgE↑

***PSMB10** AD.* # 620807
***POLD3** AR.* # 620869. Athymia, global developmental delay

Figure 4. Immunodeficiencies affecting cellular and humoral immunity
Combined immunodeficiencies: Generally less profound than SCID (continued)

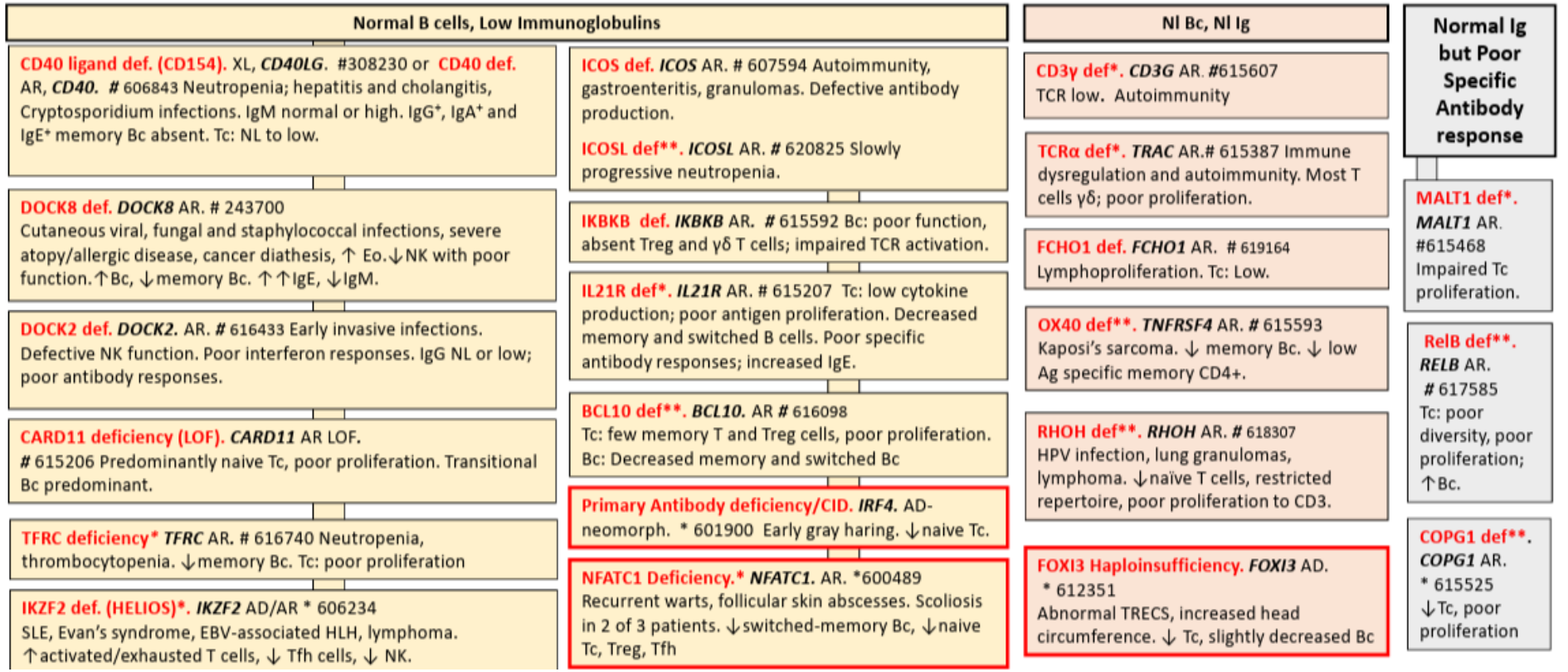


Figure 5. CID with associated or syndromic features

Congenital thrombocytopenia

Recurrent bacterial and viral infections; eczema; bloody diarrhea; autoimmunity

XL: **Wiskott Aldrich Sd or XL thrombocytopenia *WAS (LOF)*.**

301000, 313900

Lymphoma; IgA nephropathy; vasculitis. Small platelets; ↓ IgM. poor response to polysaccharides; ↑ IgA and IgE. Nl Bc. Tc: Progressive decrease in numbers; Low Tc responses to anti-CD3.

AR: **WIP deficiency*. *WIPF1,***

614493

WAS protein absent. +/- small platelets; ↑IgE. Bc: Nl to low.

AR: **Defective Arp2/3-mediated filament branching. *ARPC1B.***

617718

Colitis, vasculitis. Normal sized platelets; ↑ Eo, IgA, IgE

IKZF2 DN (ICHAD syndrome). ***IKZF2.*** AD. * 606234
Early-onset immune dysregulation, developmental delay, autism, sensorineural hearing loss, cleft palate and craniofacial anomalies, athelia. Tc lymphopenia, low TRECS.

DNA Repair Defects: Recurrent infection

Increased radiosensitivity and chromosomal instability

Ataxia telangiectasia. *ATM* AR.
208900
Ataxia; telangiectasia; malignancies; ↑AFP, IgM; ↓ IgA, IgE and IgG subclasses. Tc: Progressive decrease, poor proliferation to mitogens

Nijmegen breakage Sd. *NBS1* AR.
251260
Microcephaly; bird-like face; lymphomas; solid tumors;. ↓ IgA, IgE and IgG subclasses; ↑ IgM. Bc: Variably reduced. Tc: progressive decrease.

Nijmegen breakage syndrome-like disorder*. *RAD50* AR. #613078 IUGR, Microcephaly, mental retardation, bird-like face, short stature. ↓Tc, B cell deficiency. Progressive BMF.

Bloom sd. *BLM* AR. # 210900
Microcephaly; Short stature; bird like face; sun-sensitive erythema; neoplasia. Low Ig.

PMS2 def. *PMS2* AR.# 619101
Café-au-lait spots ; lymphoma, colorectal carcinoma, brain tumors. ↓ Bc, IgG, IgA; ↑ IgM and abnormal antibody responses.

POLE1 (Polymerase ε subunit 1) deficiency (FILS syndrome)*. *POLE1*
AR. # 615139 Recurrent infections; meningitis; facial dysmorphism, livedo, short stature. ↓ IgM, ↓ memory Bc. Decreased Tc proliferation.

RNF168 def* (RIDDLE sd). *RNF168*
AR.# 611943 Short stature; ataxia; learning difficulties; facial dysmorphism; microcephaly. ↓ IgG or IgA.

Ligase I deficiency *. *LIGI* AR.
619774 Growth retardation; sun sensitivity; lymphoma. Macrocytic red blood cells. ↓ Ig, Reduced Ab response. Lymphopenia, increased γδTc, decreased mitogen response.

NSMCE3 deficiency*. *NSMCE3* AR.
617241 Severe lung disease (possibly viral); thymic hypoplasia, Chromosomal breakage. Decreased Ab responses to PPS, normal to elevated IgM. ↓ Tc, poor proliferation.

NK cell deficiency

MCM4 def. *MCM4* AR. #609981
Short stature., microcephaly Bc lymphoma; Adrenal failure

GINS1 def*. *GINS1* AR. # 617827
IUGR. Neutropenia. Tc and Bc: low or normal. High IgA, Low IgG and IgM.

GINS4 def*. *GINS4* AR. * 610611
IUGR, growth delay, Neutropenia, cryptorchidism, tonsillar hypertrophy, recurrent fever

MCM10 def. *MCM10*** AR (LOF).
619313 Severe viral infection, cardiomyopathy. Mild lymphopenia (↓ T memory cells), ↓Bc. ↓ IgG, HLH-like biomarkers.

AR: **Immunodeficiency with centromeric instability and facial anomalies: ICF1. *DNMT3B*** # 242860***;*** **ICF2:*ZBTB24*** # 614069***;*** **ICF3:*CDCA7*** # 616910***;*** **ICF4:*HELLS*** # 616911. Facial dysmorphism; macroglossia; malignancies. Cytopenias; multiradial configurations of chromosomes 1,9,16. ↓ Ig; Tc and Bc: decreased or Nl.

Other DNA defects

POLE2 (Polymerase ε subunit 2) deficiency. *POLE2*** AR. * 602670
Recurrent infection, disseminated BCG infections, autoimmunity, facial dysmorphism; ↓Ig; ↓ ↓ Bc. Lymphopenia, lack of TRECS, absent proliferation to specific antigens.

Rothmund-Thomson syndrome. *RECQL4* AR. # 268400
Variable immunodeficiency, poikiloderma, skeletal and dental abnormalities increased cancer risk, especially osteosarcoma, growth delay

Immuno-Osseous Dysplasias
Short stature, recurrent infections

Cartilage Hair Hypoplasia *RMRP* AR.
250250 Metaphyseal chondrodysplasia, sparse hair, BMF; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine. Ig: Nl or ↓. Tc: Varies from ↓↓ (SCID) to Nl; impaired lymphocyte proliferation.

Schimke Sd *SMARCAL1* AR. # 242900
Spondiloepiphyseal dysplasia, IUGR; nephropathy; BMF. Tc: ↓ (may present as SCID)

MOPD1 Deficiency. *RNU4ATAC* AR.
616651
Lymphadenopathy, Spondyloepiphyseal dysplasia, IUGR, retinal dystrophy, facial dysmorphism; +/- microcephaly. ↓ NK function and Bc. ↓Ig.

Immunoskeletal dysplasia with neurodevelopmental abnormalities*. *EXTL3* AR. # 617425 Cervical spinal stenosis, neurodevelopmental impairment. Eosinophilia***;*** ↓Tc, Ig: nl to↓

MYSM1 def* *MYSM1* AR. # 618116
BMF, myelodysplasia. Skeletal anomalies; cataracts; developmental delay. ↓Tc, naïve Tc, NKc and Bc. ↓Ig.

Figure 6. CID with associated or syndromic features (continued)

Thymic Defects with Additional Congenital Anomalies
Recurrent infections

FOXN1 haploinsufficiency. ***FOXN1*** AD. # 618806 Skin involvement (eczema, dermatitis), nail dystrophy. T cell lymphopenia (CD8+) may normalize by adulthood.

CHARGE Sd. ***CHD7*** AD # 214800 /***SEMA3E*** AD * 608166. Coloboma of eye, heart anomaly, choanal atresia, intellectual disability, genital and ear anomalies; CNS malformation. Nl or ↓Tc and Ig (low TRECS)

Hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, facial dysmorphism, intellectual disability. Nl or ↓Tc and Ig. (low TRECs)
DiGeorge/velocardiofacial Sd. Chr22q11.2 deletion Sd. 22q11.2DS AD. # 188400
TBX1 deficiency. ***TBX1*** AD. # 192430, # 217095, # 187500

Chromosome 10p13-p14 deletion Syndrome. ***10p13-p14DS.*** AD. % 601362 Hypoparathyroidism; renal disease; deafness; growth retardation; facial dysmorphism; cardiac defects may be present

Anhidrotic Ectodermal Dysplasia with ID

Anhidrotic ectodermal dysplasia, various infections (bacteria, mycobacteria, viruses and fungi), variable defects of skin, hair and teeth. Impaired TCR activation.

NEMO deficiency. ***IKBKG (NEMO).*** XL # 300291
Conical incisors. Monocyte dysfunction. IgG↓, some with ↑ IgA, IgM, poor specific antibody responses. ↓ memory and switched Bc. Tc: Nl/ ↓.

EDA-ID due to NFKBIA GOF mutation. ***NFKBIA (IKBA)*** AD. # 612132 Tc and monocyte dysfunction ↓ IgG and IgA, ↑ IgM, poor specific antibody responses. ↓ memory and switched Bc, impaired BCR activation.

EDA-ID due to IKKB GOF mutation* ***IKBB.*** AD. #618204 Late onset. ↓Tc. Bc: Nl number, poor function. ↓ Ig.

Hyper IgE syndromes (HIES)
Syndromes associated with elevated IgE and/or atopic disease

STAT3 signaling pathway
Eczema (atopy), recurrent bacterial (Staphylococcal) and fungal infections, pneumatoceles, high serum IgE and Eosinophilia

AD-HIES (Job sd). ***STAT3.*** AD LOF # 147060
Distinctive facial features (broad nasal bridge); PJP; hyperextensible joints, osteoporosis and bone fractures, scoliosis, retention of primary teeth; coronary and cerebral aneurysms. ↓specific antibody production, ↓ memory Bc. Tc: ↓ Th-17 & Tfh

IL6R deficiency*. ***IL6R*** AR. # 618944
Cold abscesses, high circulating IL-6 Levels. ↓Tfh, ↑Th2. ↓ specific antibody production. ↓ switched memory Bc

IL6ST partial deficiency. ***IL6ST***
AR (LOF, partial deficiency)*: # 618523
Bone fractures, scoliosis, retention of primary teeth, craniosynostosis. ↓ memory Bc.
AD: # 619752
Connective tissue defects(scoliosis, face, joints, fractures, palate, tooth retention). Nl/low IgG and IgA. ↓ to Nl NKc, ↓ memory Bc

ZNF341 deficiency. ***ZNF341.*** AR. # 618282
Mild facial dysmorphism, hyperextensible joints, bone fractures, retention of primary teeth. ↓ Th-17 & NK, ↓ memory Bc, ↑IgG

Recurrent staphylococcal skin infection. AutoAb to IL-6.
Staphylococcal infections

IL6ST complete deficiency. ***IL6ST*** **AR (LOF, complete deficiency)*: # 619751**
Fatal Stuve-Weidemann-like syndrome; skeletal dysplasia, lung dysfunction, renal abnormalities, thrombocytopenia. Defective acute phase response. Complete unresponsiveness to IL-6 family cytokines. Death *in utero* or *in neonatal* period occurred for most affected individuals.

Other disorders associated with high IgE
Recurrent bacterial and fungal infections, high serum IgE and *Eosinophilia*

Comel Netherton Sd; ***SPINK5*** AR. # 256500
Congenital ichthyosis, bamboo hair, atopic diathesis; failure to thrive. ↑ IgA; ↓memory Bc

PGM3 deficiency. ***PGM3*** AR. # 615816
Severe atopy; autoimmunity; skeletal anomalies: short stature, brachydactyly, dysmorphic facial features. Cognitive impairment; delayed CNS myelination in some. Ig: Nl or ↑. ↓ Bc and memory Bc.

CARD11 deficiency. ***CARD11*** AD LOF (dominant negative). # 617638 Variable atopy, cutaneous viral infections, lymphoma. Th2 skewing, ↓Tc proliferation. Nl to low Bc.

Loeys-Dietz syndrome. ***TGFBR1,*** # 609192 ***TGFBR2*** # 610168, ***SMAD3*** # 613795 AD. Eczema, food allergies, hyperextensible joints, scoliosis, retention of primary teeth; arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate.

STAT6-GOF. ***STAT6.*** AD. # 620532
Early-onset atopic dermatitis, food allergies with anaphylaxis, GI disease with reflux, dysphagia, and eosinophilic esophagitis, asthma. Short stature. Th2 skewing

ERBIN deficiency.** ***ERBB21P*** AD. * 606944
Hyperextensible joints, scoliosis, arterial dilatation in some. Moderately increased IgE; ↑ Treg.

Figure 7. CID with associated or syndromic features (continued)

Defects of Vitamin B12 and Folate Metabolism

Megaloblastic anemia, failure to thrive, recurrent infections, intellectual disability (if untreated) Ig: decreased.

Transcobalamin 2 deficiency. ***TCN2*** AR. # 275350 Pancytopenia.

Deficiency causing hereditary folate malabsorption. ***SLC46A1*** AR. #229050

SLC19A1**.** AR. # 620603
Mucositis.↓ proliferation to mitogen. ↓ Bc.

Methylene-tetrahydrofolate dehydrogenase 1 deficiency* ***MTHFD1*** AR. # 617780
PJP; neutropenia; seizures. ↓ Bc, ↓ Tc.

Calcium channel defects

ORAI-1 deficiency*. ***ORAI1***. AR. # 612782
STIM1 deficiency*. ***STIM1.*** AR. # 612783
Autoimmunity, EDA, non-progressive myopathy. Defective TCR mediated activation.

CRACR2A deficiency*. ***CRACR2A.*** AR. *614178
Later onset, recurrent infections. ↓ Tc and Ig.
ITPR3 def. ***ITPR3.*** AR. * 147267
Autoimmune cytopenia. Recurrent infections, enteropathy. ↓ Tc, Bc and Ig.

Other CID with syndromic features: Recurrent infections

Neurologic syndrome:

Purine nucleoside phosphorylase deficiency. ***PNP*** AR. # 613179 AIHA, neurological impairment. Ig: NI/Low Tc: Progressive decrease

Hepatic veno-occlusive disease with immunodeficiency (VODI). ***SP110*** AR. # 235550 Opportunistic infections, HSM, cerebrospinal leukodystrophy. ↓ Ig. ↓ memory Tc and memory Bc

Immunodeficiency, developmental delay and hypohomocysteinemia, IMDDHH*. Activating de-novo mutations in *NFE2L2*. AD. #617744 Growth retardation, developmental delay; white matter cerebral lesions, ↓homocysteine. ↓ Ig. ↓ switched-memory Bc.

Kabuki Sd. ***KMT2D (MLL2).*** AD. # 147920 ***KDM6A:*** XL. #300867
Typical facial abnormalities, cleft or high arched palate, skeletal abnormalities, short stature, intellectual disability, congenital heart defects. Autoimmunity may be present. Low IgA, occasionally low IgG.

Wiedemann-Steiner Sd. ***KMT2A (MLL).*** AD. # 605130
Short stature; facial dysmorphism; hypertelorism; hairy elbows; developmental delay, intellectual disability. ↓ Ig, decreased memory Bc.

Vici syndrome. ***EPG5*** AR. # 242840 Agenesis of the corpus callosum, cataracts, cardiomyopathy, skin hypopigmentation, hypotonia, intellectual disability, microcephaly, CMC. Ig: ↓ IgG2. Bc: Defective. ↓↓ CD4+ cells.

BCL11B deficiency. ***BCL11B.*** AD. #617237 Congenital abnormalities: neonatal teeth, facial dysmorphism; absent corpus callosum; neurocognitive deficits. Tc: Low, poor proliferation.

Jacobsen Sd. ***11q23del*** AD. # 147791
Multiple warts; facial dysmorphism, growth retardation. ↓Tc, NK, Bc and switched memory Bc. ↓Ig.

DIAPH1 def*. ***DIAPH1*** AR. #616632 Seizures, cortical blindness, microcephaly syndrome (SCBMS), B-lymphoma in some patients. ↓naive Tc, ↓memory Bc, ↓IgM.

SGPL1 deficiency. ***SGPL1.*** AR. # 617575 Nephrotic syndrome, adrenal insufficiency, neurological defects. ↓ Tc, Bc and Ig. NKc: NI/↓

Immunodeficiency with multiple intestinal atresia. ***TTC7A*** AR. # 243150 Multiple intestinal atresias, often with intrauterine polyhydramnios and early demise. ↓ Ig. Bc: NI/ ↓. Tc: Variable (may present with SCID at birth)

PI4KA def. ***PI4KA*** AR. #616531 Multiple intestinal atresias, IBD. Autoimmune/autoinflammatory, limb spasticity, developmental delay, intellectual disability, seizures, ataxia, arthrogryposis. ↓ Ig. ↓Bc and memory Bc.

Hennekam-lymphangiectasia-lymphedema syndrome*. ***CCBE1*** AR # 235510/ ***FAT4*** AR # 616006. Lymphangiectasia, lymphedema, facial and dysmorphisms. ↓ Ig. Bc/Tc: Variable.

STAT5b deficiency. ***STAT5B.*** AR. #245590 Short stature, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity. ↓ Treg. ↑ Ig, IgE.
AD DN # 618985: Growth failure and eczema only. ↑ IgE.

Hypereosinophilic syndrome due to somatic mutations in STAT5b*. ***STAT5b.*** Somatic GOF.
Atopic dermatitis, urticarial rash, diarrhea. Eosinophilia.

Tricho-Hepato-Enteric syndrome. ***TTC37*** AR #222470 /***SKIV2L*** AR #614602. IUGR, wooly hair, facial dysmorphism, early onset intractable diarrhea, liver cirrhosis, platelet abnormalities. Impaired IFNγ production, ↓ Ig. Bc: ↓ switched-memory Bc.

IKZF3 def*. ***IKZF3*** AD. # 619437
EBV susceptibility, B cell lymphoma. Impaired Bc development, ↓↓ Ig.

PTCRA def. ***PTCRA.*** AR. * 606817 Lymphoproliferation, autoimmunity. Smaller thymus in some patients. ↓Tc, normalized with age. ↓naive αβTc.

FLT3L def. ***FLT3L.*** AR. * 600007 Failure to thrive. Hypoplastic anemia, monocytopenia, DC-penia, absence of dermal DCs. ↓ Bc. ↑ Ig.

Figure 8. Predominantly antibody deficiencies. Hypogammaglobulinemia

IgG, IgA and/or IgM ↓↓: Exclude second causes: drugs [Hx], myeloma, CLL, lymphoma. Ig loss (not hypo-IgM) in urine, gastro-intestinal or skin. → B Lymphocyte (CD19+) enumeration (FCM)

Bc absent

Severe bacterial infection. ↓ All Ig isotypes

X-Linked Agammaglobulinemia. *BTK.*
300755 Pro Bc: NI. May be associated with inflammation/colitis

AR:

µ heavy chain Def. *IGHM* # 601495

Igα def*. *CD79A*, # 613501 **Igβ def*. *CD79B*** # 612692, **BLNK def*. *BLNK*** # 613502, **λ5 def**. *IGLL1*** # 613500, Pro Bc: NI

E47 transcription factor def*. *TCF3* # 619824 FTT.

p85 def. *PIK3R1.*** # 615214 Cytopenia. ProBc:↓

p110δ def**. ***PIK3CD***. # 619281 Autoimmune complications.

ZIP7 def*. ***SLC39A7***. # 619693 Blistering dermatosis, FTT, thrombocytopenia

FNIP1 def*. *FNIP1* # Hypertrophic cardiomyopathy, severe or intermittent neutropenia. Mild Tc lymphocytosis.

PAX5 deficiency. *PAX5.*** *167414 Autism spectrum disorder, sensorimotor and cognitive defects.

AD:

E47 transcription factor def*. *TCF3.* # 616941

Hoffman syndrome*. *TOP2B.* # 609296 Facial dysmorphism, limb anomalies

PU.1 def*. *SPI1*. # 619707

Bc >1 %: Common Variable Immunodeficiency (CVID) Phenotype

Clinical phenotypes vary: most have recurrent infections, some have polyclonal lymphoproliferation, autoimmune cytopenias and/or granulomatous disease

Recurrent infections only

CD19 deficiency*. *CD19* *AR.* #613493 ↓memory Bc

CD81 deficiency*. *CD81* *AR.* # 613496 ↓memory Bc, no CD19 expression

CD20 deficiency. *CD20*** *AR.* # 613495 ↓memory Bc, NI/↑ IgA, IgM

CD21 deficiency*. *CD21* *AR.* # 614699 ↓switched memory Bc, impaired anti-pneumococcal response.

SEC61A1 deficiency.* ***SEC61A1*** *AD.* # 620670

TWEAK deficiency.** ***TWEAK*** *(TNFSF12)* AD. *602695 Thrombocytopenia. Neutropenia.

ARHGEF1 deficiency.** ***ARHGEF*** *AR.* # 618459 ↓memory Bc

SH3KBP1 deficiency** ***SH3KBP1*** *(CIN85) XL.* # 300310

Recurrent infections with Autoimmunity

IKAROS haploinsufficiency. *IKZF1* AD # 616873. Increased risk of ALL. ↓ pro-Bc.

NFKB2 deficiency. *NFKB2* AD. #615577 Endocrinopathies (ie, central adrenal insufficiency). ↓memory Bc

IRF2BP2 deficiency. *IRF2BP2*** AD. #617765 Possible inflammatory disease. ↓ switched memory Bc.

RAC2 deficiency. *RAC2*** *AR.* # 618987 Urticaria. Defective neutrophil chemotaxis. NI/ ↓Bc

CTNNBL1 def. *CTNNBL1.*** AR (LOF). # 619846 Hyperplastic GC's. ↓Tc, reduced memory Bc. ↑IgM.

TNFSF13 def. *TNFSF13*** (APRIL) AR LOF. * 604472 Alopecia areata. ↑IgM+/↓sw memory Bc, ↓plasmacytes.

Recurrent infections, lymphoproliferation and autoimmunity

Activated p110δ syndrome (APDS1). *PIK3CD.* AD GOF. # 615513 EBV± CMV viremia, Lymphadenopathy, lymphoma. ↓memory Bc and ↑ transitional Bc, IgM.

Activated p110δ syndrome (APDS2). *PIK3R1*. AD GOF. #616005 Similar to APDS1 + Developmental delay.

PTEN Deficiency (LOF). *PTEN.* *AD.* #158350 Developmental delay.

NFKB1 deficiency. *NFKB1* AD. # 616576 COPD. ↓ class-swtiched Bc, memory Bc.

PIK3CG deficiency*. *PIK3CG* AR LOF. # 619802 Autoinflammation. Eosinophilia, HLH-like; ↑ inflammatory markers. NKc dysfunction, ↓memory Bc.

TACI deficiency. *TNFRSF13B* *(TACI)* AD or AR. # 240500 Variable penetrance.

BAFF receptor deficiency*. *TNFRSF13C* *(BAFF-R)* AR. # 613494 Variable clinical expression. NI IgA.

Recurrent infections, and other features

ATP6AP1 deficiency. *ATP6AP1*. XL. # 300972 Hepatopathy, leukopenia, low copper. Neurological abnormalities.

KARS1 deficiency. *KARS1.* AR. # 619147 Severe developmental delay, sensorineural deafness, acute disseminated encephalomyelitis. Impaired B cell metabolism (decreased mitochondrial numbers and activity)

TRNT1 deficiency. *TRNT1* AR. # 616084 Congenital sideroblastic anemia, deafness, developmental delay. Bc deficiency, hypogamma.

Mannosyl-oligosaccharide glucosidase deficiency (MOGS)*. *MOGS* *(GCS1)* AR. # 606056 Severe neurologic disease, facial dysmorphism; also known as congenital disorder of glycosylation type IIb (CDG-IIb)

POU2AF1 def. *POU2AF1*** AR. *601206 Progressive CNS disease with spastic tetraparesis.↓switched memory Bc

Figure 9. Predominantly antibody deficiencies. Other antibody deficiencies

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

Hyper IgM Syndromes

Recurrent bacterial infections, enlarged lymph nodes and germinal centers

AID deficiency.

AICDA. AR or AD. # 605258

Nl memory Bc, but lacking somatic hypermutation in AR form.

UNG deficiency. ***UNG*** *AR.* # 608106

MSH6 def. ***MSH6*** *AR.* # 619097

Family or personal history of cancer. Variable IgG, defects, ↑IgM in some, ↓ switched memory Bc.

INO80 def*. ***INO80*** *AR.* *610169

↓ switched memory Bc.

CTNNBL1 def.** ***CTNNBL1.*** AR (LOF). # 619846 Autoimmune cytopenias. ↓Tc & memory Bc.

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

Usually asymptomatic. Bacterial infections in some.

Selective IgA deficiency. ***Unknown.***
Autoimmunity mildly increased. Very low to absent IgA with other isotypes normal, normal subclasses and specific antibodies.

Transient hypogammaglobuliemia of infancy. Unknown.
Normal ability to produce antibodies to vaccine antigens. IgG and IgA decreased.

IgG subclass deficiency with IgA deficiency. ***Unknown.***
Reduced IgA with decrease in one or more IgG subclass.

Isolated IgG subclass deficiency. ***Unknown.***
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.
One or more IgG and/or IgA subclasses as well as IgE may be absent.

Selective IgM deficiency. ***Unknown.*** Absent serum IgM.

Kappa chain deficiency*. ***IGKC*** *AR.* # 614102
All immunoglobulins have lambda light chain.

Bc lymphocytosis due to constitutive NF-κB activation

CARD11 GOF. ***CARD11.*** AD GOF. # 616452 BENTA syndrome.
Splenomegaly, lymphadenopathy, poor vaccine responses.

Figure 10. Diseases of immune dysregulation
Hemophagocytic lymphohistiocytosis and EBV susceptibility

Familial Hemophagocytic Lymphohistiocytosis (FHL)

FHL With Hypopigmentation:

Partial albinism, fever, HSM, HLH.

↓↓ NK and CTL activities:

cytotoxicity and/or degranulation

Griscelli Sd type 2. ***RAB27A*** AR. #607624 Cytopenias.

Chediak Higashi Sd. ***LYST*** AR. # 214500 Recurrent infections, bleeding tendency, progressive neurological dysfunction. Giant lysosomes (WBC), neutropenia, cytopenias. Increased activated Tc.

Hermansky-Pudlak sd type 2. ***AP3B1*** AR. # 608233 Recurrent infections, pulmonary fibrosis, increased bleeding, neutropenia.

Hermansky-Pudlak syndrome, type 10.** ***AP3D1*** AR. # 617050 Severe neutropenia, recurrent infections, seizures, hearing loss and neurodevelopmental delay.

GIMAP6 Def*. ***GIMAP6.*** AR GOF. *616960 Lymphadenopathy. Vasculitis of CNS, skin, and lungs with pulmonary hypertension. Recurrent infections. Antiphospholipid and anticardiolipin autoAB. AIHA.

FHL without Hypopigmentation:

Fever, HSM, HLH, cytopenias. NI Bc. Increased activated Tc. ↓↓ NK and CTL activities:

cytotoxicity and/or degranulation

Perforin deficiency (FHL2). ***PRF1*** AR. # 603553

UNC13D / Munc13-4 deficiency (FHL3). ***UNC13D*** AR. # 608898

Syntaxin 11 deficiency (FHL4). ***STX11*** AR. # 603552

STXBP2 / Munc18-2 deficiency (FHL5). ***STXBP2*** AR or AD # 613101. Enteropathy

RHOG deficiency.** ***RHOG*** AR. * 179505 NI Tc, mild ↓Bc; ↑ IgM, IgG

SLC7A7 deficiency. ***SLC7A7*** AR. # 222700 Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis Hyper-inflammatory response of macrophages. NI Tc and NK cell function

DPP9 deficiency*. ***DPP9*** AR. # 620331 Recurrent infections (herpes), pancytopenia, failure to thrive, skin pigmentation abnormalities. ↑Tc.

Diseases associated with EBV susceptibility

EBV associated lymphoproliferation and lymphoma

RLTPR (CARMIL2) deficiency. **RLTPR** AR. # 618131 Recurrent infections, warts, molluscum contagiosum. EBV+ malignancy, atopy. NI/↓Ig, poor T dependent antibody response. ↓memory Bc ↓ Treg, ↑CD4+, poor Tc function.

CTPS1 deficiency. ***CTPS1*** AR. # 615897 Recurrent/chronic bacterial and viral infections (EBV, VZV). NI/↓Tc, ↓ memory Bc. Poor proliferation to Ag.

XL magnesium EBV and neoplasia (XMEN). ***MAGT1*** *XL.* # 300853 Viral infections, respiratory and GI infections. Glycosylation disorder. Progressive hypogamma. ↓CD4, ↓RTE cells, poor proliferation to CD3. ↓memory Bc.

PRKCD deficiency. ***PRKCD*** AR. # 615559 Recurrent infections, SLE-like autoimmunity (nephrotic and antiphospholipid Sd). ↓ IgG. ↓memory Bc

RASGRP1 deficiency*. ***RASGRP1*** AR. # 618534 Recurrent infections. ↓NK function; ↑IgA. Bc and Tc: Poor activation, proliferation, motility

FAAP24 deficiency.** ***FAAP24*** AR. * 610884 ↑ activated Tc. Failure to kill autologous EBV transformed Bc. NI NK cell

ITK deficiency. ***ITK*** AR. *# 615468* NI or low IgG. Progressive CD4 T cell lymphopenia

TET2 deficiency*. ***TET2***. AR LOF. # 619126 ALPS-like, recurrent viral infections, HSM, autoimmunity, FTT, developmental delay. DNA hypermethylation, defective FAS-mediated apoptosis. ↑DNT. ↓Memory Bc.

CD70 deficiency*. ***CD70*** *(TNFSF7)* AR. # 618261 Autoimmunity and recurrent infections in some patients. ↓Ig; poor Ab responses. ↓ memory Bc. ↓Treg, poor Tc activation and function.

CD137 deficiency*. ***TNFRSF9*** AR. # 620282 Chronic active EBV infection, recurrent infections. ↓IgA and IgG, ↓response to antigens, ↓Tc proliferation

CD137L deficiency.** ***TNFSF9.*** AR. *606182 Disseminated EBV in B and CD8+ T cells, smooth muscle cell tumors.

IL27RA deficiency*. ***IL27RA.*** AR. *605350 Acute and severe primary EBV infection with a favourable outcome

Sporadic infectious mononucleosis and chronic EBV infection. **AutoAb to IL-27.** Infectious mononucleosis, chronic EBV

EBV associated HLH and lymphoproliferation

Triggered by EBV infection

SAP def (XLP1). ***SH2DIA.*** XL, # 308240 Aplastic anemia, Lymphoma. ↓ Ig, absent iNKT cells. Impaired NK cell and CTL cytotoxic activity. ↓ Memory Bc.

XIAP def (XLP2). ***XIAP*** XL. # 300635 Splenomegaly, Colitis, IBD, hepatitis. ↓Ig, ↓iNKT cells. ↑ T cells susceptibility to apoptosis. Normal or reduced memory Bc.

CD27 def. ***CD27*** AR *(TNFRSF7)* # 615122. Aplastic anemia, ↓iNKTc, B-lymphoma. ↓Ig

Figure 11. Diseases of immune dysregulation. Syndromes with autoimmunity and others

Syndromes with Autoimmunity (1)

With lymphoproliferation

ALPS: Autoimmune Lymphoproliferative Syndrome
Chronic adenopathy, Splenomegaly, Autoimmune cytopenias, defective lymphocyte apoptosis. ↑DNT

ALPS-FAS. ***TNFRSF6***. AD or AR/**Somatic**. # 601859 Increased lymphoma risk, NI/↑ IgA/IgA, elevated serum FasL, IL-10, vitamin B12.
ALPS-FASLG. ***TNFSF6.*** *AD*. # 601859 SLE, soluble FasL is not elevated
ALPS-Caspase10*. ***CASP10.*** AD. # 603909
Caspase 8 def*. ***CASP8.*** *AR*. # 607271 Bacterial/viral infections. ↓Ig.
RAS-associated autoimmune leukoproliferative disease (RALD).
N-RAS GOF. K-RAS GOF. Somatic.

FADD deficiency.* ***FADD.*** AR. # 613759 Functional hyposplenism, bacterial and viral infections, recurrent episodes of encephalopathy and liver dysfunction. Defective lymphocyte apoptosis. ↑DNT.

Tripeptidyl-Peptidase II Deficiency*. ***TPP2***. *AR*. # 619220 Variable lymphoproliferation, severe autoimmune cytopenias, recurrent infections. Developmental delay.↓ Tc /Bc, ↑Ig.

NCKAP1L def*. ***NCKAP1L.*** AR. # 618982 Recurrent infections, atopy, ulcers, lymphadenopathy, HSM, fever, FTT, HLH. Hyperinflammation and cytokine overproduction (↑Th1), ↑ Tc proliferation. NI/↑ Ig levels. ↑naïve Bc.

TRAF3 haploinsufficiency*. ***TRAF3.*** AD. *601896 Lymphadenopathy, splenomegaly. Recurrent infections, bronchiectasis. Enteropathy, dermatitis, Sjogren's syndrome. ↓CD3+ and CD4+ Tc, ↑memory Tc, Treg and Tfh cells. Bc lymphoproliferation. ↑IgG /IgM

NFAT1 deficiency.** ***NFATC2.*** AR. # 620232 Joint contractures, osteochondromas, B cell lymphoma. No autoimmunity. EBV lymphoproliferation. ↓Ig.

No Regulatory T Cell Defect Autoimmunity (organ and/or cytopenia). Multiple AutoAb.

APECED: Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APS-1). ***AIRE.***
AR/ AD. # 240300 Polyendocrinopathy, (Addison disease, hypopara-thyroidism…) CMC, dental enamel hypoplasia, alopecia, enteropathy, pernicious anemia.

ITCH deficiency*. ***ITCH.*** *AR*. # 613385 Early-onset chronic lung disease (interstitial pneumonitis), thyroiditis, type I diabetes, chronic diarrhea, enteropathy, and hepatitis, developmental delay, dysmorphic facial features.

PDCD1 deficiency.** ***PDCD1.*** AR. *600244 Tuberculosis, T1D, hypothyroidism and JIA, fatal pulmonary autoimmunity, HSM, ↑IgG/IgA. Mildly lymphopenia. ↑DNT.

JAK1 GOF*. ***JAK1.*** AD GOF. # 618999 HSM, eosinophilic enteritis, thyroid disease, viral infections. Short stature.↑Eo

JAK1 GOF (S703I). ***JAK1.*** Somatic GOF. Asymetric pustular rash, chronic GI tract inflammation, eosinophilic colitis. Membranous glomerulonephritis, asthma. ↑Eo

Monogenic Lupus*. ***TLR7.*** XLD GOF. # 301080 Childhood onset SLE, hypocomplementemia, malar rash, autoimmune cytopenia, arthralgias, and glomerulonephritis. One patient with optic neuritis, and transverse myelitis.
UNC93B1. AD/AR GOF. * 608204 Early onset SLE or Chillblain lupus with refractory autoimmune cytopenia, and erythematous rash, HSM, glomerulonephritis, arthritis, and panniculitis. ↓CD4+ Tc

PTPN2 LOF*. ***TLR7.*** AD. *176887 Childhood onset SLE or Evans sd. Incomplete penetrance. Positive AutoAb.

SOCS1 haploinsufficiency. ***SOCS1.*** AD. # 619375 Recurrent bacterial infections, severe multisystemic autoimmunity (cytopenia and organ-specific), HSM, neutropenia. ↓ Tc. ↓sw memory Bc

Prolidase deficiency. ***PEPD.*** AR. # 170100 Chronic skin ulcers, eczema, infections. Facial dysmorphism.

CBLB deficiency*. ***CBLB.*** AR. # 620430 Polyendocrinopathy (Thyroid and T1D), autoimmune cytopenias, vitiligo, fevers, and polyserositis.

SH2B3 deficiency*. ***SH2B3.*** AR *605093. (H)SM with thrombocytosis, neutrophilia, myeloid and megakaryocytic hyperplasia in BM. Autoimmune hepatitis, thyroiditis, T1D, and alopecia areata. Monogenic lupus.

PD-L1 Deficiency.** ***CD274.*** AR. *605402 Neonatal onset autoimmunity including T1D. Higher CD38 and HLA-DR expression. ↓NK lymphocytes

ARPC5 deficiency*. ***ARPC5.*** AR. # 620565 Recurrent and severe infections, severe early-onset autoimmunity, inflammation, and dysmorphisms. Low-NI CD4+ Tc, ↓ naive CD8+ Tc, ↑Bc and NKTc, neutrophiila.

IRE1α deficiency*. ***ERN1.*** AD. * 604033 Familial autoimmunity (SLE, Sjögren syndrome, ITP, Hashimoto thyroiditis and limited cutaneous sclerosis).

PLCG1 GOF.** ***PLCG1.*** AD. # 620514 Cytopenias. Lymphadenopathies. May have low NK cells.

LACC1 deficiency. ***LACC1.*** AR. # 618795 Systemic juvenile arthritis or polyarticular juvenile arthritis

Figure 12. Diseases of immune dysregulation. Syndromes with autoimmunity and others

Syndromes with Autoimmunity (2)

Regulatory T Cell Defects

Autoimmunity (organ and/or cytopenia). Absence and/or impaired function of Treg (CD4+CD25+ Tc)

IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked. *FOXP3* XL. # 304790 Enteropathy, early onset diabetes, thyroiditis, AIHA, thrombocytopenia, eczema, ↑IgE/IgA.

LRBA deficiency. *LRBA.* AR. # 614700 Recurrent infections, IBD. ↓IgG/IgA in most. ↓ or Nl Bc and CD4 count

STAT3 GOF mutation. *STAT3.* AD. # 615952 Lymphoproliferation, recurrent infections. ↑ Th17 cell differentiation, ↓ Tc and Bc.

FERMT1 deficiency. *FERMT1* AR. # 173650 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. *603023 Diabetes, colitis, thyroiditis…, allergy, lymphoproliferation, Evans Syndrome, recurrent infections. Normal/mildly decreased Bc.

NBEAL2 deficiency. *NBEAL2.* AR. # 139090 Grey platelet syndrome (macrothrombocytopenia, α-granule deficient platelets, bleeding disorders) splenomegaly and progression to myelofibrosis. Autoimmune lymphoproliferative syndrome, EBV reactivation, HLH ↓CTLA4 expression

CTLA4 deficiency (ALPS-V). ***CTLA4*** AD. # 616100 Cytopenias, enteropathy, interstitial lung disease, extra-lymphoid lymphocytic infiltration, recurrent infections. ↓ Tc and Bc.

BACH2 deficiency. *BACH2* AD. # 618394 Lymphocytic colitis, IBD, sinopulmonary infections. Impaired memory Bc development. Progressive Tc lymphopenia.

CD25 deficiency*. *IL2RA* AR. # 606367 Lymphoproliferation, recurrent infections. Impaired Tc proliferation.

CD122 deficiency. *IL2RB* AR. # 618495 Lymphoproliferation, lymphadenopathy, HSM, AIHA, dermatitis, enteropathy. Viral (EBV, CMV) infections. ↑Ig, ↑ memory CD8+Tc, memory Bc

DEF6 deficiency*. *DEF6* AR. # 619573 HSM, enteropathy, AIHA, recurrent infections. ↓Tc, ↓ or Nl Bc.

Immune Dysregulation with Colitis

Inflammatory Bowel Disease (IBD) recurrent infections

IL-10R deficiency*. AR. Folliculitis, arthritis, lymphoma.
IL10RA #613148 Leukocytes unresponsive to IL-10.
IL10RB. # 612567 Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29

RIPK1 deficiency. *RIPK1.* AR. # 618108 Progressive polyarthritis. Low Tc, low or nl Bc.

IL-10 deficiency*. *IL10.* AR. *124092 Folliculitis, arthritis. No functional IL-10 secretion.

TGFB1 deficiency*. *TGFB1.* AR. # 618213 Microcephaly, encephalopathy. ↓Tc proliferation in response to anti-CD3

ELF4 deficiency*. *ELF4.* XL. # 301074 Fevers, ulcers. Responded to IL-1, TNF or IL-12p40 blockade

NFAT5 haploinsufficiency. *NFAT5.*** AD. * 604708 Decreased memory Bc and plasmablasts.

IL21 def. *IL21*** AR. # 615767 Tc: NL / low function. ↓gG, poor specific antibody responses;↑ IgE

DOCK11 deficiency. *DOCK11.* XL. # 301109 Severe early-onset autoimmunity affecting various organs. Autoimmune cytopenia. Susceptibility to infections with hyperinflammatory response. ↓ switched memory Bc

iRHOM deficiency*. *RHBDF2.* AR. * 614404 Pneumatoceles, eczema, HSM, skin abscesses,. Haemorrhagic colitis. ↑ IgE

MD2 deficiency*. *LY96.* AR. *605243 Very early onset IBD, recurrent infections, pneumonia, and otitis media

TLR4 deficiency*. *TLR4.* AR. *603030

Figure 13. Congenital defects of phagocyte number, function, or both. Neutropenia (without anti-PMN)

Syndrome associated

Neutropenia, Recurrent bacterial infections

Shwachman-Diamond Syndrome. ***SBDS*** *AR.* # 260400 ***EFL1**** *AR.* # 617941 ***DNAJC21*** *AR.* # 617052 Pancytopenia, exocrine pancreatic insufficiency, metaphyseal dysplasia, short stature.

SRP54 deficiency*. ***SRP54*** AD. # 618752 Neutropenia and exocrine pancreatic insufficiency. Some with neurologic deficits.

Glycogen storage disease type 1b. ***G6PT1*** *AR.* # 232220 Short stature, doll-like face. Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly.

3-Methylglutaconic aciduria. ***CLPB*** *AD/AR.* #616271, #619835 Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR.

Clericuzio syndrome (Poikiloderma with neutropenia). ***USB1*** *AR.* # 604173 Retinopathy, developmental delay, short stature, facial dysmorphism, poikiloderma.

SMARCD2 deficiency*. ***SMARCD2*** *AR.* # 617475 Specific granule deficiency, delayed development, facial dysmorphism, bones defect, myelodysplasia

HYOU1 deficiency*. ***HYOU1*** *AR.* # 233600 Hypoglycemia, inflammatory complications.

G6PC3 deficiency (SCN4). ***G6PC3*** *AR.* # 612541 Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs. Thrombocytopenia, anemia, leukopenia.

Cohen syndrome. ***COH1*** *AR.* # 216550 Dysmorphism, mental retardation, obesity, deafness.

Barth Syndrome (3-Methylglutaconic aciduria type II). ***TAZ*** *XL.* # 302060 Cardiomyopathy, myopathy, growth retardation, motor delay.

HAX1 deficiency (Kostmann Disease) (SCN3). **HAX1** AR. # 610738 Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia

SRP19*/SRPRA deficiency.** ***SRP19/SRPRA*** AR. *182175, *182180 Exocrine pancreatic insufficiency, growth insufficiency, bronchiectasis.

DBF4 deficiency.** ***DBF4*** AR. *604281 Neurocognitive developmental aberrations, facial dysmorphism.

P14/LAMTOR2 deficiency.** ***LAMTOR2*** *AR.* # 610798 Partial albinism, growth failure. Hypogammaglobulinemia, reduced CD8 cytotoxicity.

Neutropenia without associated syndrome

Severe or intermittent neutropenia, Recurrent bacterial (and fungal) infections

Elastase deficiency. (SCN1). ***ELANE*** *AD.* # 202700 Susceptibility to MDS/leukemia. Severe congenital neutropenia or cyclic neutropenia (perform CBC twice weekly/ 4 weeks) # 162800.

X-linked neutropenia/ myelodysplasia WAS GOF. ***WAS*** XL GOF. # 300299 Myeloid maturation arrest, monocytopenia, variable lymphoid anomalies.

G-CSF receptor deficiency*. ***CSF3R*** *AR.* # 617014 Unresponsive to G-CSF treatment, may respond to GM-CSF.

Neutropenia with combined immune deficiency *. ***MKL1*** *AR.* # 618847 Mild thrombocytopenia.

GFI 1 deficiency (SCN2)*. ***GFI1.*** *AD.* # 613107 B/T lymphopenia

CXCR2 deficiency*. ***CXCR2*** AR LOF. # 619407 Myelokathexis, recurrent gingivitis, oral ulcers. ↑IgA/IgG

VPS45 deficiency (SCN5)*. ***VPS45*** AR. # 615285 Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly.

Specific granule deficiency*. ***CEBPE*** AR. # 245480 Skin infections. Neutrophils with bilobed nuclei.

JAGN1 deficiency. ***JAGN1*** *AR.* # 616022 Osteopenia. Myeloid maturation arrest.

CLPB deficiency. ***CLPB*** *AR.* #619813 Myeloid maturation arrest.

Figure 14. Congenital defects of phagocyte. Functional defects

Syndrome associated

Cystic fibrosis. ***CFTR.*** AR.
219700
Pancreatic insufficiency, Respiratory infections, elevated sweat chloride

Papillon-Lefèvre sd. ***CTSC*** AR.
245000
Periodontitis, palmoplantar hyperkeratosis in some patients, premature teeth loss

Localized juvenile periodontitis. ***FPR1*** AR.
*136537
Periodontitis only

β-Actin. ***ACTB*** AD. #607371, # 620475
Mental retardation, short stature. Thrombocytopenia in some.

Leukocyte adhesion deficiency (LAD)
Recurrent bacterial infections. Impaired pus formation and wound healing. Skin ulcers. Leukocytosis with neutrophilia (WBC > 25000)

LAD I. AR
ITGB2 # 116920
Delayed cord separation with omphalitis+++. Periodontitis leads to early loss of teeth. Severity of the disease correlates with the degree of deficiency in CD18 (FCM). (WBC 20,000–150,000 with 60–85 % neutrophils)

LAD II (Congenital disorder of glycosylation, type IIc). AR ***SLC35C1*** # 266265
Mild LAD type 1 features with Hh-blood group, growth retardation, developmental delay, facial dysmorphism (depressed nasal bridge).

LAD III AR
FERMT3 # 612840
Severe bleeding disorder. Defective platelet aggregation.

Rac 2 def*. ***RAC2*** AD LOF. # 608203 Poor wound healing. CGD-like phenotype (abnormal DHR assay)

No Syndrome associated:

DHR assay (or NBT test) ?

Normal

Pulmonary alveolar proteinosis.
CSF2RA*, XL # 300770. ***CSF2RB****, AR. # 614370
Alveolar proteinosis: severe respiratory distress

Pulmonary alveolar proteinosis.
AutoAb to GM-CSF. Pulmonary alveolar proteinosis, cryptococcal meningitis, disseminated nocardiosis

CCR2 deficiency*. **CCR2**, AR.
219600
Pulmonary alveolar proteinosis (PAP), progressive polycystic lung disease, and recurrent infections, BCG disease.

WDR1 deficiency*. ***WDR1*** *AR.* # 150550
Poor wound healing, severe stomatitis, neutrophil nuclei herniate. Mild neutropenia. Some with autoimmunity.

Abnormal

CGD: Early onset of severe and recurrent infections, abscesses.
Autoinflammatory phenotype, Granulomata obstructing respiratory, urinary or gastrointestinal tracts. IBD and perianal disease: up to 30 %
Pathogens: *S. aureus*, *Aspergillus*, *Candida*, *Burkholderia cepacia*, *Chromobacterium violaceum*, *Nocardia*, and invasive *Serratia marcescens*. BCG adverse effects in up to 20 %. Microscopic granulomas.

XL CGD: ***CYBB*** ($gp91^{phox}$) # 306400
NCF1 ($p47^{phox}$), AR # 233700
CYBA ($p22^{phox}$), AR # 233690
NCF4 ($p40^{phox}$), AR # 613960
NCF2* ($p67^{phox}$), AR # 233710
CYBC1*, AR # 618935

G6PD def Class I. ***G6PD*** XL. # 300908
Hemolytic anemia, Infections.

Figure 15. Defects in Intrinsic and Innate immunity. Predisposition to viral infection

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)

Figure 16. Defects in intrinsic and innate immunity. Predisposition to bacterial, fungal, and parasitic infections

Predisposition to Bacterial 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 P. aeruginosa*. Atypical mycobacteria. Neutropenia. Improve with age. Specific screening tests (lack of proinflammatory cytokine production and CD62L shedding).
IRAK4 def. ***IRAK4*** AR #607676
MyD88 def. ***MYD88*** AR. #612260

Isolated congenital asplenia.
Bacteremia (encapsulated bacteria). No spleen.
RPSA AD. #271400
HMOX* AR. #614034 +Hemolysis, nephritis, inflammation

IRAK-1 def.** ***IRAK1*** *XL*. *300283
X-linked MECP2 deficiency-related syndrome due to a large de novo Xq28 chromosomal deletion encompassing both *MECP2* and *IRAK1*

TIRAP def.** ***TIRAP*** *AR*. #614382
Staphylococcal disease during childhood.

IRF4 haploinsufficiency*.
IRF4 AD. *601900 Whipple's disease

Predisposition to Parasitic and Fungal infections

Predisposition to Chronic Mucocutaneous Candidiasis (CMC)
CMC in infancy or early childhood, without ectodermal dysplasia

STAT1 GOF. ***STAT1*** AD. # 614162 Various fungal, bacterial and viral (HSV) infections, autoimmunity (thyroiditis, diabetes, cytopenias), enteropathy. ↓Th17 cells

IL-17RA deficiency. ***IL17RA*** AR. # 613953 Folliculitis. Susceptibility to mucocutaneous *S aureus* (skin and lung) and chronic bacterial infections.

IL-17RC deficiency*. ***IL17RC*** AR. # 616445

IL-17F deficiency.** ***IL17F*** AD. # 613956

ACT1 deficiency.** ***TRAF3IP2*** AR. # 615527 Blepharitis, folliculitis and macroglossia.

JNK1 haploinsufficiency def.** ***MAPK8*** AD (haplo-insufficiency). *601158 Connective tissue disorder (similar to Ehlers-Danlos syndrome). ↓ Th17 cells

CARD9 def. ***CARD9*** AR. # 212050
Invasive candidiasis infection, deep dermatophytoses, invasive fungal infections.

Trypanosomiasis ***APOL1*** AD. *603743

Chronic mucocutaneous candidiasis
(isolated or with APECED syndrome).
AutoAb to IL-17 and/or IL-22.
Endocrinopathy.

Mendelian Susceptibility to Mycobacterial Disease: MSMD

Severe phenotypes:

Complete IFNGR1 Def and **IFNGR2 Def.*** ***IFNGR1,*** # 209950 ***IFNGR2***. # 614889 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. # 618963
ISG15 def. ***ISG15*** AR. # 616126 Brain calcification. IFNg production defect.
IRF1 deficiency*. ***IRF1. AR.*** # 620668 Histoplasmosis in 2 patients.
MCTS1 deficiency*. ***MCTS1.*** **XL.** # 301115
STAT1 def*. ***STAT1*** AR LOF. #613796 Severe viral infections

Moderate phenotypes:

Susceptibility to mycobacteria only
Macrophage gp91 phox def*. ***CYBB*** *XL* # 300645
IRF8 def*. ***IRF8*** AD. # 614893
T-bet def.** ***TBX21*** AR LOF. # 619630

With susceptibility to Salmonella
SPPL2a deficiency*. ***SPPL2A*** AR. # 619549
Tyk2 deficiency, ***TYK2*** **AR.** #611521 Susceptibility to viruses, +/- elevated IgE. multiple cytokine signaling defect. ***P1104A TYK2 homozygosity*** MSMD or tuberculosis.

With Susceptibility to *Salmonella and CMC*
IL-12 and IL-23 receptor b1 chain def. ***IL12RB1*** AR. # 614891
IL-12p40 (IL-12 and IL-23) def*. ***IL12B*** AR. # 614890
IL-12Rb2 deficiency.** ***IL12RB2*** *AR* *601642
IL-23R deficiency.** ***IL23R*** *AR*. *607562
STAT1 LOF*) # 614892
Partial IFNγR2,** ***IFNGR2 STAT1*** (AD/AR. # 614889
Partial IFNGR1* ***IFNGR1*** AD. # 615978

With susceptibility to other pathogens
RORγt def*. ***RORC*** AR. # 616622 Candidal infections. Complete absence of IL-17A/F-producing Tc, ↓ IFNg.
JAK1 (LOF),** ***JAK1*** AR. *147795 Susceptibility to viruses, urothelial carcinoma. ↓ IFNg.

Adult-onset immunodeficiency with susceptibility to mycobacteria. Auto-Ab to IFNγ.
Mycobacterial, fungal, salmonella, VZV infections.

Others

Hidradenitis suppurativa.
Draining sinuses, painful skin abscesses, disfiguring scars
PSENEN AD. #613736
NCSTN AD. #142690
***PSEN ***AD. #613737

Acute liver failure due to NBAS def. ***NBAS*** AR.
616483
Fever induces liver failure

Acute necrotizing encephalopathy.
RANBP2 AD. #608033

GATA2 def. ***GATA2,*** AD. #614038, #614172
Susceptibility to Mycocbacteria, HPV, Histoplasmosis, Lymphedema. Alveolar proteinosis, myelodysplasia/ AML/CMML. Multi lineage cytopenias. ↓Mo, Bc, NK, DCs.

TLR8 GOF*. ***TLR8*** XL GOF/**Somatic.** #301078
Severe cytopenias, HSM, lymphadenopathy; progressive autoinflammatory disease. ↑proinflammatory serum cytokines.

Figure 17. Auto-inflammatory disorders

Recurrent inflammation
Recurrent fever, ↑IL-1/IL-18

Inflammasome-related, ↑IL-1/IL-18

Familial Mediterranean Fever (FMF). ***MEFV.*** AR or AD (Usually M694del variant)**.** # 249100, #134610
DA: 1–4 days **FA:** Variable.
Polyserositis, Abdominal pain, Arthritis, Amyloidosis. Erysipelas-like erythema. Predisposes to vasculitis, inflammatory bowel disease and amyloidosis.
Colchicine-responsive +++.

Mevalonate kinase def (Hyper IgD sd). ***MVK.*** AR. #260920
DA: 3–7 days **FA**: 1–2 months. Cervical adenopathy. Oral aphtosis. Diarrhea. Mevalonate aciduria during attacks. Leukocytosis with high IgD levels.

PMVK deficiency*. ***PMVK.*** AR. *607622
Arthritis, and cytopenia. Similar to MVK deficiency, ↑ IL1-β.

RIPK1 def*. ***RIPK1.*** AD. #618852 **DA**: Several days **FA:** 1-few weeks (cyclic).
Lymphadenopathy, HSM, ulcers, arthralgia, GI features. ↑DNT.

NLRC4-MAS (macrophage activating syndrome)*. ***NLRC4*** AD GOF. #616050
Severe enterocolitis and macrophage activation syndrome (HLH). Arthralgia, Myalgia. Triggered by cold exposure.

Other mechanism

TNF receptor-associated periodic syndrome; TRAPS. ***TNFRSF1A.*** AD. # 142680
DA: 1-4 weeks **FA:** Variable
Prolonged fever. Serositis, painful erythema, Periorbital edema and conjunctivitis. Arthralgia, localized myalgia. Amyloidosis.

C2orf69 def. ***C2orf69.*** AR. #619423
Brain abnormalities (hypomyelination, microcephaly), liver dysfunction, early onset severe and recurrent autoinflammation, leukoencephalopathy with recurrent seizures, often fatal.

Bacterial infections, autoinflammation, amylopectinosis: dilated cardiomyopathy, myopathy. Bc: Nl, ↓ memory Bc.

HOIL1 deficiency. ***RBCK1*** AR. *#610924* Poor Ab responses to polysaccharides.
HOIP deficiency*. ***RNF31*** AR. #620632 Lymphangiectasia. Ig: decreased.

CEBPE multimorphic*. ***CEBPE.*** AR GOF. # 260570
DA: 4–5 days **FA**: 2–4 weeks, later more seldom. Recurrent abdominal pain, aseptic fever, systemic inflammation; abscesses, ulceration, infections; mild bleeding diathesis. Mild lymphopenia, ↓Tc.

TBK1 def*. ***TBK1*** AR.#620880 Recurrent fever, erythematous skin rashes, vasculitis, oral aphthous lesions, polyarthritis. Seizures, delayed neurocognitive development, treated with TNF inhibitors.

Systemic inflammation with prominent skin findings

Familial Cold Autoinflammatory Syndrome (CAPS). ***NLRP3,*** AD GOF #120100 ***NLRP12.*** AD GOF. #611762
DA: 24-48H, maculopapular rash, arthritis, chills, fever and leukocytosis after cold exposure.

Muckle Wells syndrome (CAPS) ***NLRP3.*** AD GOF. #191900
Ethnic group: North European.
Episodic skin rash, arthralgias, and fever. Late-onset sensorineural deafness and renal amyloidosis. Keratosis fugax hereditaria.

Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA). ***NLRP3.*** AD GOF. #607115
Neonatal onset rash, with fever and inflammation. Aseptic and chronic meningitis, chronic arthropathy. Mental retardation, Sensorineural deafness. and Visual loss in some patients.

Cryopyrin-associated periodic syndromes (CAPS). ***NLRP3. Somatic.***
Urticaria-like rash, arthropathy, neurological symptoms

A20 haploinsufficiency ***TNFAIP3.*** AD LOF. #616744
Arthralgia, mucosal ulcers, ocular inflammation. Skin rash, uveitis, autoimmunity.

PLAID (PLCg2 associated antibody deficiency and immune dysregulation), or APLAID (Autoinflammation, antibody deficiency, and immune dysregulation)*. ***PLCG2.*** AD GOF. #614468, #614878
Cold Urticaria: recurrent blistering skin lesions. Impaired humoral immunity. Recurrent infections. Hypogammaglobulinemia, autoimmunity.

NLRP1 deficiency*. ***NLRP1.*** AR. #617388
Recurrent fever. Dyskeratosis, autoimmunity and arthritis.

NLRP1 GOF. ***NLRP1*** AD GOF. #615225 Palmoplantar carcinoma, corneal scarring; recurrent respiratory papillomatosis. Increased IL1β.

Figure 18. Auto-inflammatory disorders (continued)

Type 1 Interferonopathies (↑Type 1 IFN)

Aicardi-Goutières Syndromes
Highly variable phenotype: Progressive encephalopathy, ICC, Cerebral atrophy, Chilblains, leukodystrophy, Thrombocytopenia, Elevated hepatic transaminases. Chronic cerebrospinal fluid (CSF) lymphocytosis

TREX1 AR-AD #225750 (+SLE),
RNASEH2A*, #610333 ***RNASEH2C**** #610329 AR
SAMHD1 AR #612952
LSM11* AR LOF #619486
ARF1* AD *103180
RNU7-1 AR LOF # 619487
+spastic paraplegia:
RNASEH2B AR #610181, ***ADAR1*** AR/AD #615010, ***IFIH1*** GOF AD #615846 (+ SLE)

DNAse II def*. ***DNASE2*** AR #619858. Severe anemia, thrombocytopenia, HSM, recurrent fevers, chronic diarrhea

RelA haploinsufficiency*. ***RELA,*** AD. # 618287 Chronic mucocutaneous ulceration. Behcet-like syndrome. Autoimmune cytopenia Impaired NFkB activation; reduced production of inflammatory cytokines
RELA interferonopathy*. ***RELA*** AD DN. +periodic fever, inflammatory bowel diseases (IBDs), juvenile idiopathic arthritis (JIA), and skin involvement

ATAD3A def*. ***ATAD3A*** AD or AR. #617183 Delayed psychomotor development, intellectual disability, truncal hypotonia, spasticity, and peripheral neuropathy.

Pediatric systemic lupus erythematosus. ***DNASE1L3*** AR. #614420
Very early onset SLE.

USP18 def *. ***USP18*** AR. #617397
Pseudo TORCH syndrome: ICC, brain malformation, liver dysfunction. Mycobacterial disease.

STAT2 loss of negative regulation*. ***STAT2*** AR. #618886
Pseudo TORCH syndrome. Phenocopy of USP18 def.

STING-associated vasculopathy with onset in infancy (SAVI). * ***TMEM173.*** AD #615934
Skin vasculopathy (severe lesions), interstitial lung disease, systemic autoinflammation and ICC, FCL.
AR GOF: +failure to thrive, fever, dyspnea, polyarthritis, autoAbs, ↑inflammatory markers

ADA2 deficiency. ***ADA2*** AR. #615688 Polyarteritis nodosa, childhood-onset, recurrent ischemic stroke and fever, autoimmunity, hypogamma.

XL reticulate pigmentary disorder. ***POLA1*** XL. #301220 Hyperpigmentation, reticulate pattern. Inflammatory lung and Gastroenteritis or colitis. Corneal scarring, characteristic facies

OAS1 GOF*. ***OAS1.*** AD GOF. #618042 Pulmonary alveolar proteinosis, skin rash. ↓Ig, leukocytosis.

Spondyloenchondro-dysplasia with immune dysregulation (SPENCD). ***ACP5*** AR. # 607944 Short stature, facial dysmorphism, spasticity, ICC, auto-immunity, skeletal dysplasia, possibly recurrent bacterial and viral infections.

CDC42 def. ***CDC42*** AD. # 616737 Neonatal onset: pancytopenia, fever, rash, hepatosplenomegaly, multisystemic inflammation, myelofibrosis/ proliferation, enterocolitis, neuro-developmental delay, failure to thrive, facial dysmorphism.

CANDLE Sd (chronic atypical neutrophilic dermatitis with lipodystrophy)/PRAAS. Panniculitis, lipodystrophy, fevers.
PSMB8, AR and AD #256040. ICC.
PSMG2*, AR. # 619183 AIHA.
PSMB10*, AR. #619175
PSMB9*, AR or digenic. #620796
PSMB4*, AR or digenic. #617591
POMP*, AD. #618048 Variable immunodeficiency.

PSMB9 GOF*. ***PSMB9*** AD GOF. #620796 Severe auto-inflammation (neonatal-onset fever, chilblain-like skin rash, myositis, pulmonary hypertension, basal ganglia calcification), periodic inflammatory exacerbation, immuno-deficiency, ↑ IL-6, IL-18, IP-10, IFN- α, ↑ liver enzymes in blood and CSF. Mild pancytopenia. ↓IgG and Bc. ↓TREC and KREC. ↓monocytes, CD8 T, and γδ Tc.

Autoinflammation with neurodevelopmental disease* ***PSMD12.***
AR. #617516
Delayed psychomotor development, intellectual disability, behavioral disorders, mild craniofacial anomalies.

Figure 19. Auto-inflammatory disorders (continued)

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. #604416
DA: 5 days
FA: Fixed interval: 4-6 weeks
Erosive arthritis, nonhealing sterile ulcers, inflammatory skin rash, Myositis. Acute-phase response during attacks

Chronic recurrent multifocal osteomyelitis and congenital dyserythropoieticanemia * (Majeed syndrome). ***LPIN2*** AR. #609628
DA: Few days **FA:** 1-3 / month
Chronic recurrent multifocal osteomyelitis, severe pain, tender soft tissue swelling, Transfusion-dependent anemia, cutaneous inflammatory disorders

Cherubism. ***SH3BP2*** AR. #118400
Bone degeneration in jaws, facial swelling.

DIRA (Deficiency of the Interleukin 1 Receptor Antagonist)*. ***IL1RN*** AR. #612852
Neonatal onset of sterile multifocal osteomyelitis, periostitis and pustulosis.

Loss of IL-1R1 sensitivity to IL-Ra (LIRSA).** ***IL1R1*** AD. #259680
Sterile osteomyelitis (bone pain, arthritis), poor growth.

Predominant on the skin

Blau syndrome. ***NOD2*** (CARD15). AD. #186580 Uveitis, Granulomatous arthritis, dermatitis. Camptodactyly, Cranial neuropathies, 30% develop Crohn colitis.

CAMPS ***CARD14***. AD. #602723 Psoriasis.

DITRA (Deficiency of IL-36 receptor antagonist). ***IL36RN.*** AR. #614204 Life-threatening, pustular psoriasis, high-grade fever, generalized rash. Leukocytosis.

AP1S3 deficiency. ***AP1S3***. AR. #616106
Pustular psoriasis

ADAM17 deficiency*. ***ADAM17.*** AR. # 614328 Early onset diarrhea and skin lesions. Severe bacteremia. Defective TNFα production.

SLC29A3 disorder. ***SLC29A3***. AR. #602782 Hyperpigmentation hypertrichosis, HSM, hearing loss, short stature, lymphadenopathy.

Otulipenia/ORAS*. ***OTULIN***. AR. #617099 Neonatal onset of recurrent fever, Arthralgia, lipodystrophy. Dermatitis, diarrhea, Neutrophilia.

HCK GOF.** ***HCK.*** AD GOF#620296. Cutaneous vasculitis and chronic pulmonary inflammation/ fibrosis, inflammatory leukocyte infiltration of the lungs and skin, anemia, HSM, respiratory failure, clinical improvement with ruxolitinib.

Others

Late adulthood onset treatment-refractory inflammatory syndrome VEXAS. ***UBA1.*** Somatic LOF.

Often fatal, Late onset treatment-refractory inflammatory syndrome (fevers, cytopenias, dysplastic bone marrow, interstitial nephritis, chondritis, vasculitis).
↑ serum inflammatory markers. ↓peripheral lymphocyte counts. ↓ Bc.

COPA defect. ***COPA*** *AD.* #616414 Autoimmune inflammatory arthritis, interstitial lung disease, renal disease. Th17 dysregulation and autoantibody production.

T-cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency). ***HAVCR2*** AR.#618398 Subcutaneous panniculitis, HLH, polyclonal cutaneous T cell infiltrates or T-cell lymphoma

SYK GOF*. ***SYK.*** AD GOF.#619381 Recurrent infections, lymphocytic organ infiltration (gut, skin, CNS, lung, liver), B cell lymphoma in two patients. Dysgamma (↓ IgM, IgG).

IKBKG (NEMO exon 5 deletion) def*. ***IKBKG.*** XL.#301081 Fever, skin rash, systemic autoinflammation, infections, CNS involvement, panniculitis, uveitis, HSM. Lipodystrophy, autoimmune cytopenias. ↑ type 1 IFN production. ↓Ig

Retinal dystrophy, optic nerve oedema, splenomegaly, anhidrosis, and headache (ROSAH). ***ALPK1.*** AD. #614979 Retinal dystrophy, optic nerve edema, splenomegaly, anhidrosis, and migraine headache, fever, arthritis, colitis, dental abnormalities

ALPI deficiency*. ***ALP1.*** AR. *171740 / **TRIM22 def*.** ***TRIM22***. AR. *606559 Inflammatory bowel disease.

SHARPIN deficiency*. ***SHARPIN.*** AR.#620795 Arthritis, recurrent fever, colitis, amylopectinosis. Leukocytosis.

Systemic autoinflammatory disease with vasculitis (SAIDV)*. ***LYN.*** AD GOF. #620376
Diffuse purpuric rash/atopic dermatitis, fever, HSM, liver fibrosis/ calcifications, arthritis, periorbital edema, conjunctivitis, colitis. Leukocytosis, thrombocytopenia.

OTULIN related autoinflammatory syndrome*. ***OTULIN.*** AD DN. Spontaneous inflammation. increased TNF induced cell death.
OTULIN haploinsufficiency*. ***OTULIN.*** AD. Susceptibility to Staphyloccus aureus infections in epithelial cells

Disabling pansclerotic morphea of childhood (DPMC). ***STAT4*** AD GOF. #620443 Skin sclerosis, poor wound healing, joint contractures, mucosal ulcerations. Low CD4 T cells.

Figure 20. Complement deficiencies

Infectious phenotype

(Disseminated) Neisserial infections

Absent CH50 and AH50 activity. Defective bactericidal activity.

C9 def. *C9* AR. #613825 Mild susceptibility

C5 def. *C5* AR. #609536

C6 def. *C6* AR. #612446

C7 def. *C7* AR. #610102

C8 def.
C8A, C8B, C8G AR. #613790, # 613789

Normal CH50. Absent AH50 activity

Properdin def.
PFC XL. #312060

Factor D def.*
CFD AR. #613912

Factor I def*. AR. #610984 Pyogenic infections. C3 glomerulopathy

Factor H def*. AR. # 609814

Recurrent infections

C3 LOF. *C3* AR. #613779 GN bacterial infections. Absent CH50 and AH50 activity. SLE and/or glomerulonephritis possible.

MASP2 def. *MASP2* AR. #613791 Pyogenic infections. Inflammatory lung disease, autoimmunity

Ficolin 3 def*. *FCN3* AR. #613860 Respiratory infections, abscesses. Autoimmunity in adults

Factor B. *CFB LOF.*** AR. #615561 Infections with encapsulated organisms. Deficient AH50.

Non-infectious phenotype

SLE-like syndrome, recurrent skin lesions. Chronic Infections with encapsulated organisms. Chronic glomerulonephritis.

Absent CH50 hemolytic activity

C1q def. *C1QA, C1QB*, C1QC*.* AR. #613652, #620321, #620322,

C1r /C1sdef. *C1R, C1S.* AR. %216950

Ehlers Danlos phenotype

C2 def. *C2.* AR. #217000 Vasculitis, Polymyositis, atherosclerosis

Complete C4 def.
C4A+C4B. AR. #614380 Type 1 Diabetes mellitus.

Atypical Hemolytic Uremic Syndrome: hemolytic anemia, thrombocytopenia, renal impairment

Factor H def. *CFH.* AR or AD. # 235400 C3 glomerulopathy, preeclampsia. C3 consumption.
Factor H –related protein deficiencies *CFHR1, CFHR3.* AR or AD. # 235400 Later onset, autoantibodies to Factor H.
CFHR5. AD. #614809 C3 glomerulopathy.

Atypical Hemolytic Uremic Syndrome. AutoAb to Factor H. Spontaneous activation of the alternative complement pathway

Membrane Cofactor Protein deficiency. *CD46* AD, AR. #612922 Preeclampsia. Less severe than Factor H def.

C3 GOF. *C3* AD. #612925 Increased activation of complement

Factor B GOF. *CFB.* AD GOF. #612924 Increased spontaneous AH50.

Factor I deficiency*. AD. #612923 Preeclampsia. C3 consumption.

Thrombomodulin def*. *THBD.* AD. #612926 Normal CH50, AH50

Others

C1inhibitor. *SERPING1* AD. #106100 Hereditary angioedema.: episodic local edema (respiratory and gastrointestinal). C4/C2 consumption

Acquired angioedema. AutoAb to C1 inhibitor. Angioedema

Membrane Attack Complex Inhibitor deficiency. *CD59* AR. #612300 Hemolytic anemia. Relapsing-remitting polyneuropathy.

CD55 deficiency (CHAPLE disease). *CD55* AR. #226300 Protein losing enteropathy, thrombosis. ↓Ig in some.

Periodontal Ehlers Danlos. *C1R, C1S*. AD GOF. #130080, #617174 Hyperpigmentation, skin fragility, bruising. Joint laxity. Extensive gingivitis, premature loss of teeth. Normal CH50.

Figure 21. Bone marrow failure disorders

Fanconi anemia

Small stature, mental retardation, kidney, heart and skeleton malformations, typical facies, hearing loss, cafe-au-lait spots. High predisposition to cancer.

Increased chromosomal breakage, pancytopenia.

Fanconi anemia Type A-W: #227650

-AR

FANCA, FANCC, BRCA2, FANCD2, FANCE, FANCF, XRCC9, FANCI, BRIP1, FANCL, FANCM, PALB2, RAD51C, SLX4, ERCC4, RAD51, BRCA1, UBE2T, XRCC2, MAD2L2, RFWD3,

-XL

FANCB

Dyskeratosis congenita (DKC)

Abnormal skin pigmentation, nail dystrophy, and premalignant oral leukoplakia.
Short telomeres. Progressive BMF in 80%.
Pulmonary and hepatic fibrosis, sparse scalp hair and eyelashes; palmar hyperkeratosis; pancytopenia; +/- recurrent infections.

Exclude other causes:
Fanconi anemia,
Blackfan-Diamond

Dyskeratosis congenita: #127550

DKC1: *XL,* Bc and Tc: Progressive decrease.

NOLA2 (NHP2), NOLA3 (NOP10): *AR, Tc:* Decreased. ***RTEL1:*** AD, *Tc:* Decreased. ***TERC, TINF2, ACD:*** AD, *Tc:* variable. ***TERT, TPP1:*** AD/AR, *Tc:* variable. ***DCLRE1B, WRAP53*:*** AR, *Tc:* variable.

Hoyeraal-Hreidarsson Syndrome (HHS)
#127550
Severe phenotype with developmental delay, IUGR, microcephaly.

AR, ***TINF2, RTEL1, TERT, PARN, ACD, DCLRE1B***
XL, ***DKC1***

Bone marrow failure sd (BMFS)

Aplastic anemia, pancytopenia or Myelodysplasia

BMFS1 -SRP72 def*.
SRP72, AD #614675
Congenital nerve deafness

BMFS2 (Hebo def)*.
ERCC6L2 AR. #615715
Facial dysmorphism; microcephaly, learning difficulties.

BMFS5*
TP53, AD #618165
Erythroid hypoplasia, B-cell deficiency. Poor growth, microcephaly, developmental delay, seizures.

Others

MIRAGE sd. ***SAMD9*** AD GOF. #617053
IUGR, short stature, gonadal abnormalities, developmental delay, adrenal failure, MDS with chromosome 7 aberrations, recurrent infections, enteropathy, asplenia.

Ataxia pancytopenia sd*. ***SAMD9L*** AD GOF. #159550
Cytopenia, cerebellar ataxia and predisposition to MDS with chromosome 7 aberrations or AML

COATS plus Sd: Intracranial calcification, leukodystrophy, brain cysts: Ataxia, spasticity, seizures. Retinal telangiectasia and exudates, gastrointestinal hemorrhage due to vascular ectasia, osteopenia. Hypocellular bone marrow, pancytopenia, IUGR, premature aging. Abnormal telomeres.
CTC1 AR. #612199
STN1* AR. #617341 Liver fibrosis.

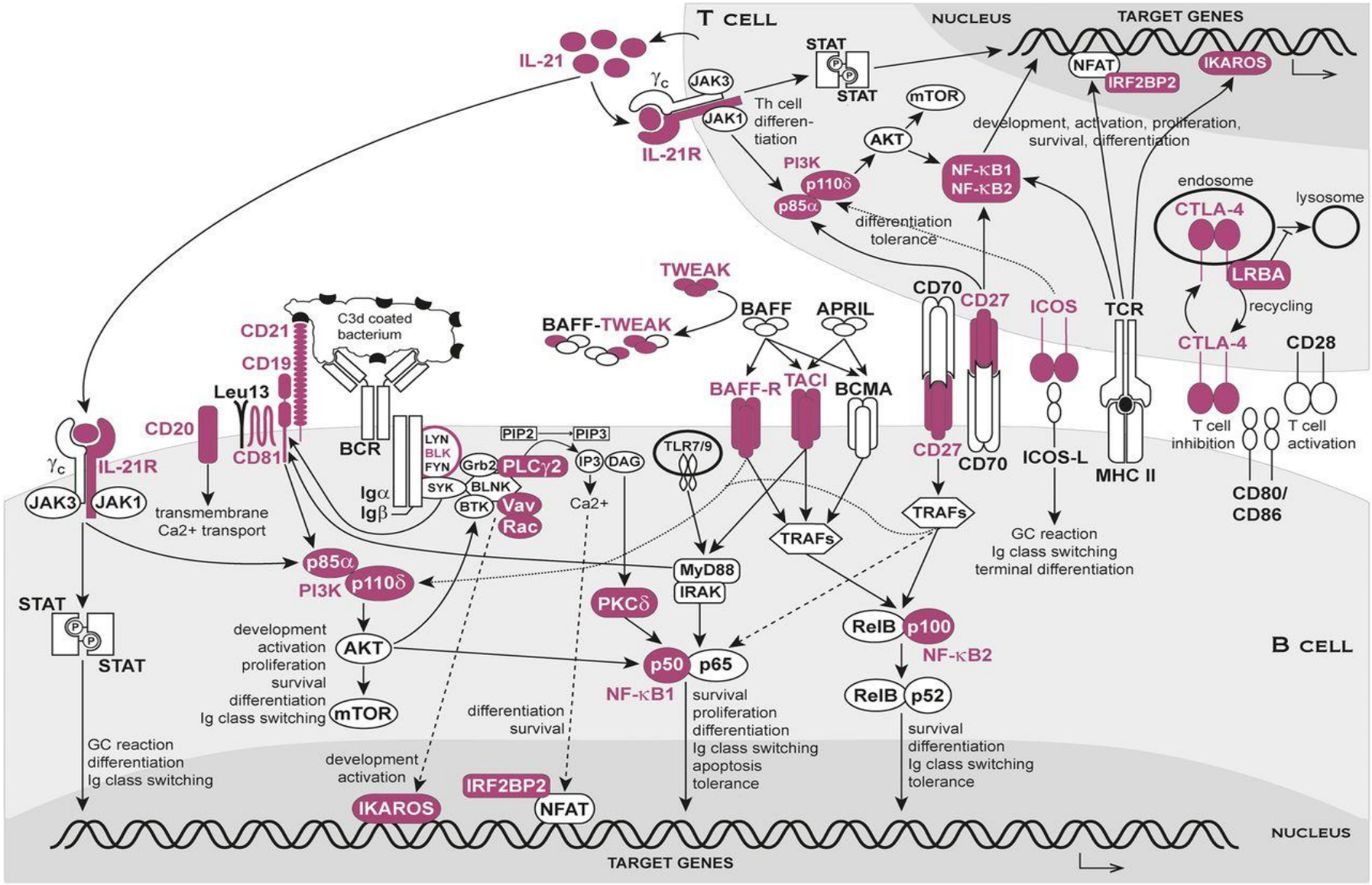
Osteopetrosis. Macrocephaly, choanal stenosis, feeding difficulties, blindness, deafness, facial palsy. Hypocalcemia.
AR ***PLEKHM1***.** #611497, ***TCIRG1*** #259700, ***SNX10**** #615085
AR/AD ***CLCN7**** #611490, AR ***OSTM1**** #259720 + neurologic features
TNFSF11**, AR. #259710 + severe growth retardation
AR ***TNFRSF11A**,*** **#** 612301 Severe form, with hypogammaglobulinemia

MECOM def*. ***MECOM*** AD LOF. #616738
Thrombocytopenia/pancytopenia, radioulnar synostosis, clinodactyly, cardiac and renal malformations. Bc deficiency.

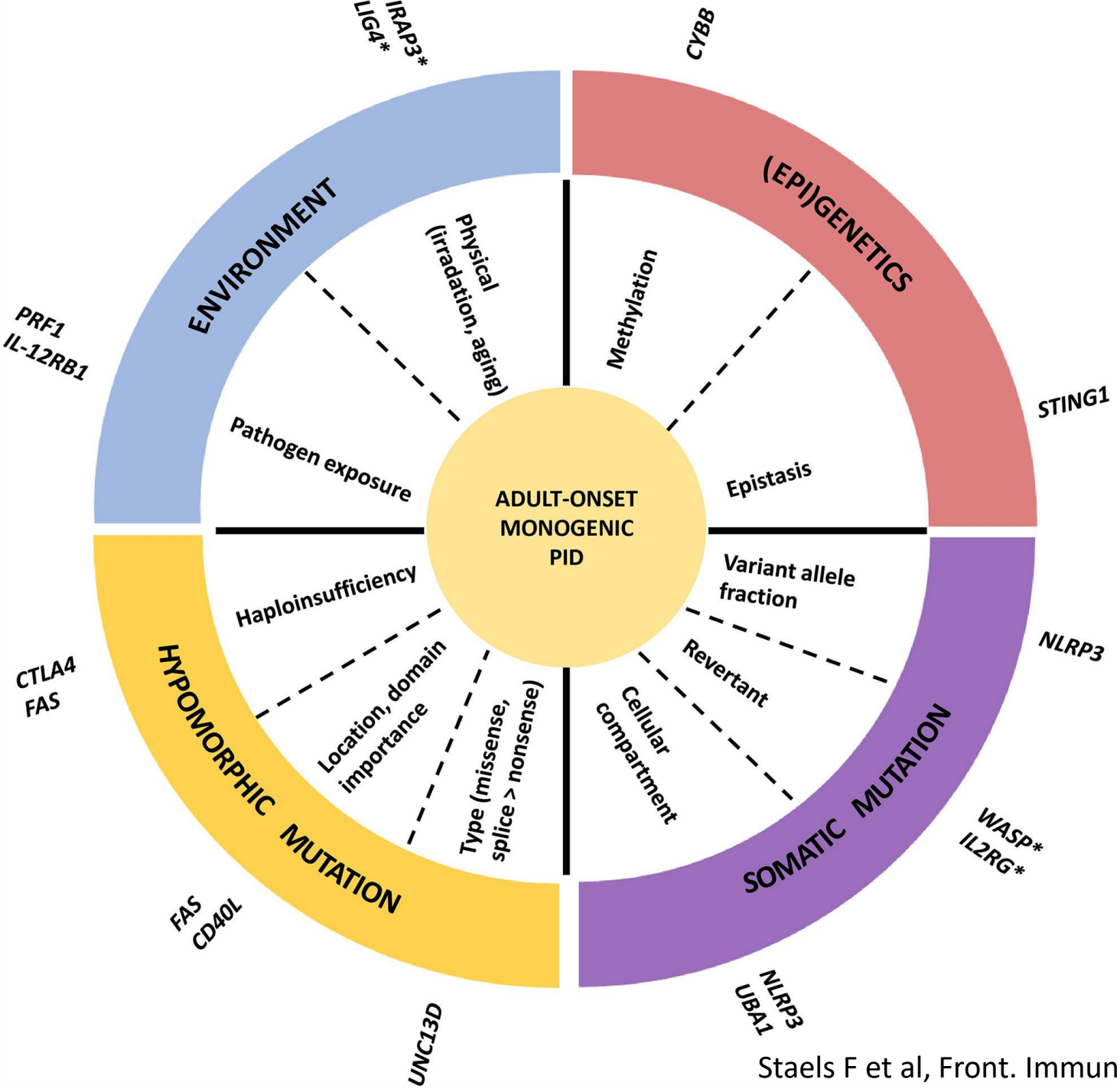
BMF and diabetes mellitus sd*. ***DUT*** AR. #620044 Diabetes. Abnormal skin pigmentation, short stature.

Kategória	Molekuláris alap / példák	Klinikai jellegzetességek
Kombinált immundefektusok (SCID, CID)	pl. *IL2RG*, *JAK3*, *ADA*, *RAG1/2*	Súlyos T- és B-sejt-hiány, életveszélyes fertőzések már csecsemőkorban
Antitestdefektusok	*BTK*, *IGHM*, *TNFRSF13B (TACI)*, *AID*	Baktériumfertőzések, hypogammaglobulinémia
Fagocita diszfunkciók	*CYBB*, *NCF1*, *ELANE*, *G6PC3*	Staphylococcus- és gombafertőzések, gyulladásos gócok
Komplementdefektusok	*C1q, C2, C3, C5–C9*	Autoimmun betegségek, Neisseria-fertőzések
Dysregulációs szindrómák	*FOXP3 (IPEX)*, *CTLA4*, *LRBA*, *STAT3*	Autoimmunitás, limfoproliferáció, citokin-túlműködés
Innate immunitás hibái	*TLR3, MYD88, IRAK4*	Vírusfertőzések, különösen herpeszvírusok és pneumococcusok
Autoinflammációs kórképek	*NLRP3, MEFV, TNFRSF1A*	Lázrohamok, gyulladásos tünetek infekció nélkül

A CVID gének által kódolt fehérjék (lila színnel jelölve)

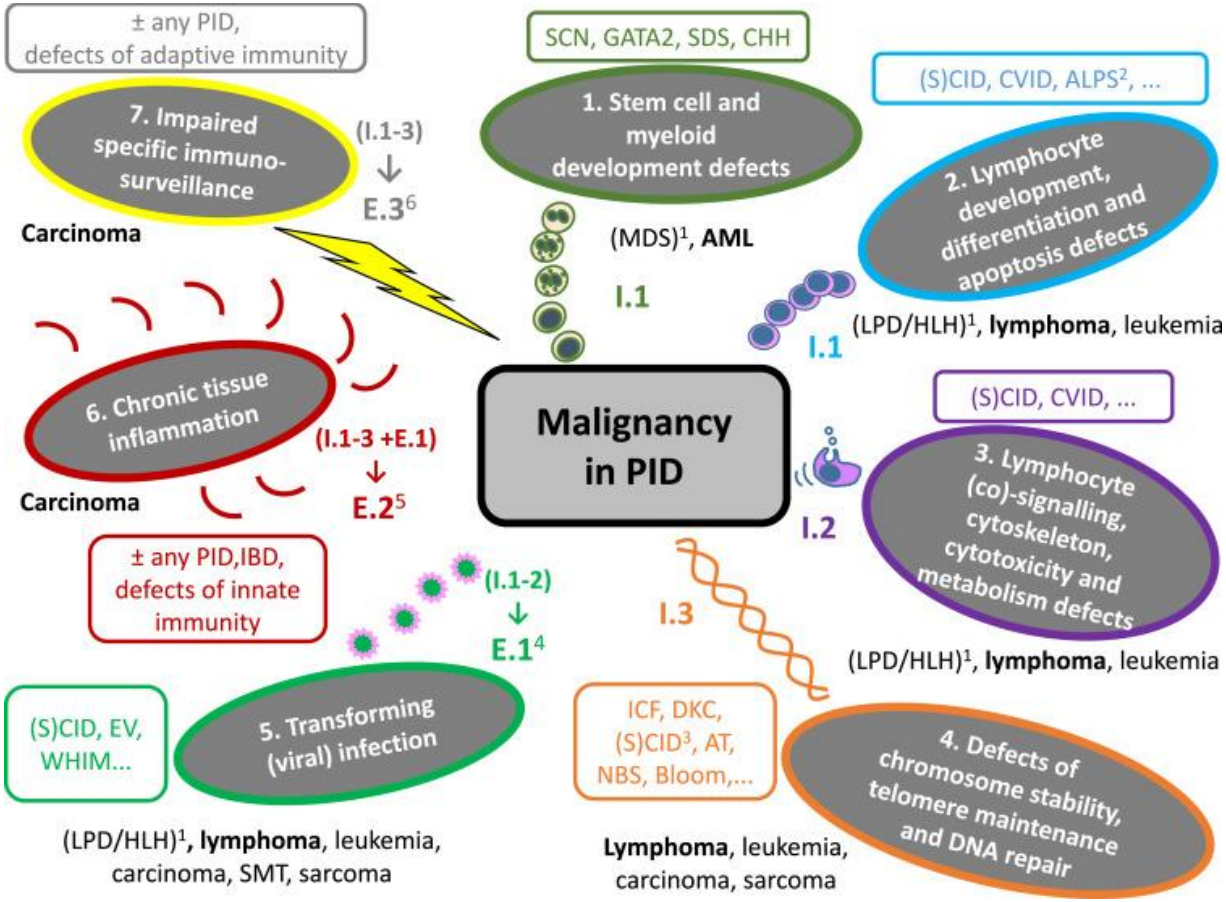


Delfien J A Bogaert et al. J Med Genet 2016;53:575-590



Staels F et al, Front. Immunol. 2021.

A daganathajlam patomechanizmusa PID-ben



Hauck et al JACI 2017

Intrinsic	Extrinsic
I.1. Stem cell, myeloid and lymphoid development, differentiation and apoptosis defects	E.1. Transforming (viral) infection
I.2. Lymphocyte (co-)signaling, cytoskeleton, cytotoxicity and metabolism defects	E.2. Chronic tissue inflammation
I.3. Defects of chromosome instability, telomere maintenance an DNA repair	E.3. Impaired specific tumor immunosurveillance

A PID nem (csak) gyermekbetegség

- Több beteg éri meg a felnőttkort
- Késői diagnózisok (CVID átlag 5-7 év a tünetek kezdete után)
  - számos specialista kezeli, de nem derül fény az egységes eredetre
- Felnőttkori megjelenés
  - Polygénes betegségek
  - Monogénes betegségek (kis penetranciájú germline mutációk, hypomorph mutációk, „leaky” esetek)

Túlélési adatok

- CVID (változó immunhiány) 10 éves túlélése

1971	1993	2008
37%	78%	90%

- Hemofíliás betegek életkilátása

1900	1960	2017
13 év	20 év	77 év

Forrás: http://www.pptaglobal.org/

A PID nem (csak) gyermekbetegség

- Több beteg éri meg a felnőttkort
- Késői diagnózisok (CVID átlag 5-7 év a tünetek kezdete után)
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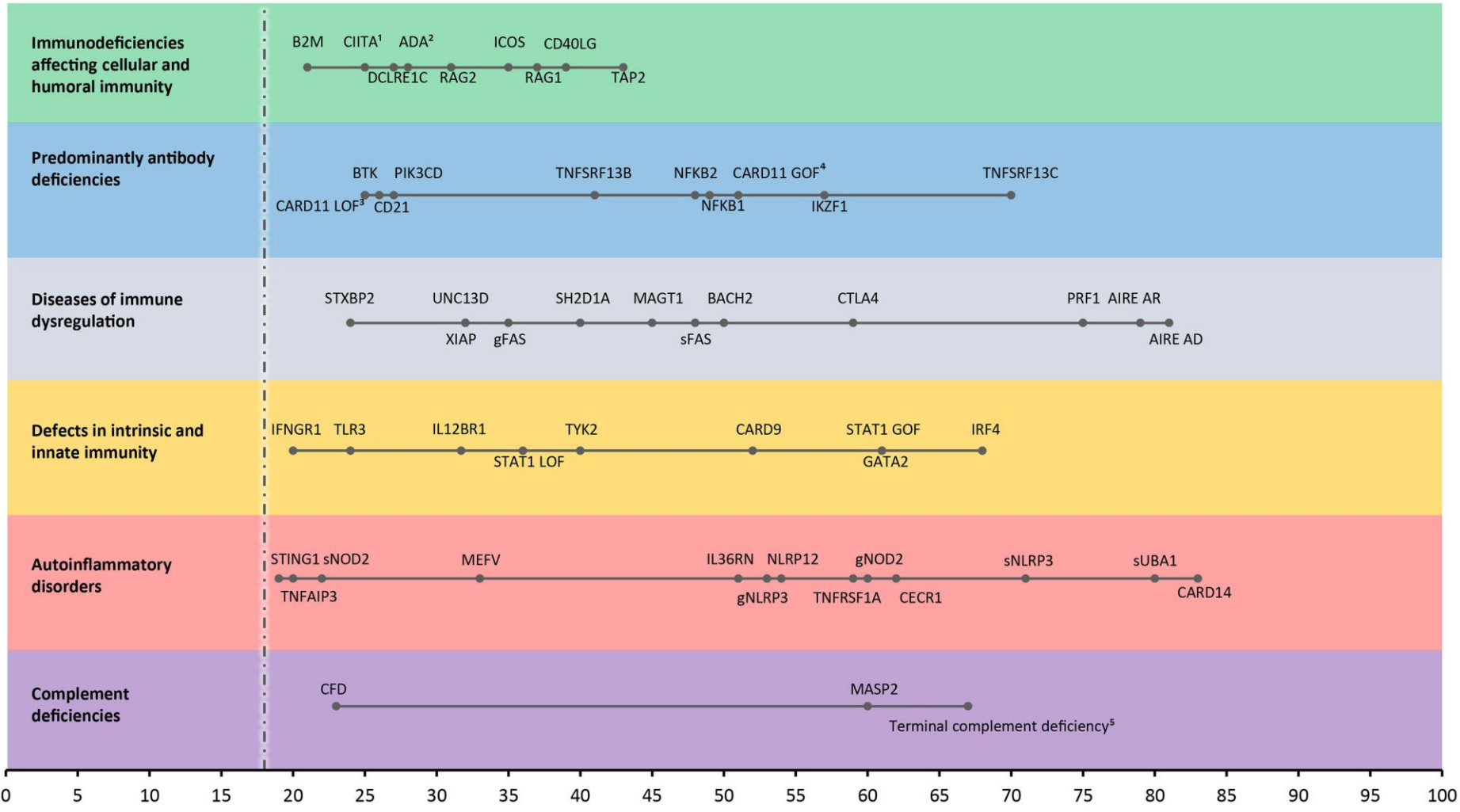
  - Monogénes betegségek (kis penetranciájú germline mutációk, hypomorph mutációk, „leaky” esetek)

Mutációk és életkor



Staels F et al, Front. Immunol. 2021.

Aktivált PI3K-delta szindróma (APDS)

- Phosphatidylinositol 3-kináz δ (PI3K δ) katalitikus alegységet kódoló PIK3CD gén - GOF mutáció
- Szül. 2008, leány
- 3 hónapos korától nem klasszifikálható gyulladásos bélbetegség (IBD-like)
- Gyakori felső légúti hurutok
- 2020. októbertől súlyos, elhúzódó EBV infekció. A májban, lépben, vesékben és tüdõparenchymában multiplex gócokból szövettan: EBV-asszociált grade 2 lymphomatoid granulomatosis (CD20+)
- 2020 decembertől 4 x 375mg/m2 rituximab - extrém rapid klinikai javulás.
- 2021. február elejétől újra panaszok, EBV kópiaszáma alacsony. Képalkotó vizsgálatokon: korábbi hasi és mellkasi terimék egy részének regressziója, más részének progressziója és új eltérések megjelenése.
- 2021.02.25-én biopsziázott új nyelv alatti góc továbbra is lymphomatoid granulomatosis grade 2-nek felelt meg, a proliferáló sejtek korábbinál magasabb (30%) arányával, CD20 negativitásával, többségükben CD30 pozitivitással.
- Malignus transzformáció: 6x CHOP és 6x anti-CD30 antitest (brentuximab vedotin)- PET CT neg (2021. 05.) Genetika: APDS
- Relapszus (2021. 08.) CD30 neg, CD20poz – Th.: sirolimus, IFNγ, rituximab, szteroid
- Folyamatos szisztémás tünetek, PET CT-n metabolikus aktivitás
- 2022.01. Allogén idegen donoros őssejt-transzplantáció – teljes panasz- és tünetmentesség

Terápiás megfontolások

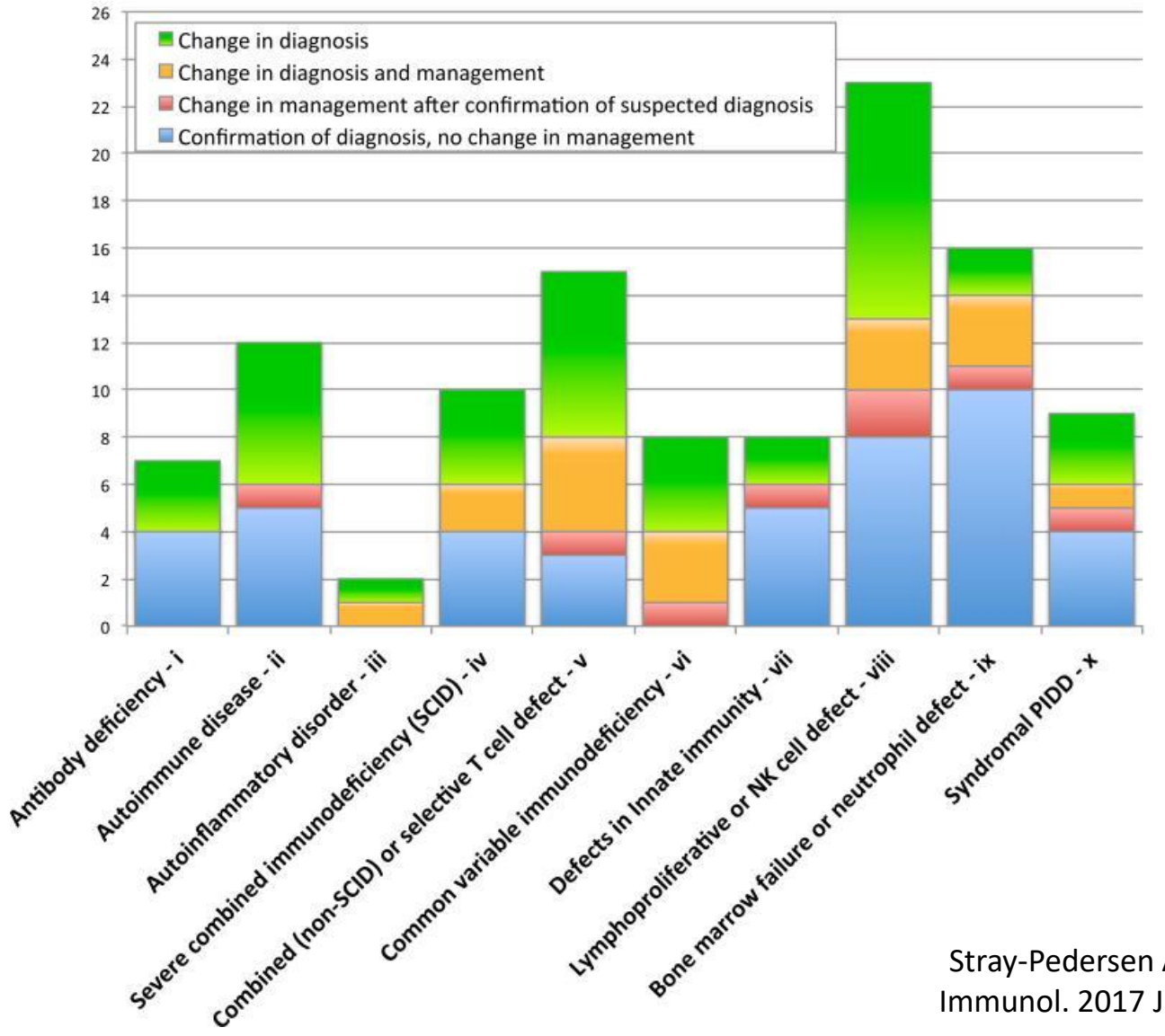
- Mikor (mit) kezelünk?
- Nagyon heterogén patomechanizmus, immunfunkciók, terápiás válaszkészség, toxicitás
- Genetika meghatározó szerepe
- Individualizált kezelés (sugárérzékenység, gyógyszertoxicitás, monoklonális antitestek, checkpoint inhibitorok, BiTe antitestek)
  - Célzott terápia APDS: szelektív PI3K inhibitor - leniolisib, mTOR gátlás – sirolimus
  - JAK-STAT jelátvitel (STAT1 és STAT3 GOF) – ruxolitinib
  - SYK GOF: fostamatinib
  - CTLA4 haploinsuff.: abatacept
- Vérképző-őssejttranszplantáció (allogén)

Miben segít a genetikai diagnózis?

- A diagnózis felállításában (a klinikai kép és az immunológiai eltérések nagyfokú átfedést mutathatnak, így ezek alapján csak a kórképek egy része diagnosztizálható)
- Öröklésmenet feltárásában, genetika tanácsadás
- Prognózis meghatározásában, a szövődmények korai felismerésében és kezelésében
- Segítség a terápiás döntések meghozatalában
- Új terápiás lehetőségek

A genetikai eredmény hatása a diagnózisra és a terápiára

n=110 families



Stray-Pedersen A et al.:J Allergy Clin Immunol. 2017 Jan; 139(1): 232–245.

Table 1. Targeted therapies used in PID

Molecular structure	Molecular target	Drug	Indication
Macrolide compound	mTOR	Sirolimus	NLCR4-GOF POMP deficiency CTLA-4 haploinsufficiency APDS
CTLA-4 IgG fusion protein	B7-1 (CD80), B7-2 (CD86)	Abatacept Belatacept	CTLA-4 haploinsufficiency LRBA deficiency CTLA-4 haploinsufficiency
Recombinant human IL-1R antagonist	IL-1R	Anakinra	Cryopyrin-associated periodic fever syndromes
Antihuman IL-1 IgG1 mAb IgG1 linked to IL-1R and IL-1R accessory protein	IL-1β	Canakinumab Rilonacept	CAPS FCAS MWS DIRA
IgG1k recombinant humanized mAb	IL-6R	Tocilizumab	STAT3-GOF
Fusion protein Chimeric mAb Humanized mAb	TNF-α	Etanercept Infliximab Adalimumab	SAVI CANDLE syndrome POMP deficiency
Small molecule inhibitor	JAK1 and JAK 2 JAK 1 and JAK3 P110	Ruxolitinib Baricitinib Tofacitinib Leniolisib	STAT3-GOF[a] STAT1-GOF CANDLE syndrome APDS
Recombinant IL-18 binding protein	IL-18-binding protein	Tadekinig-α	NLCR4-GOF

SAVI, STING-associated vasculopathy with onset in infancy. [a] Only ruxolitinib and tofacitinib.

Delmonte O.M. · Notarangelo L.D. Med Princ Pract 2020;29:101–112

Elastase deficiency (Severe congential neutropenia [SCN] 1)	*ELANE*	AD	130130	N	Myeloid differentiation	Susceptibility to MDS/leukemia Severe congenital neutropenia or cyclic neutropenia
GFI 1 deficiency (SCN2)	*GFI1*	AD	600871	N	Myeloid differentiation	B/T lymphopenia
HAX1 deficiency (Kostmann Disease) (SCN3)	*HAX1*	AR	605998	N	Myeloid differentiation	Cognitive and neurological defects in patients with defects in both HAX1 isoforms, susceptibility to MDS/leukemia
G6PC3 deficiency (SCN4)	*G6PC3*	AR	611045	N	Myeloid differentiation, chemotaxis, O_2^- production	Structural heart defects, urogenital abnormalities, inner ear deafness, and venous angiectasias of trunks and limbs
VPS45 deficiency (SCN5)	*VPS45*	AR	610035	N	Myeloid differentiation, migration	Extramedullary hematopoiesis, bone marrow fibrosis, nephromegaly
Glycogen storage disease type 1b	*G6PT1*	AR	602671	N + M	Myeloid differentiation, chemotaxis, O_2^- production	Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hepatomegaly
X-linked neutropenia/myelodysplasia	*WAS*	XL GOF	300299	N	Differentiation, mitosis. Results from GOF mutations in GTPase binding domain of WASp	Neutropenia, myeloid maturation arrest, monocytopenia, variable lymphoid anomalies
P14/LAMTOR2 deficiency	*LAMTOR2*	AR	610389	N + M	Endosomal biogenesis	Neutropenia Hypogammaglobulinemia ↓CD8 cytotoxicity, partial albinism, growth failure
Barth Syndrome (3-Methylglutaconic aciduria type II)	*TAZ*	XL	300394	N + L Mel	Mitochondrial function	Cardiomyopathy, myopathy, growth retardation, neutropenia
Cohen syndrome	*VPS13B*	AR	607817	N	Myeloid differentiation	Dysmorphism, mental retardation, obesity, deafness, neutropenia
Clericuzio syndrome (Poikiloderma with neutropenia)	*USB1*	AR	613276	N	Myeloid differentiation	Retinopathy, developmental delay, facial dysmorphisms, poikiloderma
JAGN1 deficiency	*JAGN1*	AR	616012	N	Myeloid differentiation	Myeloid maturation arrest, osteopenia
3-Methylglutaconic aciduria	*CLPB*	AR	616254	N	Myeloid differentiation Mitochondrial protein	Neurocognitive developmental aberrations, microcephaly, hypoglycemia, hypotonia, ataxia, seizures, cataracts, IUGR
G-CSF receptor deficiency	*CSF3R*	AR	138971	N	Stress granulopoiesis disturbed	
SMARCD2 deficiency	*SMARCD2*	AR	601736	N	Chromatin remodeling, Myeloid differentiation and neutrophil functional defect	Neutropenia, developmental aberrations, bones, hematopoietic stem cells, myelodysplasia
Specific granule deficiency	*CEBPE*	AR	189965	N	Terminal maturation and global dysfunction	Neutropenia, Neutrophils with bilobed nuclei
Shwachman-Diamond Syndrome	*SBDS*	AR	607444	N	Neutrophil maturation,	Pancytopenia, exocrine pancreatic

Esetismertetés 1.

- szül: 2004. 05. 20. fiú
- 5 hónapos korától bőrfertőzések, anorexia, dystrophia, sepsis
- Agranulocytosis
- Pulmonális stenosis, arc dysmorphia, előtűnő felszíni vénák
- 2007-től: Perzisztáló neutropenia (abszolút granulocyta szám 0.07 G/l és 0.59 G/l között)
- Nagy kiterjedésű, fájdalmas szájnyálkahártya fekélyek 2 hetente: sc. G-CSF injekció másnaponta
- 2011: G6PC3 (glucose-6-phosphatase, catalytic subunit 3) deficiency
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- 25 mg/nap orális empaglifozin: G-CSF 2 hónapon belül leállíthatóvá vált, a csökkent granulocyta funkció (DHR teszttel mérve) normalizálódott, és a jelentős thrombocytopenia megszűnt

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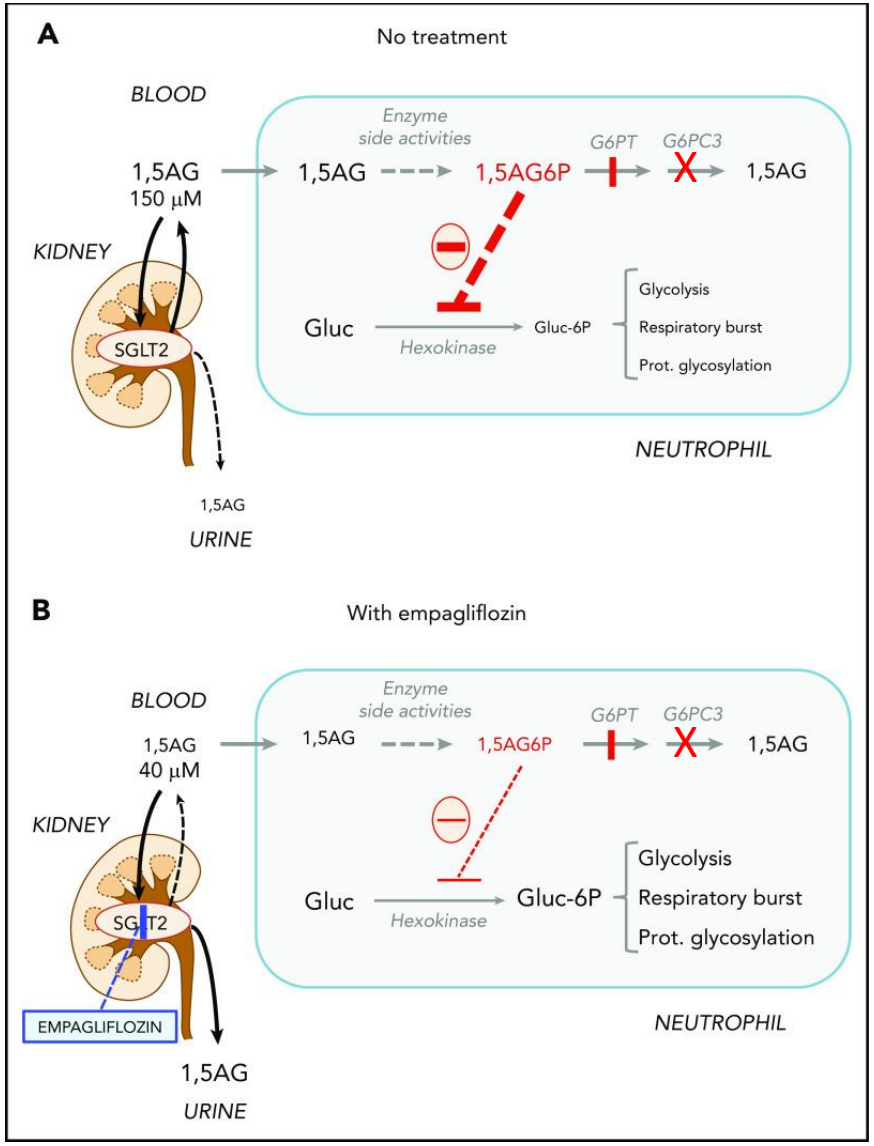
G6PC3 deficiency patofiziológiai háttere



- G6PC3 deficiencia miatt a 1,5-anhydroglucitol-6-phosphate (1,5AG6P) felhalmozódik
- 1,5AG6P toxikus a neutrophilekre a hexokinase erős gátlása miatt és lecsökkenti az intracelluláris G6P (Gluc-6P) raktárt, amely elengedhetetlen a neutrophilek túléléséhez és működéséhez
- A renális nátrium glucose cotransporter 2 (SGLT2) empagliflozin-nal történő gátlása glucosuriát okoz a renális glucose reabszorpció gátlásával, továbbá gátolja az 1,5-anhydroglucitol (1,5AG) reabszorpcióját is
- A vér 1,5AG és a neutrophil 1,5AG6P koncentráció 4x-es csökkenése
- Mindez megszünteti hexokinázok gátlását és növeli a G6P és metabolitjainak szintjét a további anyagcsere utakon: javul a glycolysis, respiratory burst és a fehérje glycosylatio

Saskia B. Wortmann et al: Blood. 2020 Aug 27; 136(9): 1033–1043.
Grünert S.C., Derks T.G.J.,… **Kriván G.,…** Zsidegh P., Wortmann S.B.: Efficacy and safety of empagliflozin in glycogen storage disease type Ib: Data from an international questionnaire. *Genet Med*. 2022 Aug;24(8):1781-1788

Esetismertetés 1.

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- 5 hónapos korától bőrfertőzések, anorexia, dystrophia, sepsis
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Lédeczi Z, Pittner R, **Kriván G**, Kardon T, Legeza B.: Empagliflozin restores neutropenia and neutrophil dysfunction in a young patient with severe congenital neutropenia type 4. *J Allergy Clin Immunol Pract*. 2022 Oct 26;S2213-2198(22)01062-5. doi: 10.1016/j.jaip.2022.10.019.

DHR teszt

Phagocyta funkció: NADPH oxidáz aktivitás mérése E. coli és PMA stimulációt követően

2020. December 15.	Stimulation index assayed with E. coli: 55.74 (norm> 30) Stimulation index assayed with PMA : **11.27** **Értékelés**: az oxidatív burst enzimeinek enyhe aktivitás **csökkenése** a **PMA-stimulált mintában**.

2021. Március 2.	Stimulation index with E. coli: 32.34 (norm> 30) Stimulation index with PMA: 55.66 **Értékelés**: az oxidatív burst enzimeinek normális aktivitása

Lédeczi Z, Pittner R, **Kriván G**, Kardon T, Legeza B.: Empagliflozin restores neutropenia and neutrophil dysfunction in a young patient with severe congenital neutropenia type 4. *J Allergy Clin Immunol Pract*. 2022 Oct 26;S2213-2198(22)01062-5. doi: 10.1016/j.jaip.2022.10.019.

Esetimertetés 2/1

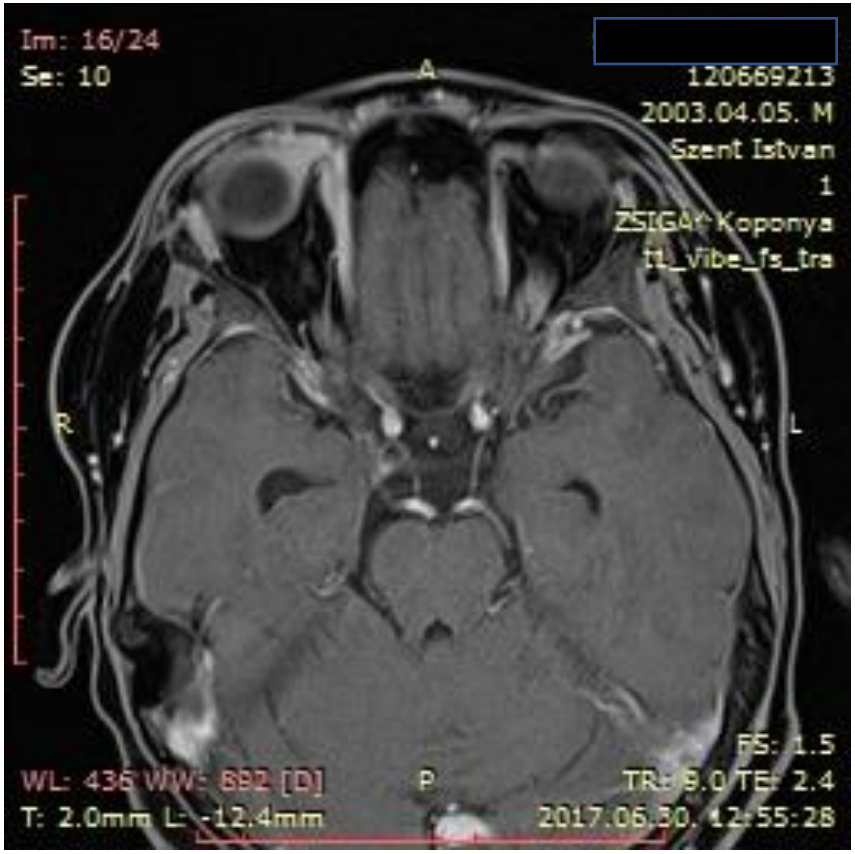
- Szül.: 2003, Fiú
- Kisdedkorától gyakori felső légúti betegségek, 5x pneumonia
- 2010: ITP, Evans sy – szteroid
- 2011: progresszív varicella, IgG: 9,49, IgA: 0,21, IgM: 1,11g/l
  - LTT: PHA csökkent, ConA és PWM normális
- 2012: IgG2 és IgG4 csökkenés, - CVID? - IVIG

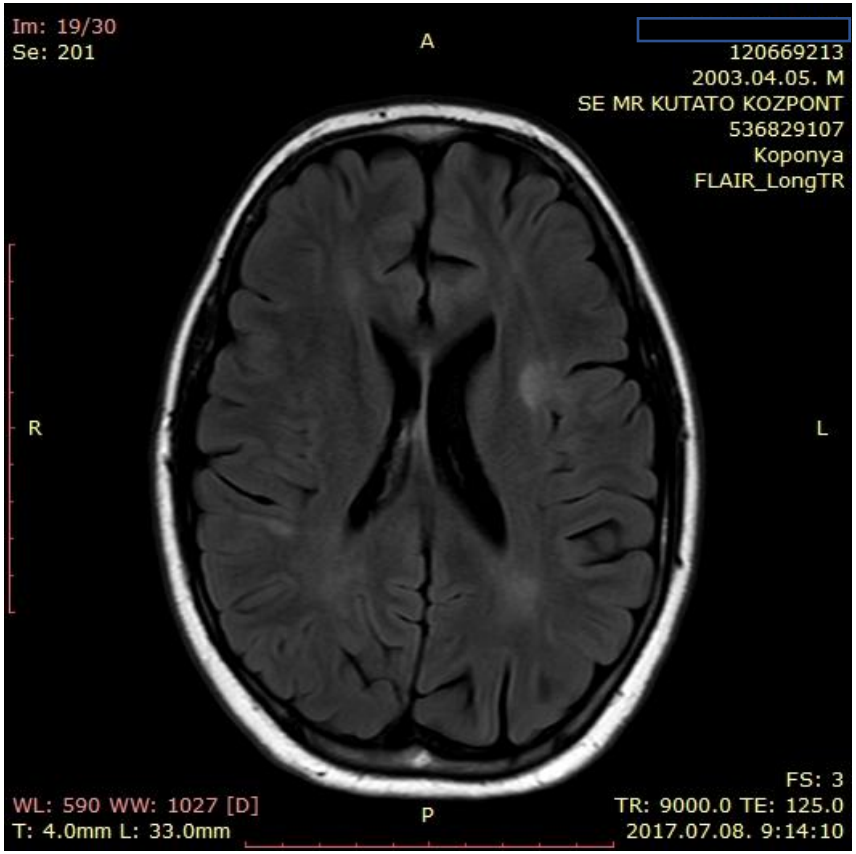
	%	Ref tart. %	Abs. szám sejt/µl	Ref tart sejt/µl
CD3+ T sejt	79,99 (+)	52-78	1158,65	800-3500
CD3+/CD8+ T sejt	47,53 (+)	9-35	388,49	200-1200
CD3+/CD4+ T sejt	27,50	25-48	398,32 (-)	400-2100
CD3-/CD16+56+ NK sejt	12,64	6-27	183,10	70-1200
CD19+ B sejt	6,47 (-)	8-24	93,74 (-)	200-600
CD4/CD8 arány	0,58 (-)	0,9-3,4		
Dupla negatív T sejt	4,96	<8		
Dupla pozitív T sejt	0,09	<2		
CD27+/IgD-/IgM- B sejt	0,00 (-)	3,3-9,6		

Esetismertetés 2/2

- 2013: ITP shub – szteroid, azatrioprin, IgA: 0
- 2016: splenomegália, krónikus ITP, hypertónia, kreatinin és húgysav emelkedés
- 2017:
  - Szteroid rezisztens ITP – eltrombopag
  - Visszatérő hasmenések: Campylobacter
  - Parotis duzzanat. Szövettan - AI sialadenitis
  - Grand mal - Orbitális és CNS granulomák – nagy dózis szteroid, levetiracetam - regresszió
- Donorkeresés

Orbita és agykoponya MRI 2017

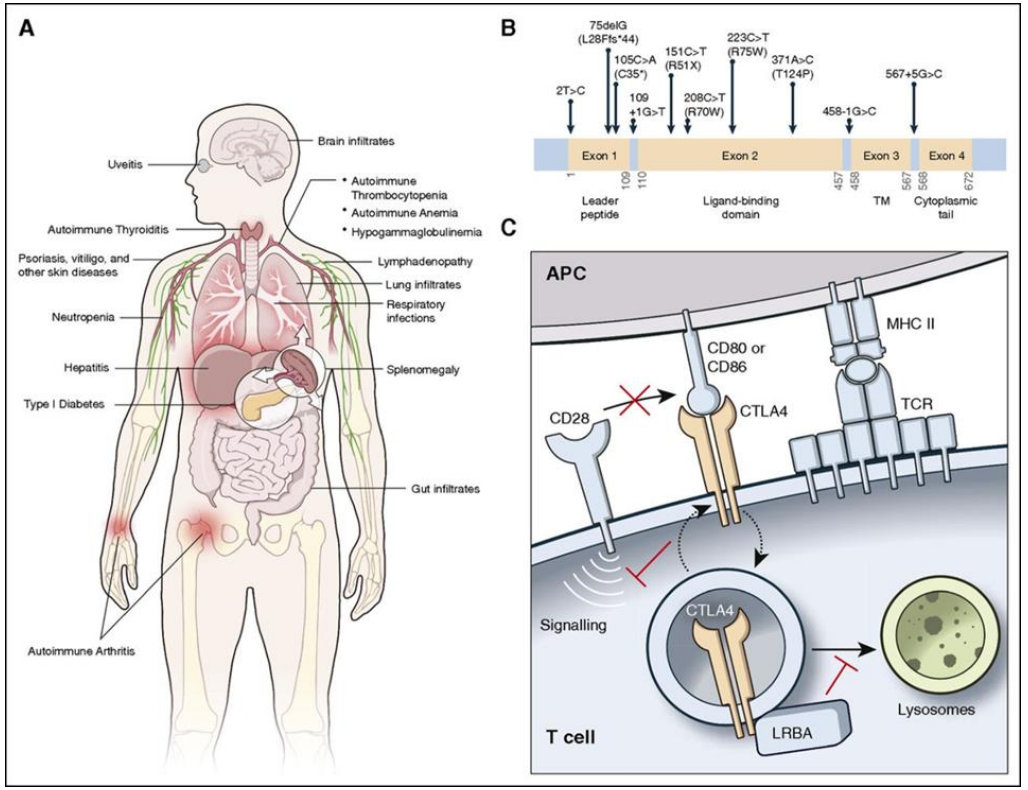




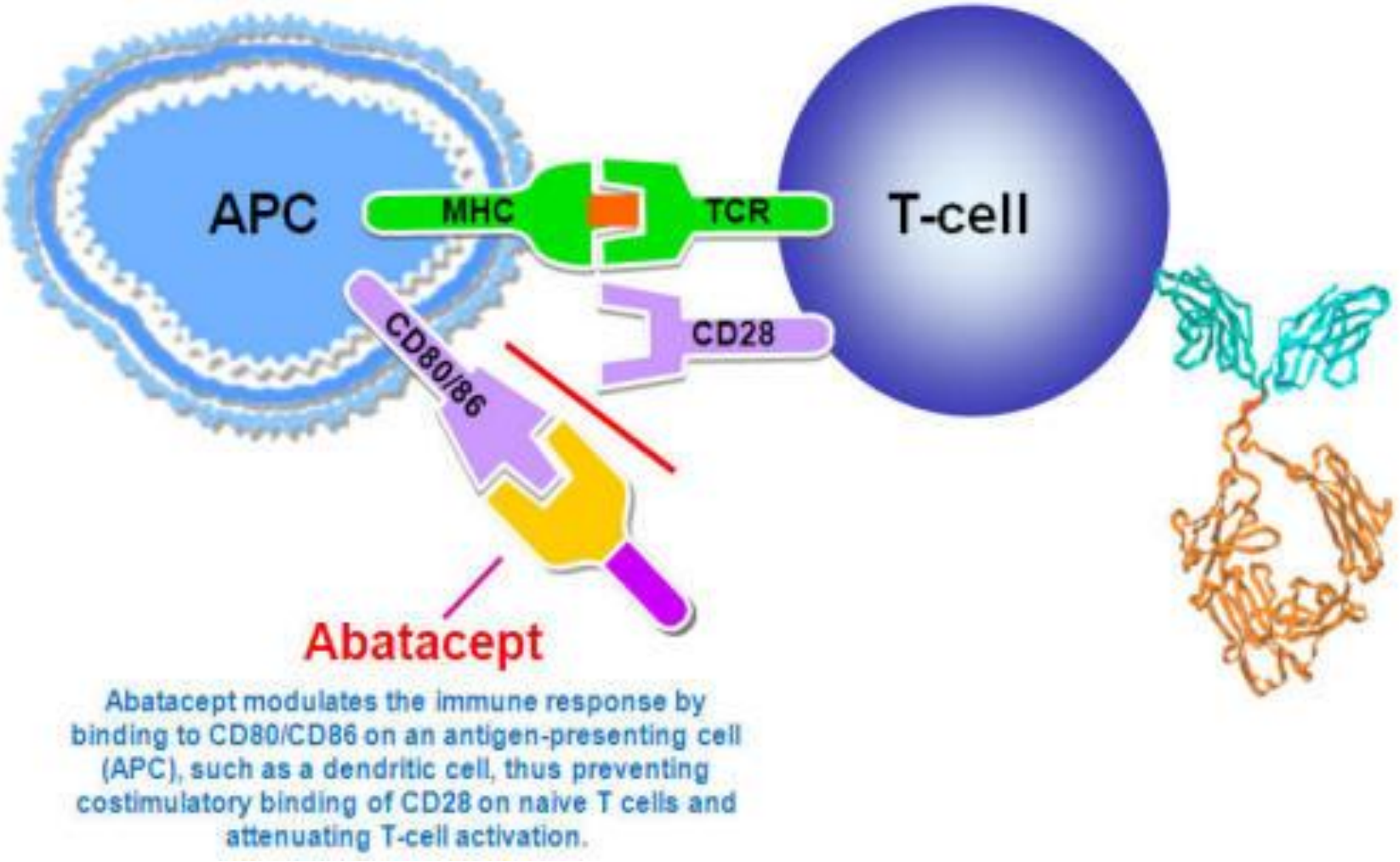
Esetismertetés 2/3

Gén	CHR	POS	R	A	Impact	AA
CTLA4	2	204735635	G	A	missense	G146R

- 2017: genetika CEMM (Bécs)
- CTLA-4 defektus
- Mater: egyező genetika
- 2018: abatacept (fúziós protein: IgG Fc + CTLA-4 EC domain)
- Imuran és Orencia mellett tünetmentes (thr: 400 G/l), azathioprin leépítés
- Donorkeresés leállt
- CML – donorkeresés újraindult
- Imatinib, granulomák - rituximab, nilotinib



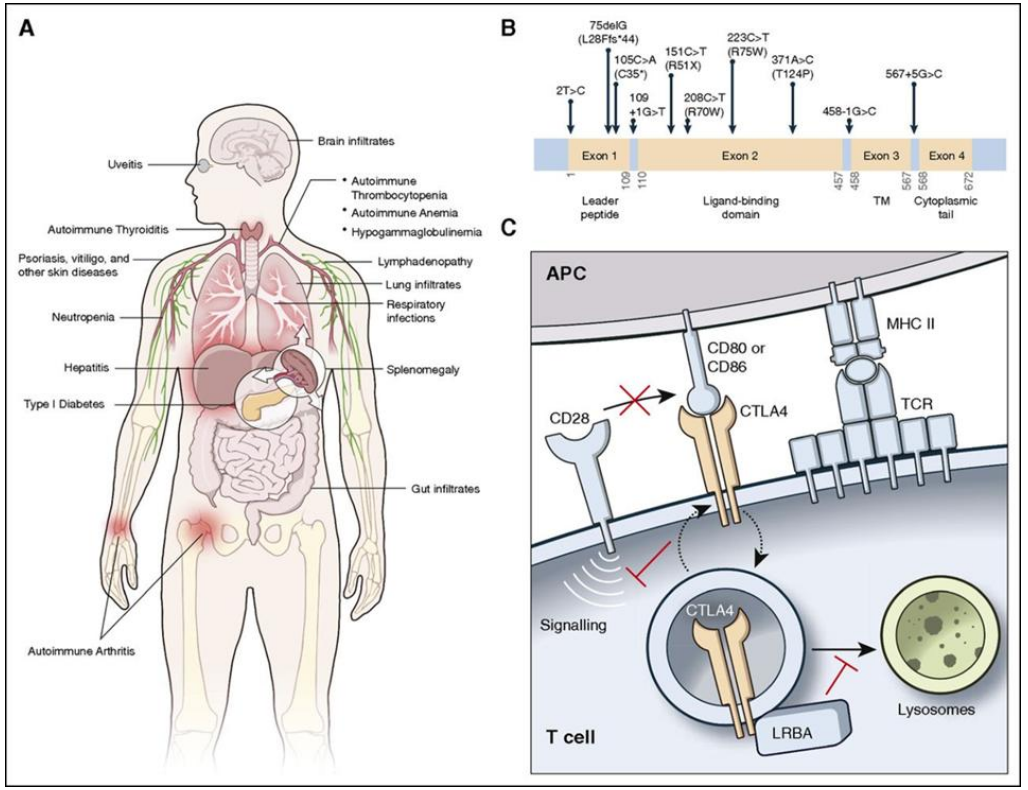
Abatacept CTLA-4 mutációban



Esetismertetés 2/4

Gén	CHR	POS	R	A	Impact	AA
CTLA4	2	204735635	G	A	missense	G146R

- 2017: genetika CEMM (Boztug)
- CTLA-4 defektus
- Mater: egyező genetika
- 2018: abatacept (fúziós protein: IgG Fc + CTLA-4 EC domain)
- Imuran és Orencia mellett tünetmentes (thr: 400 G/l), azathioprin leépítés
- Donorkeresés leállt
- CML – donorkeresés újraindult
- Imatinib, granulomák - rituximab, nilotinib
- 2021.: sikeres csontvelő-átültetés



Esetismertetés 3.

- szül: 1978. ffi
- **Családi anamnézis:** Testvér: fiatalon aplasticus anaemia, leukaemia miatt exit
- 20 éve ismert és kezelt hypothyreosis,
- **1999:** total **gastrectomia polyposis** miatt
- **2000**: appendectomia, **migráló thrombophlebitis**, hypogammaglobulianemia (IgG: 3,27 g/l, IgA: 0,3 g/l, IgM: 0,49 g/l), ALC (0,6 G/l körül)
- **2005**: **alopecia universalis**.
- **2014: lymphopenia (ALC: 0,27 G/l), thrombocytopenia** alacsony Ig szintek és az autoimmun jelenségek hátterében **CVID** igazolódott.
- 2018: súlyos atópia: Diprophos, cyclosporin, közepes dózisú methylprednisolon - mérsékelt javulás
- **2020.: Dupilumab -** javulás. Autoimmun thyreoiditise jelentősen romlott, krónikus gyulladás - vashiányos anaemia
- 2021. NGS: **CTLA4 haploinsufficiencia** - abatacept

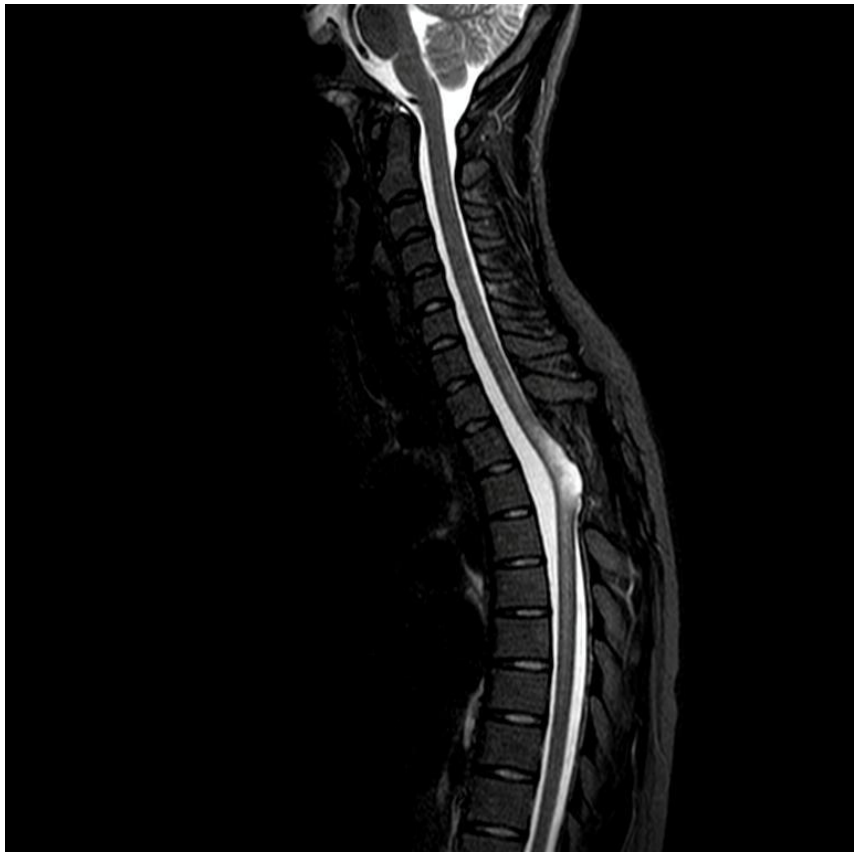
Esetismertetés 4.

- szül: 1978. ffi
- **Családi anamnézis:** Testvér: fiatalon aplasticus anaemia, leukaemia miatt exit
- 20 éve ismert és kezelt hypothyreosis,
- **1999:** total **gastrectomia polyposis** miatt
- **2000**: appendectomia, **migráló thrombophlebitis**, hypogammaglobulianemia (IgG: 3,27 g/l, IgA: 0,3 g/l, IgM: 0,49 g/l), ALC (0,6 G/l körül)
- **2005**: **alopecia universalis**.
- **2014: lymphopenia (ALC: 0,27 G/l), thrombocytopenia** alacsony Ig szintek és az autoimmun jelenségek hátterében **CVID** igazolódott.
- 2018: súlyos atópia: Diprophos, cyclosporin, közepes dózisú methylprednisolon - mérsékelt javulás
- **2020.: Dupilumab (anti IL4/13 ab) -** javulás. Autoimmun thyreoiditise jelentősen romlott, krónikus gyulladás - vashiányos anaemia
- 2021. NGS: **CTLA4 haploinsufficiencia** – abatacept
- 2022 április: Tünet- és panaszmentes

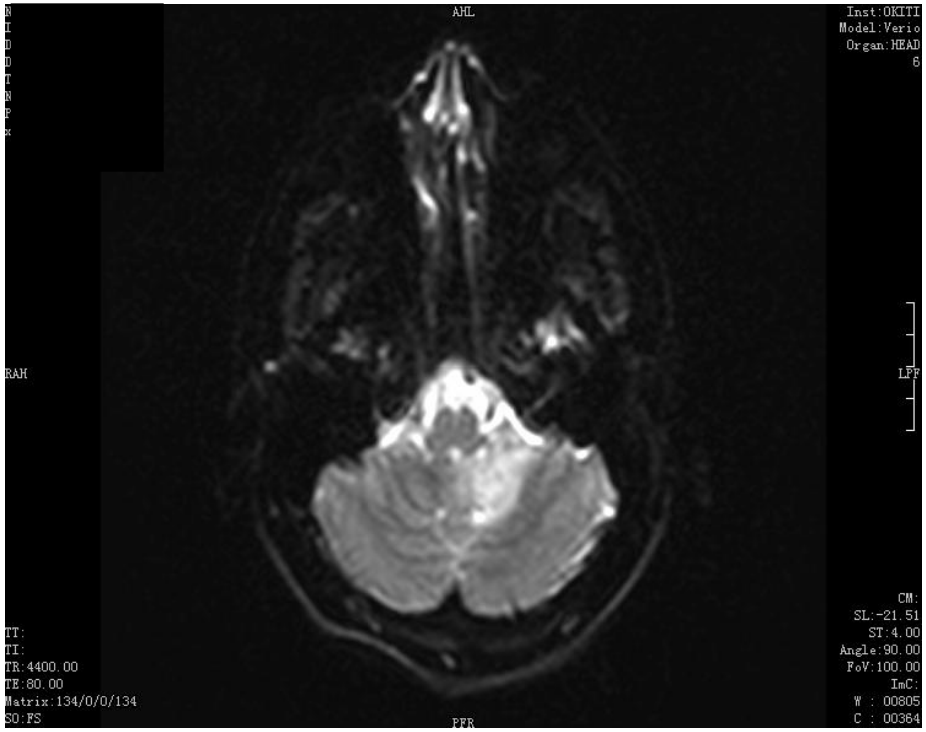
Esetismertetés 5.

- S.J. szül.: 1987. nőbeteg
- 1990-es évek vége otitisek, gyakori felső légúti hurutok
- 2007-2008. hasmenés, lymphadenopathia , lymphoma? biopszia IgG: 2 g/l, IgA és IgM: 0,22 g/l; memória B sejt:0, CVID, Ig pótlás - IVIG, ScIG
- 2008-2014: szubsztitúció komolyabb panaszok nélkül
- 2014 február: bal oldali AV paresis, törzsön szegmentális érzéskiesés, háti fájdalom
- Idegsebészeti tumor biopszia: non-caseosus granulomatosus myelitis
- Hasonló elváltozások a kisagyban is
- Relabáló – remittáló betegség lefolyás, kezelés: szteroid lökések, azathioprin, plazmaferezis, TNF alfa gátlók (infliximab) …
- 2020: rituximab 6 havonta - regresszió, steady state,
- 2021 - súlyos ITP és AI neutropenia, nycs. nagyobbodások, májenzim emelkedés, ízületi panaszok, súlyos hasmenés, bőrtünetek, csontvelői dysplasia – csontvelő Txp tervezett
- Genetika: SYK gain of function (funkciónyerő) mutáció (Vienna, CEMM)
- SYK gátlás - fostamatinib (OGYEI, NEAK)

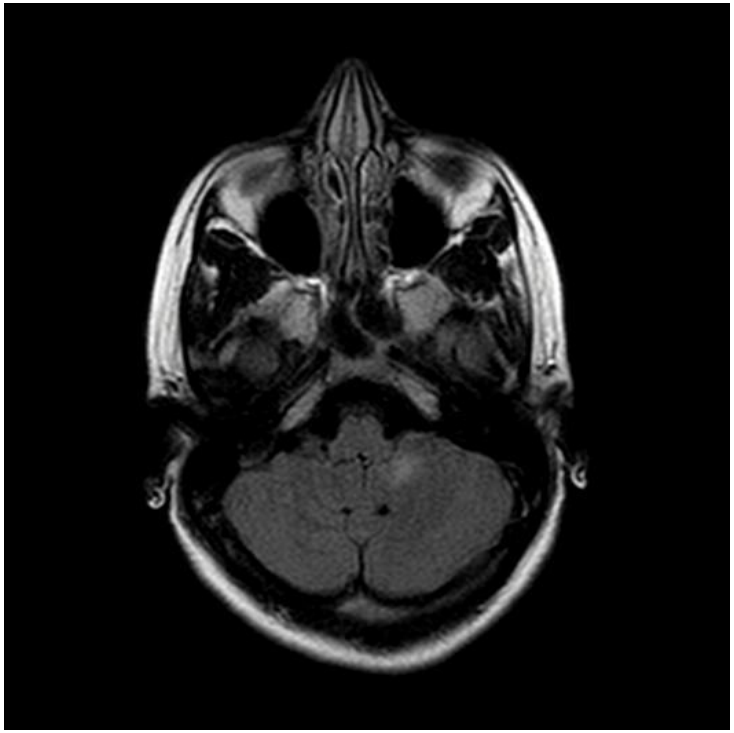
Gerinc MR
(2014 december és 2015 március)



Koponya MR

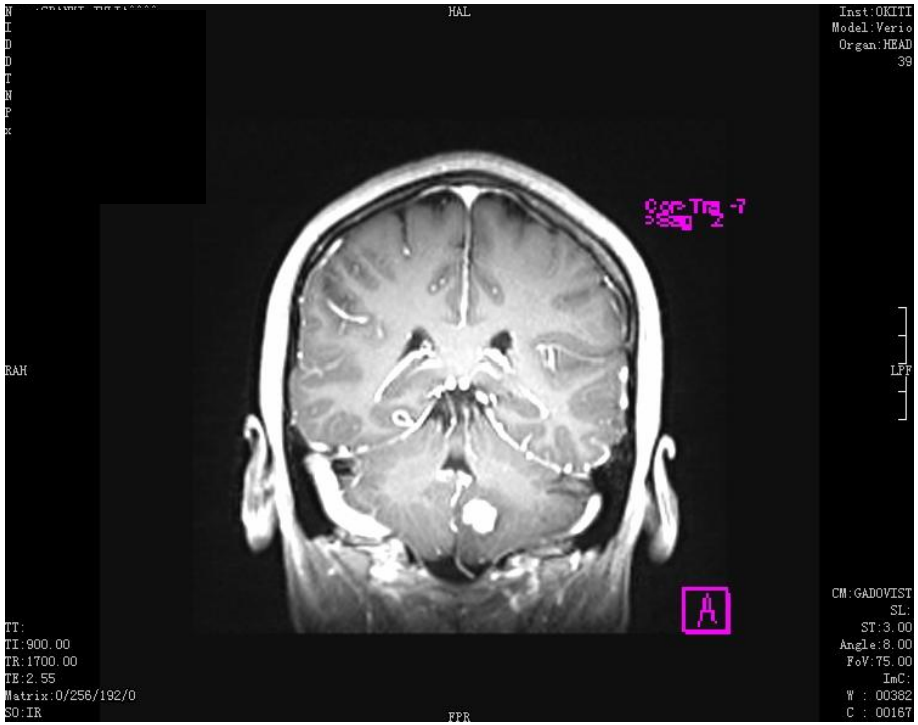


2014 december

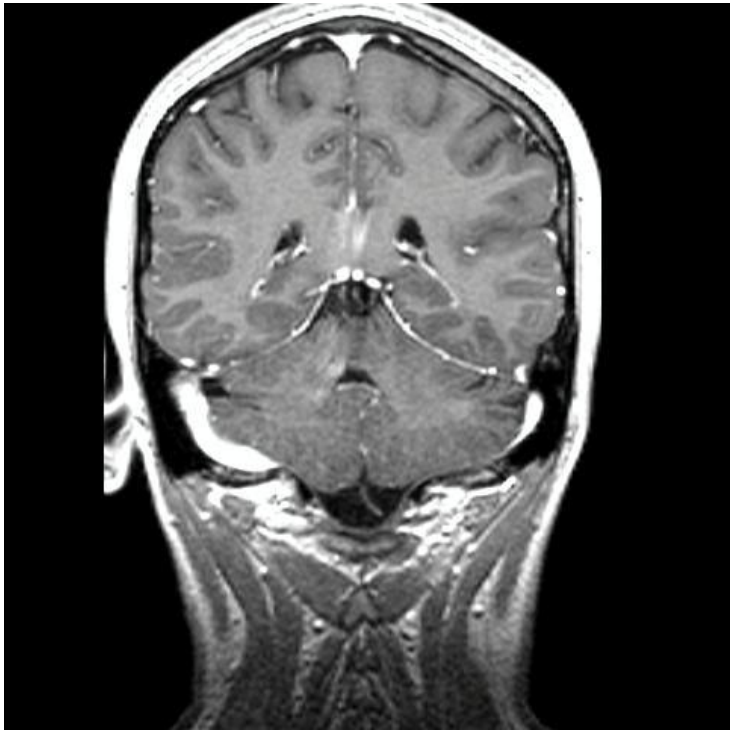


2015 március

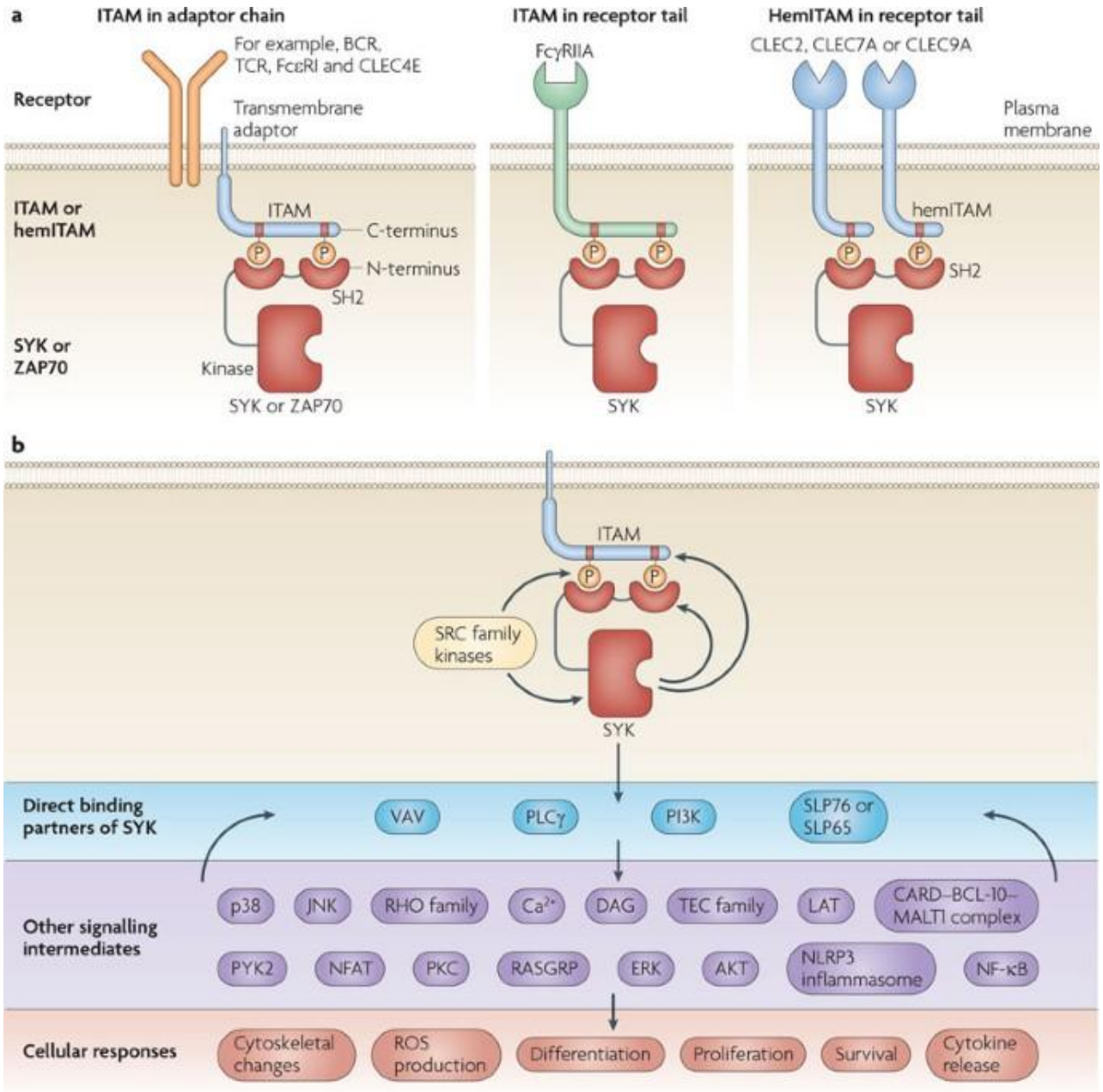
Koponya MR



2014 december



2016 január

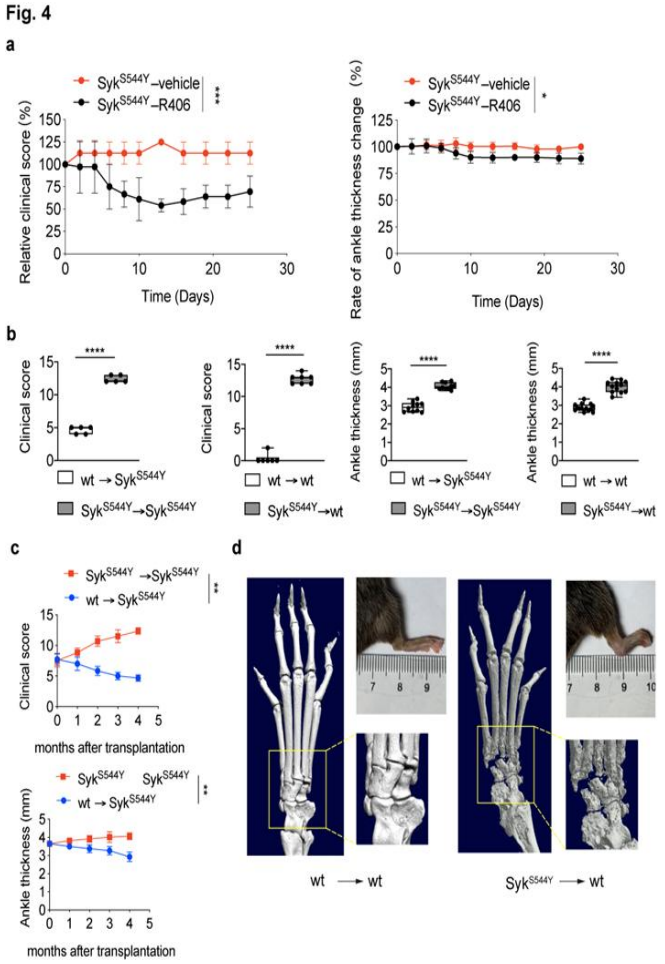

a
ITAM in adaptor chain
For example, BCR, TCR, FcεRI and CLEC4E
Receptor
Transmembrane adaptor
ITAM or hemITAM
ITAM
C-terminus
N-terminus
SH2
SYK or ZAP70
Kinase
SYK or ZAP70
ITAM in receptor tail
FcγRIIA
SYK
HemITAM in receptor tail
CLEC2, CLEC7A or CLEC9A
Plasma membrane
hemITAM
SH2
SYK
b
ITAM
SRC family kinases
SYK
Direct binding partners of SYK
VAV
PLCγ
PI3K
SLP76 or SLP65
Other signalling intermediates
p38
JNK
RHO family
Ca2+
DAG
TEC family
LAT
CARD–BCL-10–MALT1 complex
PYK2
NFAT
PKC
RASGRP
ERK
AKT
NLRP3 inflammasome
NF-κB
Cellular responses
Cytoskeletal changes
ROS production
Differentiation
Proliferation
Survival
Cytokine release

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
	p.S550Y	p.S550F	p.S550F	p.P342T	p.M450I	p.A353T
Variant Annotation						
Chr	9	9	9	9	9	9
pos (GRCh38)	90887816	90887816	90887816	90874692	90877739	90874725
nt ref	C	C	C	C	G	G
nt alt	A	T	T	A	A	A
dbSNP151	.	.	.	.	rs1304839707	rs200167353
pos (GRCh37)	93650098	93650098	93650098	93636974	93640021	93637007
1000Gp3_AF	.	.	.	.	.	.
ESP6500_AA_AF	.	.	.	.	.	.
ExAC_AF	.	.	.	.	.	2.47E-05
gnomAD_exomes_AF	.	.	.	.	7.95E-06	1.99E-05
CADD_phred	28.3	29.7	29.7	25.5	26.3	27.3
SIFT_pred	damaging	damaging	damaging	damaging	damaging	tolerated
Polyphen2_HDIV_pred	damaging	damaging	damaging	damaging	tolerated	damaging
LRT_pred	damaging	damaging	damaging	damaging	damaging	damaging
MutationTaster_pred	damaging	damaging	damaging	damaging	damaging	damaging
PROVEAN_pred	damaging	damaging	damaging	damaging	tolerated	tolerated
MetaSVM_pred	damaging	damaging	damaging	damaging	tolerated	tolerated
M-CAP_pred	damaging	damaging	damaging	damaging	damaging	damaging
fathmm-MKL_coding_pred	damaging	damaging	damaging	damaging	damaging	damaging
Clinical presentation						
Age at sampling (years)	2	0.5	35	31	34	44
Age of diagnosis	2 weeks	2 weeks	2 weeks	12 years	34 years	44 years#
Intestinal inflammation	+	+	+	+	+	+
Skin inflammation	+	+	+	+	+	–
Joint inflammation	+	–	+	–	–	+
CNS inflammtion	–	–	–	+	+	–
Lung inflammation and Brochiectasis	–	–	–	–	+	–
Recurrent infections	+	–	+	+	–	+
Diffuse large B cell lymphoma (DLBL)	–	–	–	–	+	+
Hypogammaglobineamia	+	–	–*	+	+	+

Wang L …Krivan G. Goda V et al. Nat Genet. 2021 Apr;53(4):500-510

R406 – SYK inhibitor - fostamatinib

- TAVLESSE: egyéb kezelésre refrakter krónikus felnőttkori ITP-ben törzskönyvezve
- OGYEI engedélyezte
- NEAK engedélyezte
- Tünetmentessé vált



Wang L …Krivan G. et al. Nat Genet. 2021 Apr;53(4):500-510.

Célzott terápiás lehetőségek PID-ben

Betegek	Mutáció	Klinikai (hematológiai) tünetek	Gyógyszer	Kimenetel
36é, nő	SYK GOF	Lymphopenia, thrombopenia, lymphadenopathia, splenomegália, granuloma, MDS, Ig hiány	fostamatinib	Tünetmentes
20é, ffi	CTLA-4	ITP, granuloma, CML, Ig hiány	abatacept	Txp, tünetmentes
45é, ffi	CTLA-4	ITP, AIHA, alopeciam, Ig hiány	abatacept	Nagyfokú javulás
19é, ffi	G6PC3	Agranulocytosis, thrombopenia	empaglifozin	tünetmentes
37é, nő	STAT3 GOF	Ig hiány, GLILD (granuloma)	ruxolitinib	tünetmentes
13é, nő	PIK3CD (APDS)	Ig hiány, splenomegália, thrombopenia, lymhopenia	Sirolimus leniolisib	javult Engedélyezés alatt
6é, ffi	PIK3CD (APDS)	Splenomegália, lymphadenopathia, thrombocytopenia	sirolimus	tünetmentes
15é, nő	PIK3CD (APDS)	M. Crohn, splenomegália, thrombopenia, lymphoid granulomatosis, NLH	sirolimus	Txp, tünetmentes
45é, nő	STAT1 GOF	Pm tumor, cervixcc , gombainfekciók	ruxolitinib	Engedélyezés alatt
13é, ffi	STAT1 GOF	Gombainfekciók , aphthosis	ruxolitinib	Engedélyezés alatt
8é, ffi	STAT1 GOF	Tüdőtályog, gombainf	Ruxolitinib	Engedélyezés alatt