Actualités des DIH 2020

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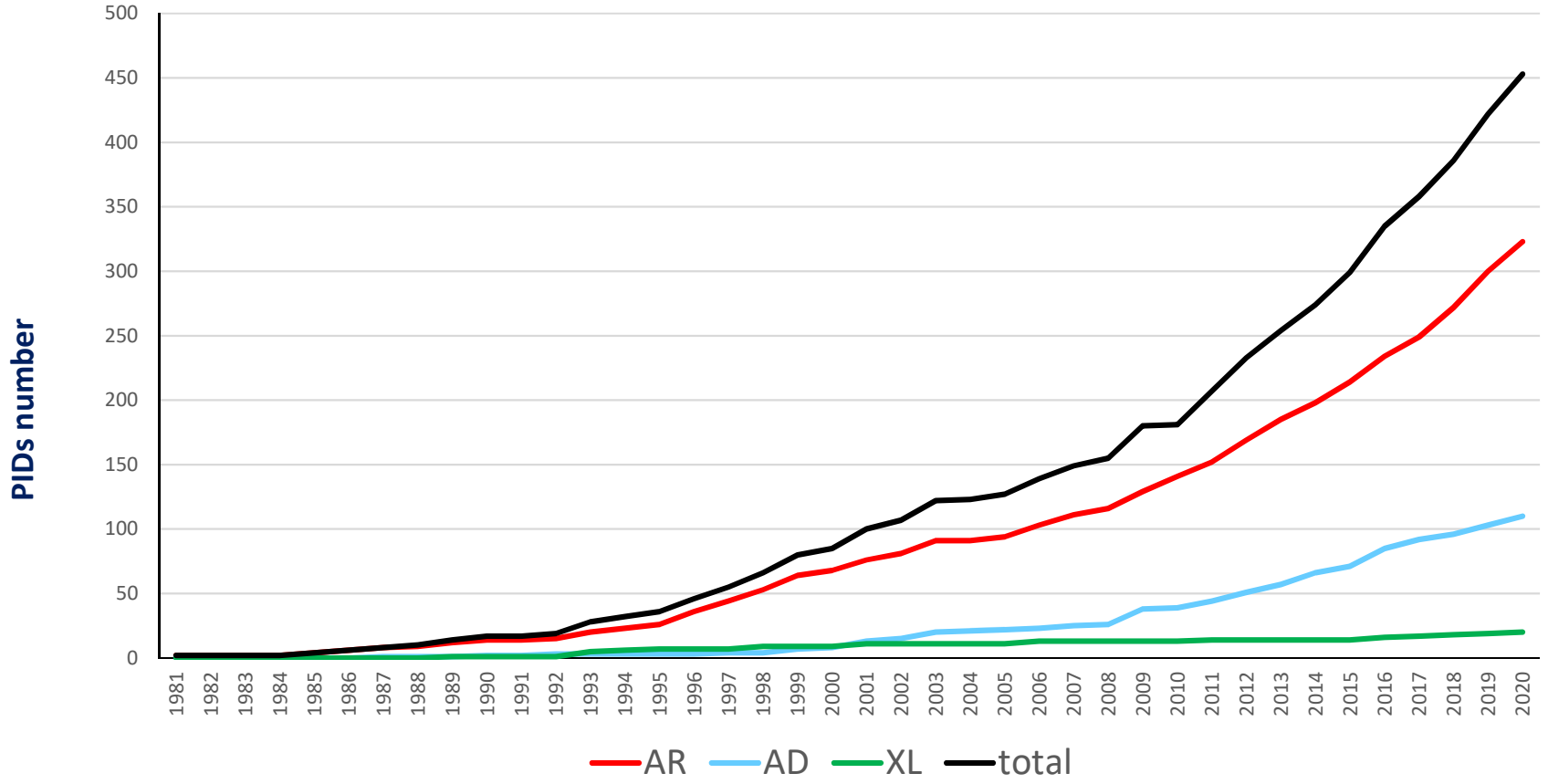
CEREDIH, 11/12/2020

PIDs' genes in 2020



In 2020: PIDs includes over 450 known genes

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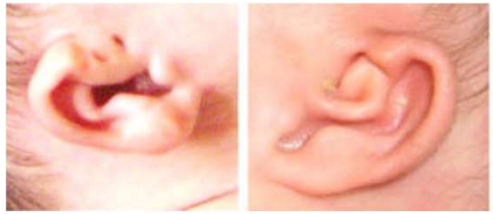
PAX1 deficiency (AR-SCID T-B+NK+)

(Paganini 2017, clin genet)



PAX1 member of the paired box (PAX) family of transcription factors and plays a critical role in pattern formation during embryogenesis.

Otofaciocervical syndrome (OTFCS2) : facial anomalies, cup-shaped low-set ears, preauricular fistulas, hearing loss, branchial defects, skeletal anomalies, mild intellectual disability.

2 patients from 1 kindred with an AR OTFCS2 and SCID with homozygous mutation in *PAX1* gene. c.1104C>A, p.(Cys368*)

- PAX1 is essential for development and function of the human thymus (Yamazaki et al. Sci Immunol 2020)

6 SCID pts from 3 kindred with ears abnormalities and homozygous P*AX1* mutations

c.463_465del (p.Asn155del), c.1104C>A, (p.Cys368*), c.439G>C, (p.Val147Leu)

Severe T lymphopenia, few TRECs, normal B cell, ~normal IgM, low IgA, ↑ IgE,↓TTL

T cell deficiency not corrected by HSCT despite donor chimerism

Severe T cell ID characterized by a primary thymic defect: FOXN1 deficiency, complete DiGeorge and CHARGE syndromes

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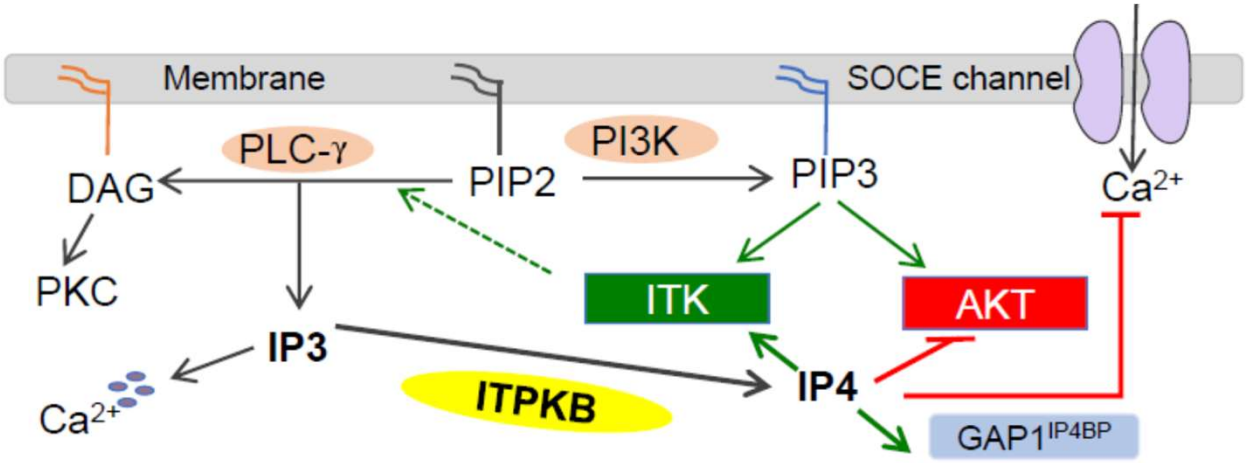
AR SCID T-B+NK+ caused by inositol-trisphosphate3-kinase B (ITPKB) deficiency (Almutairi et al. 2020, JACI)



Homozygous mutation: c.2583 delT ; p.(Arg862Glufs*4)

ITPKB gene encoded for one of 3 isoforms of Inositol-trisphosphate 3-kinase expressed in humans. It regulates immune cell function and is required for T and B cell development.

- **1 patient 6 months: failure to thrive, recurrent skin abscess, pneumonia and oral thrush, at 6 months, the absence of a thymic shadow (chest radiograph) She died at 11 months (*Staphylococcal* sepsis)**
- **Profound T lymphopenia**
- **Neutropenia, anemia, thrombocytopenia. (bone marrow failure in mice model)**

AR SLP76 (AR SCID T-B+NK+, PN and platelets dysfunction)

Inherited SLP76 deficiency in humans causes severe combined immunodeficiency, neutrophil and platelet defects. (Lev et al. , JEM 2020)

1 patient with CS parents: early-onset with infections, AHAI at the age of 2 mo, recurrent skin abscesses and skin rash. BCGite, HSMG,

Respiratory distress at 3 mo,

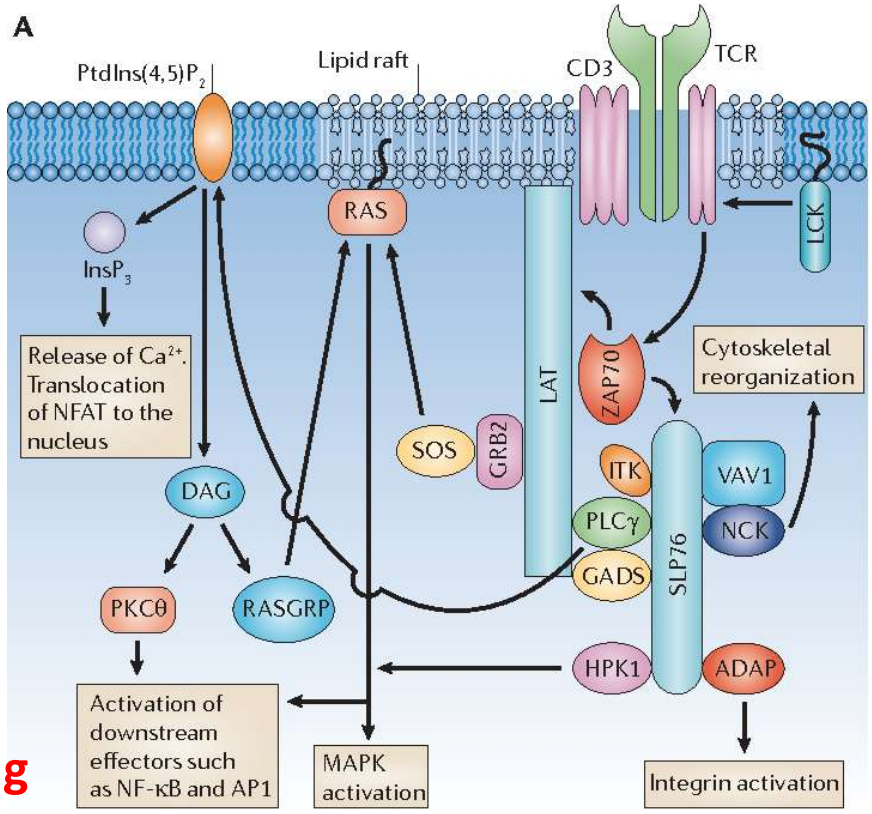
generalized seizure at 4 mo multiple brain abscesses (Aspergillus) and CMV infection.

patient died of transplant-related complications 30 d.

T CD4 lymphopenia + ↓Trecs,

Combined T and B cell immunodeficiency with severe neutrophil defects and impaired platelet aggregation.

Homozygous mutation C.957+1G>A ; K309FSx17 in the *SLP76* gene affects a donor splice site at the beginning of intron 14



SLP76 molécule adaptatice TCR via LAT

SLP76 is a key protein involved in TCR signalling and in other hematopoietic pathways

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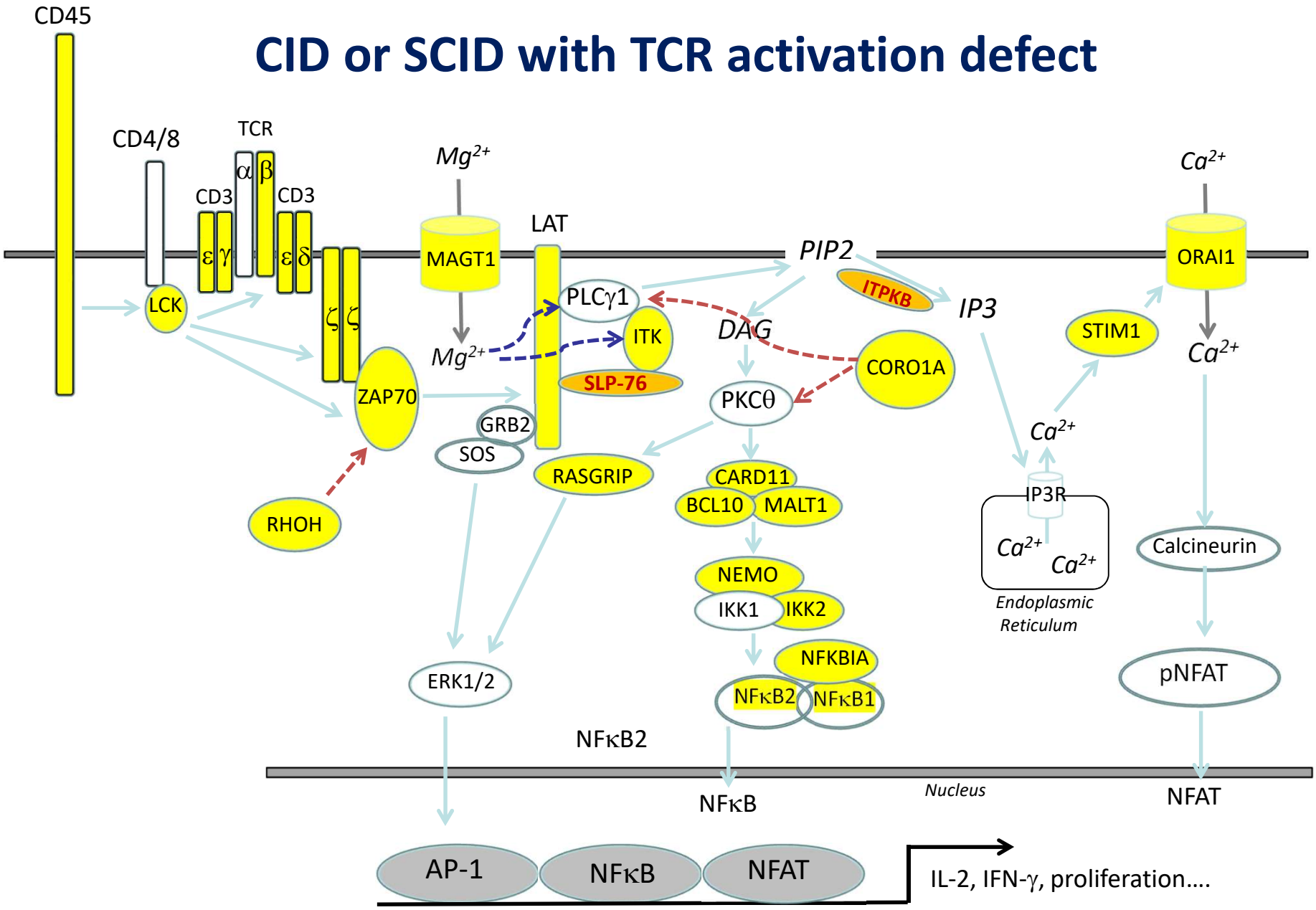
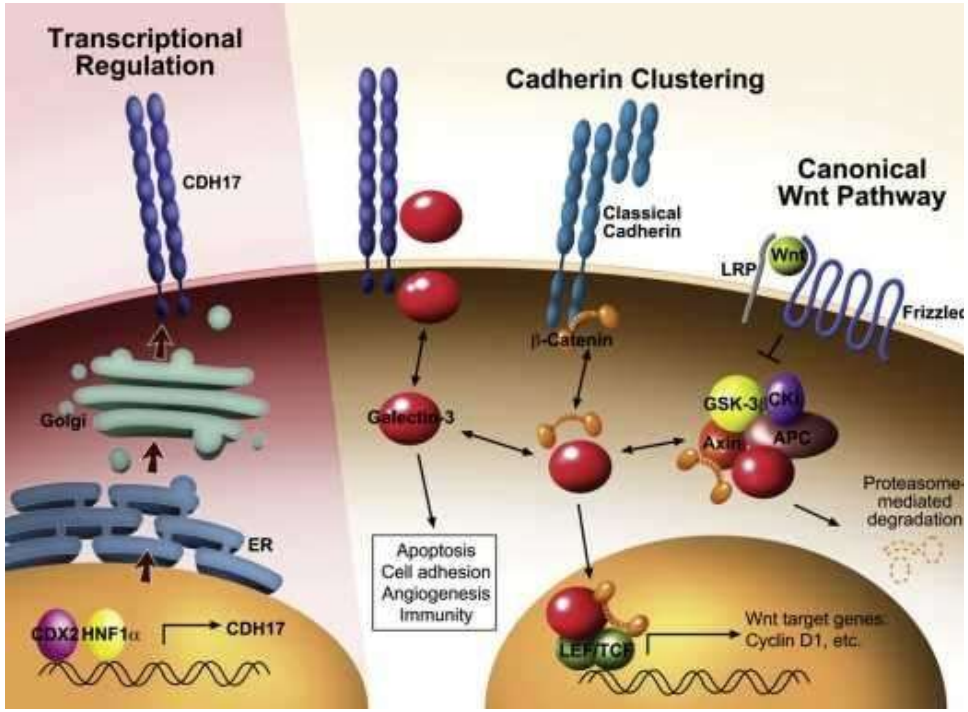
CID or SCID with TCR activation defect



CDH17 deficiency (AR-CID T-B-NK+)

(Smith et al. 2017, Blood adv)

Cadherin 17 encoded by the *CDH17* gene, member of the cadherin superfamily encoding calcium-dependent membrane-associated glycoproteins



1 patient of 5 years-old: sinopulmonary infections, EBV^{+} B cell lymphoma (DLBCL)

CDH17 compound heterozygous mutation:

c.1796+2 T>C / c.527A>G ; (p.N176S)

Severe T lymphopenia, few TRECs, low T cell proliferation;
B lymphopenia (low specific Ab), normal NK cells and function

CDH17 is expressed in human thymic epithelial cells.
CDH17 mutations may be a rare cause of leaky SCID that can be corrected by HSCT.

MAN2B2 deficiency (AR-CID)

Defining a new immune deficiency syndrome: MAN2B2-CDG. (Verheijen J, al. JACI 2020)

MAN2B2 : mannosidase alpha class 2B member 2

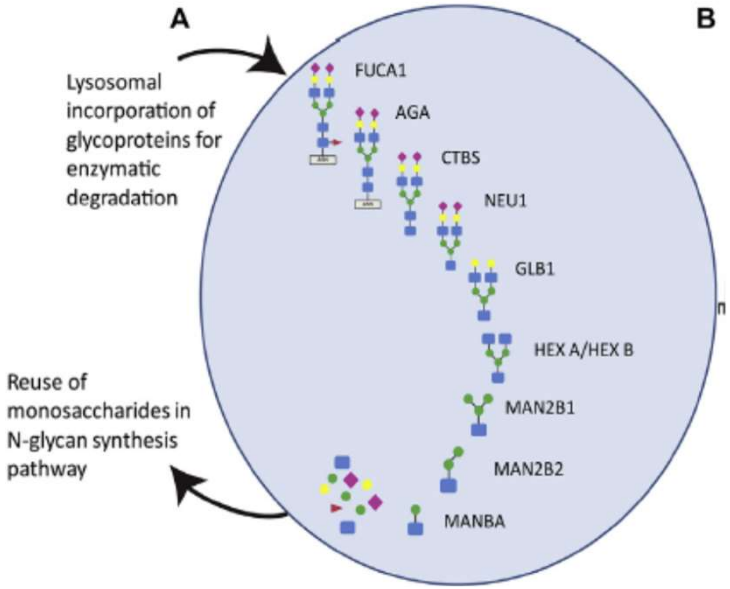
- **1 patient with CID childhood onset (2 weeks) recurrent pneumonia and thrush, small vessels vasculitis (3 mths), arthritis (9 mths), chronic diarrhea microcephaly, neurodevelopmental delay, thrombotic stroke**

- **No thymic shadow, ↓ T cells (↓ naïve, ↑ T_{EMRA}), no TRECs, ↓TCR proliferation, ↓ total B cells, ↑ plasmablasts, ↑ B CD21lowCD38low (54%), ~normal IgM, low IgA, ↑ IgE**

- **Homozygous *MAN2B2* mutation: p.Asp38Asn**

- **Mutation affecting both *N*-glycan synthesis and glycan degradation**

- **Congenital Disorder of Glycosylation (CDG)**



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POLR3E deficiency (AR-CID)

A mutation in POLR3E impairs antiviral immune response and RNA polymerase III.
(Ramanathan A, et al. PNAS 2020)

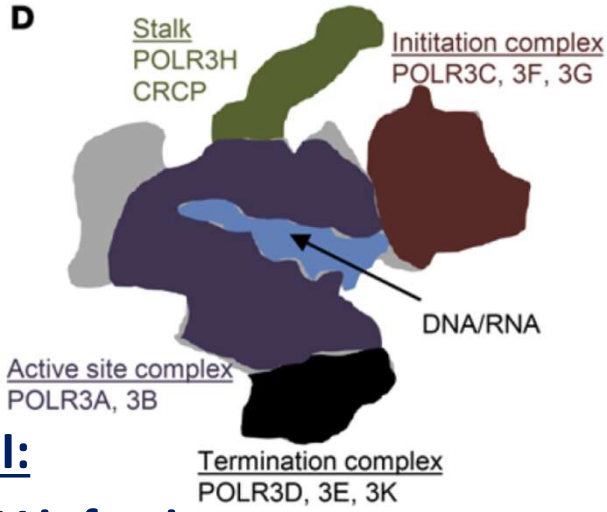
1 patient with homozygous mutation in *POLR3E* gene: p.(D40H) :

Recurrent, systemic viral infections (fatal)

Langerhans cell histiocytosis

↑ IFN-signature by virus-infected fibroblasts

Increased cell susceptibility to infection by CMV.



Heterozygous inborn errors in several subunits of PoLIII:

***POLR3A*, *POLR3C* and *POLR3F* with acute and severe VZV infections**

POL III is recruited to target genes by transcription factors that facilitate initiation and reinitiation of transcription.

Others PID with genetic defects affecting polymerases:

POLA1, POLA2,
POLD1, POLD2,
POLE1, POLE2,
POLR3A, POLR3C, POLR3E, POLR3F

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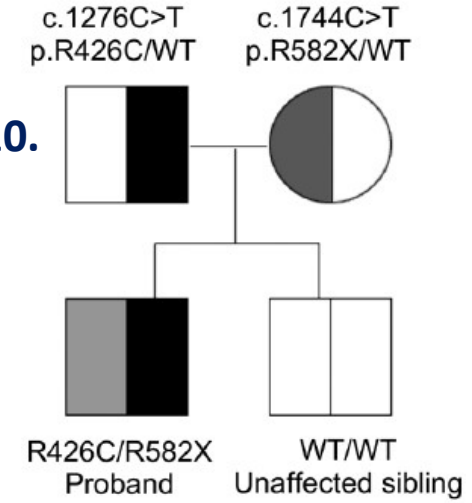
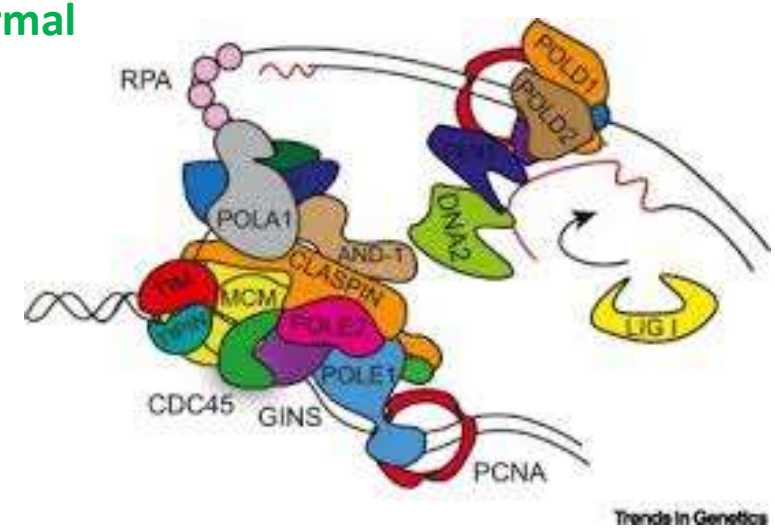
MCM10 deficiency (AR-CID)

Human NK cell deficiency as a result of biallelic mutations in MCM10.
(Mace EM, et al. J Clin Invest. 2020)



- 1 patient 16 months severe CMV infection, HLH-like,
- HSCT , died at 24 months (CMV)
- Mild lymphopenia ↓ T_{CM} , T_{EM} cells , ↓ T cells prolifs (PHA)
- ↓ ↓ ↓ NK cells only $CD56^{bright}$ (absent $CD56^{dim}$ mature NK)
- ↓ NK function, IgG slightly decrease, IgA and M normal

- human NK cell deficiency (NKD):
  - GATA binding protein 2 (*GATA2*-AD),
  - IFN regulatory factor 8 (*IRF8-AD*),
  - minichromosome maintenance 4 (*MCM4*-AR),
  - go-ichi-nisan complex subunit 1 (*GINS1* -AR)



MCM10, *GINS1* and *MCM4* deficiencies are phenocopies. Disorders of NK cell terminal maturation by abnormal requirement for the CDC45-MCM2-7-GINS (CMG) complex.

These NKD strengthens importance of the CMG complex and DNA replicative machinery in human NK cell functional maturation.

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IL-7 deficiency (AR-CID)

5 adult patients from 3 kindreds with CID phenotype:

Verrucous skin HPV (3,7) infections (5),

Squamous cell carcinomas

***Cryptococcus neoformans* meningitis**

Severe T cell lymphopenia (CD4>CD8)

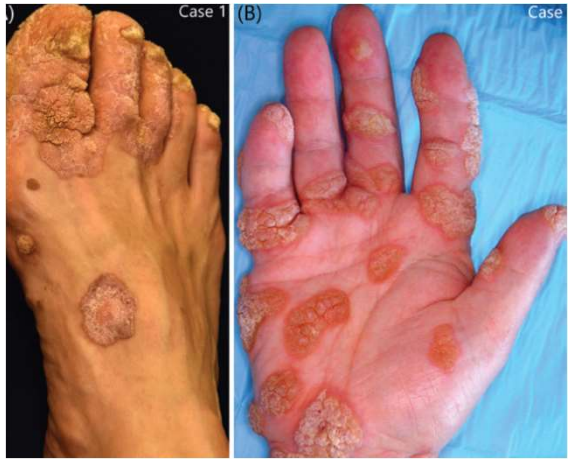
Homozygous mutations of *IL7* gene:

c.205A>T (p.R69*), c.3G>A (p.Met1?)

Milder disease that IL7R deficiency
(intact TSLPR signaling?)

(Horev et al. 2015 J AM ACAD DERMATOL)

	Patient 1	Patient 2	Patient 3	51	63
Age, y	39	46	51	51	63
Sex	Female	Female	Male	F	M
Cutaneous manifestations					
Deep palmoplantar warts	+	+	+	+	+
Verrucous papules on the dorsal aspect of the fingers and toes	+	+	+	+	+
Flat warts (tinea versicolor-like lesions)	–	+	+		
Seborrheic keratosis-like warts	–	–	+		
Palmar hyperkeratosis and diffuse thickening of the dorsal hands	–	–	+		
Nonmelanoma skin cancers	–	–	+ (SCC)		
Cryptococcal meningitis	–	+	+		
T-cell parameters					
T cells [/μL] (700-2100)	166	107	378		
CD4 T cells [/μL] (300-1400)	36	31	48	45	120
CD8 T cells [/μL] (200-900)	108	94	310		
Regulatory CD4 T cells [% of CD4 T cells] (2.9-8.1)	3.8	6.4	12.5		



Two cases of interleukin-7 (IL-7)-deficient generalized verrucosis.
(Kosumi H, et al. Clin Infect Dis. 2020), start at 10yo

Interleukin-7 plays an essential role in the development, survival, and homeostasis of T cells.

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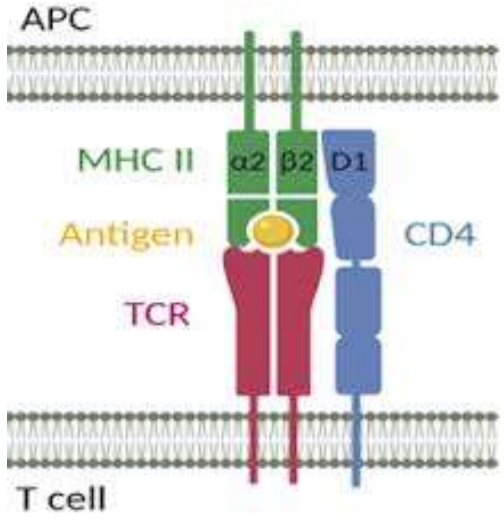
CD4 deficiency (AR-CID)

(Rosa Anita Fernandes et al., Front Immunol 2019)



Extensive, refractory warts in 1 adult patient (45y)

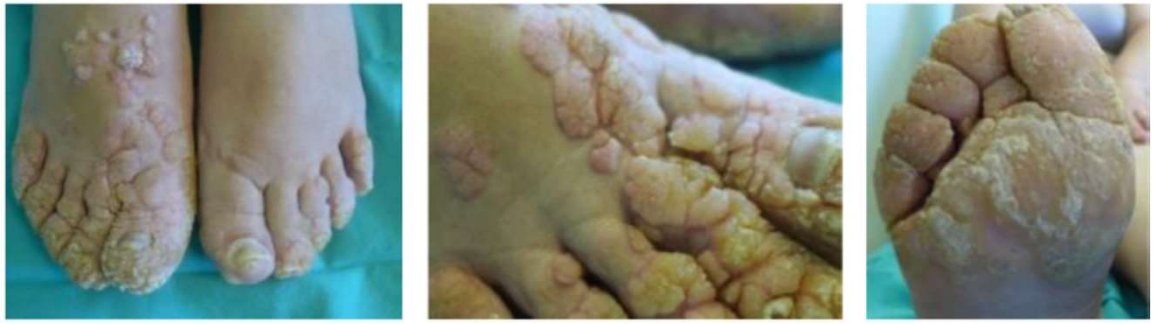
Normal lymphocyte counts:

↓ CD4+ T cells (<0.01 CD4+ T-cells/µl),

↑CD8+ T cells, ↑ DN/TCRαβ+ T cells

↑ B cells, normal NK cells, normal Ab production

Homozygous mutation: last bp of the 7 intron (g.6818420 G>A, c.1157-1G>A) caused two truncated forms of CD4 RNA/cDNA with no CD4 expression on blood T-cells, monocytes, and DCs.



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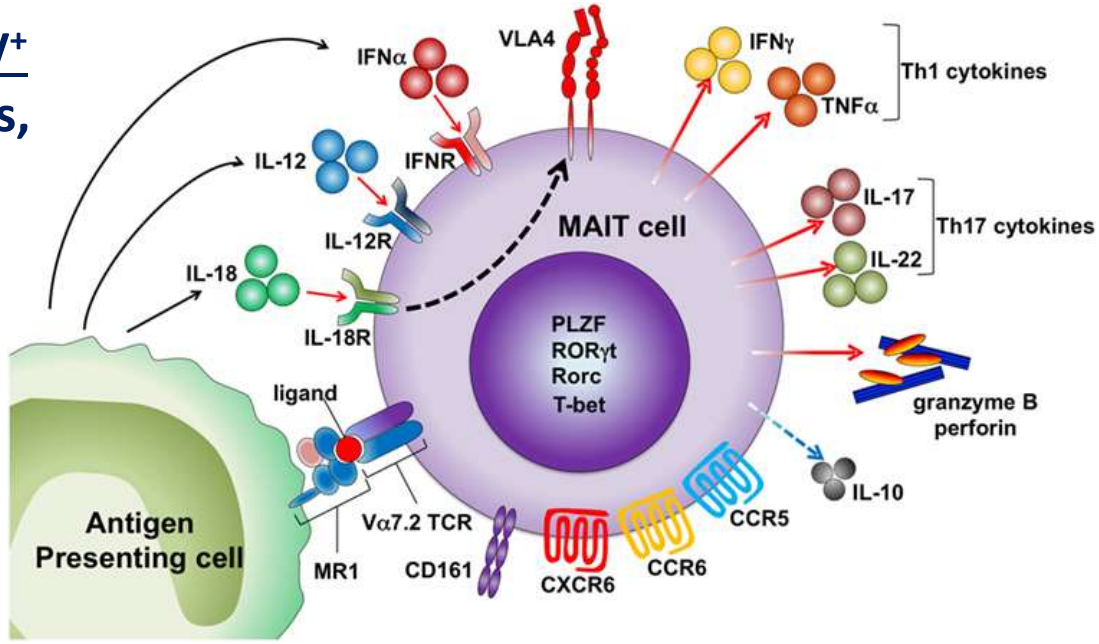
MR1 deficiency (AR-CID)

Absence of mucosal-associated invariant T cells in a person with a homozygous point mutation in MR1 (Howson LJ, et al. . Sci Immunol. 2020)

- **1 patient (31y):**
- **Tattoo-associated persistent HPV⁺ warts, *Campylobacter* GI enteritis, VZV pneumoniae**

- **No MAIT cells; but expanded Vγ9/Vδ2+ T cell population, ↑ γδ ; mildly ↓ CD4, CD8 T cells, mostly memory**



Homozygous mutation in *MR1*

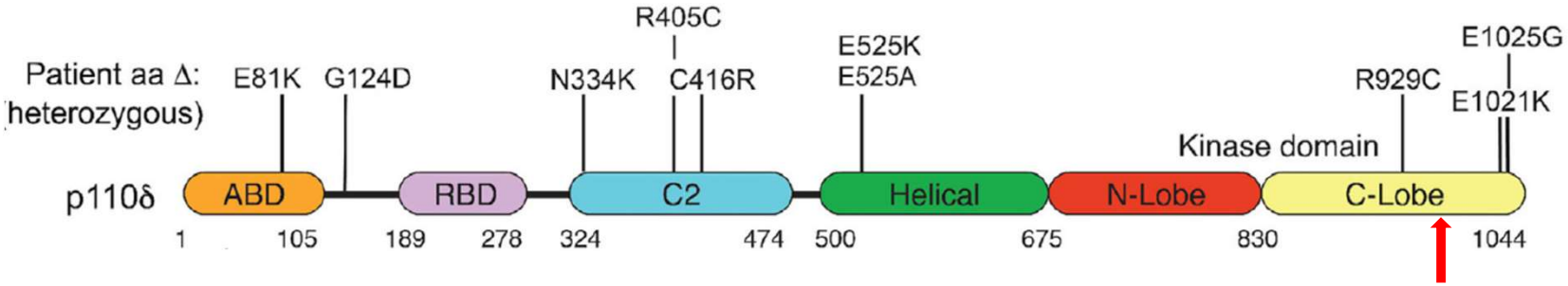
gene : c.92 G>A; p.Arg31His

MAIT maturation is dependent on the major histocompatibility complex class I-related protein (MR1) class 1b non-polymorphic molecule of the major histocompatibility system, which is expressed by different types of cells

AR *NFKB1* deficiency (AR CID)

Combined immunodeficiency caused by a novel homozygous *NFKB1* mutation.

(Mandola AB, et al. JACI 2020)

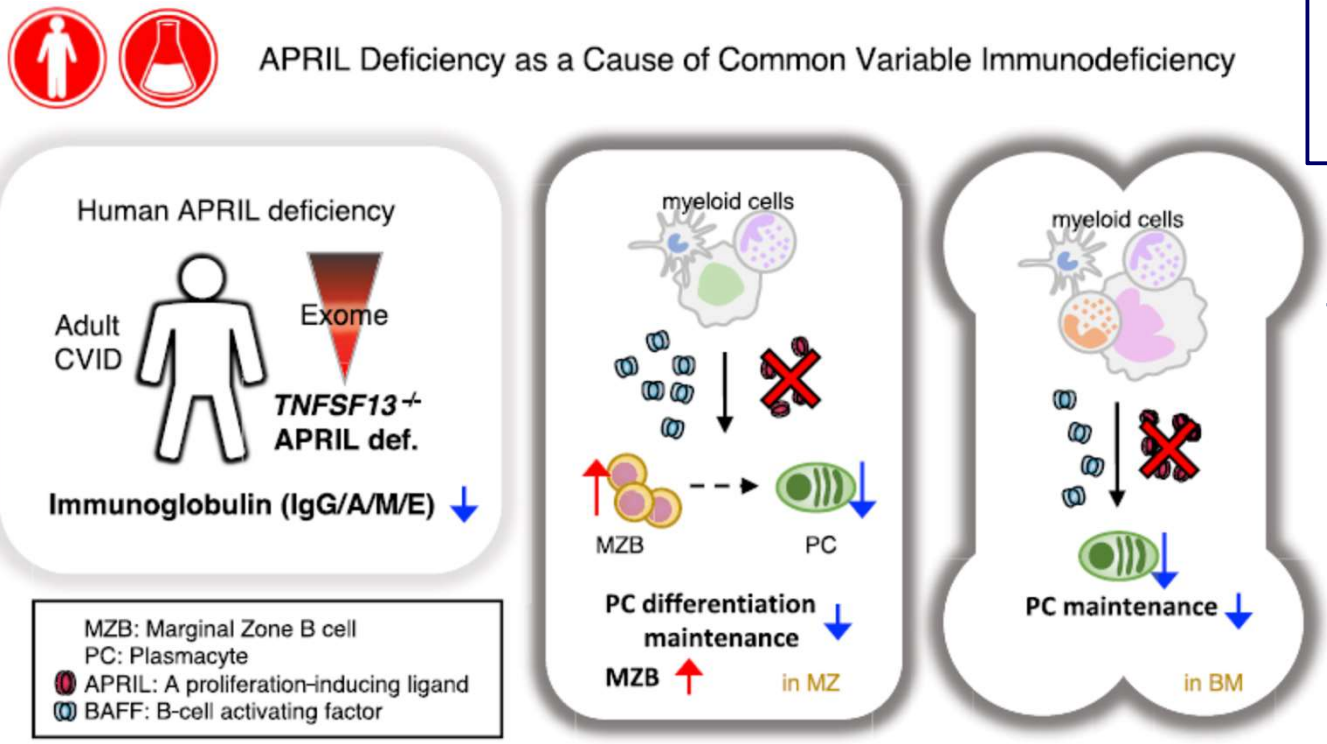


- **CID in a patient of 7 yo with failure to thrive, persistent EBV viremia and hepatitis, *Pneumocystis jirovecii* pneumonitis (7 mths), and generalized lymphadenopathy**
- **Progressive T cell lymphopenia with ↓↓ CD4 memory, ↑ CD8 T_{EM}/$_{TEMRA}$, normal B cell, ↓IgD+CD27+ memory B cells, ↑transitional B , defect specific Ab prod**
- **Homozygous mutation in *NFKB1:* c.2878G>A, p.Gly960Arg (G960R).**
- **This affected p105 phosphorylation and p50 formation on Ag and cytokine stimulation, as well as attenuating nuclear signal transmission.**
- **Blockade of NF-κB pathway signalling, resulting in aberrations in T- and B-cell maturation and function.**

APRIL/*TNFSF13* deficiency: AR CVID

APRIL-dependent lifelong plasmacyte maintenance and immunoglobulin production in humans

(Tzu-Wen Yeh et al. JACI 2020)



***TNFSF13*: homozygous**
c.507_508del;
p.Leu170Cysfs*5

1 pt CVID at 43 yo: pneumonitis, sinusitis, alopecia aerata (48y)

Hypogamma , low B memory cells and plasmablastes, Ab defects

A proliferation-inducing ligand (APRIL, TNF ligand superfamily), is secreted from myeloid cells and known to induce the differentiation of memory B cells to plasmocytes.

APRIL is critical for lifelong maintenance of plasmocytes to produce Ig in humans.

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CTNNBL1 deficiency (AR-CIVD)

(Disease-associated *CTNNBL1* mutation impairs somatic hypermutation by decreasing nuclear AID (Marcel Kuhny, //Jordan S. Orange, Eric Meffre; JCI 2020)

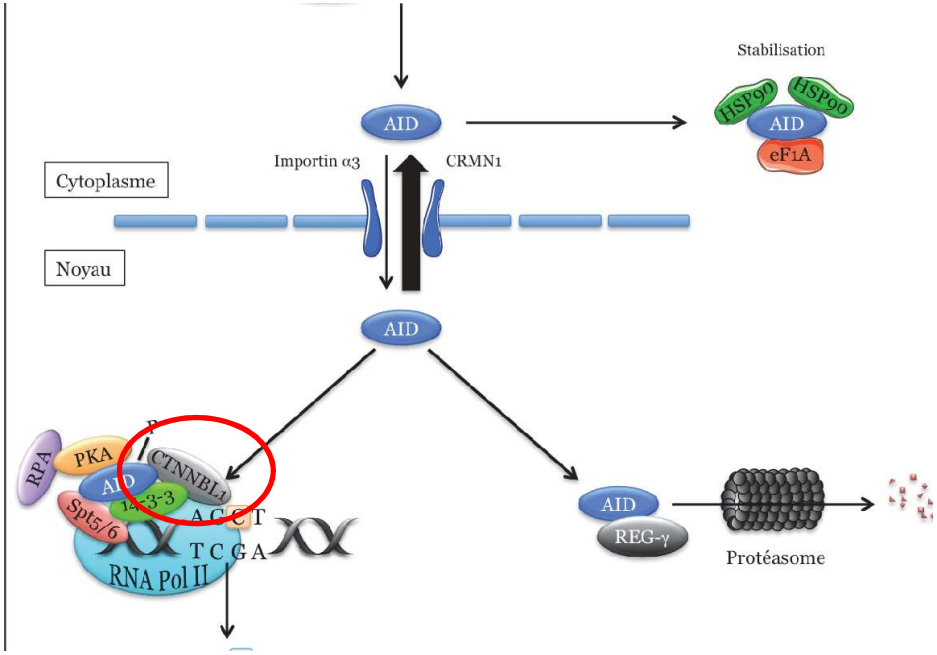
CTNNBL1: β-catenin–like protein 1

Homozygous:
c.1396A>G; p.M466V

1 patiente 15 yo with progressive hypogamma, autoimmune cytopenias, recurrent infections, hyperplastic GC's (hyperplastic GC reactions ↑ T follicular helper–like

Hypogamma, ↓ memory B cells;, expanded peripheral autoimmune/autoreactive CD19hiCD21-/loCD10-CD27- B cell subset, ↓ Tregs, Impaired CSR and SHM

Immunoglobulin levels (mg/dL)	(before IVIG)
IgG	198
IgA	13.7
IgM	5.7
IgE (IU/mL)	<4.0



Mutation M466V ↓ binding of CTNNBL1 to AID ⇒ Less nuclear translocation of AID.

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AR FNIP1 deficiency (AR-PAD)

Mutations of the gene *FNIP1* associated with a syndromic autosomal recessive immunodeficiency with cardiomyopathy and pre-excitation syndrome. (Niehues et al. Eu J I 2020)

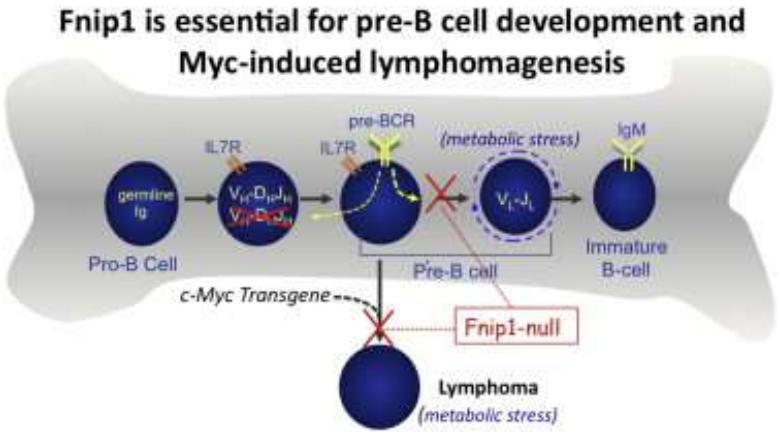
FNIP1 forms a complex with the γ2 subunit of phosphorylated Adenosine monophosphate-activated protein kinase (AMPK)= Master sensor of energy consumption and activated during energy deprivation

3 pts from 2 kindreds with homozyg. mutation in *FNIP1* gene:

K1 exon 17 (c.3353G>A; p.Ser1118Asn

K2 exon 12 (c.1289delA). p.His430Profs7*

No FNIP1 protein expression



Early onset (<6 months),
- ENT and lung infections viruses and bacteria, encapsulated bacteria (pneumonia, meningitis)
- Pulmonary: obstructive bronchitis, pneumonic abscess, bronchiectasis, fibrosis, cell-rich interstitial pneumonia.
-Gut infections (*Campylobacter, Rotavirus, Salmonella*)

- Cardiac: Wolff-Parkinson- White syndrome, metabolic myopathy, muscular hypotonia

- **↓ B cells , ↓ switched memory B cells and hypogammaglobulinemia (IgG, IgM), intermittent neutopenia**

- BOM : B-cell maturation defect at the pre-B-cell stage with an enrichment of CD34-CD10+CD21low B-cell precursors

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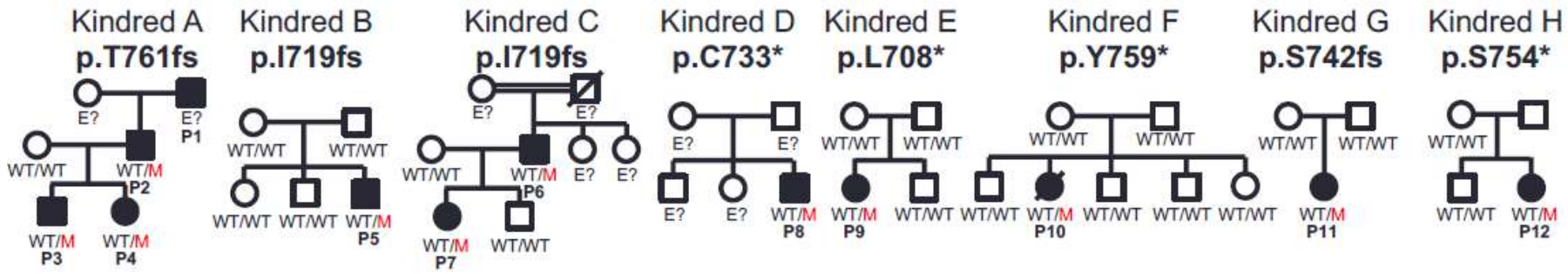
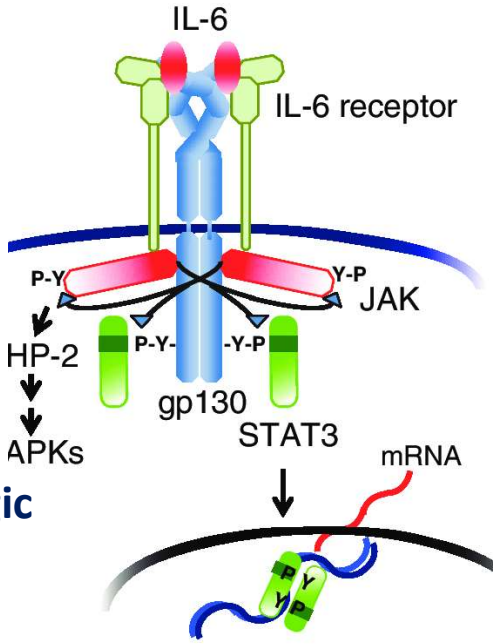
AD *IL6ST* deficiency AD HIES (DN)

Dominant-negative mutations in human IL6ST underlie hyper-IgE syndrome.

(Beziat et al. JEM 2020)



- **12 pts from 8 Kds with AD-HIES : DN *IL6ST* mutations.**
- **Mutant alleles encode GP130 receptors lacking both the recycling motif and all 4 STAT3-recruiting tyrosine residues.**
- **Overexpression, the mutant proteins accumulate at the cell surface and are LOF + DN for cellular responses to IL-6, IL-11, LIF, OSM.**
- **The patients' cells respond poorly to IL-6 and IL-11.**



- **Patients with *STAT3* or *IL6ST* mutations display infectious and allergic manifestations of IL-6R deficiency and some of the skeletal abnormalities of IL-11R deficiency.**

DN *STAT3* and *IL6ST* mutations thus appear to underlie clinical phenocopies through impairment of the IL-6 and IL-11 response pathways.

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AR *IL6ST* deficiency

- Cytokine-selective defects in GP130 : Homozygous missense variants in *IL6ST* (c.1210A>T; p.Asn404Tyr and c.1493C>T; p.Pro498Leu) cause immunodeficiency with elevated IgE and craniosynostosis (Schwerd et al.2017)

- Cytokine-complete defects in GP130: Fatal Stuve-Weidemann syndrome, 5 pts from 3 kindreds ⇒ Absence of GP130 cytokine receptor signaling causes extended Stuve-Wiedemann syndrome. (Chen YH, et al. J Exp Med. 2020)

- **Homozygous variants in *IL6ST* (c.841C>T;p.Arg281*, c.1699+4A>G)**
- **osteoporosis, skeletal dysplasia,**
- **spontaneous fractures, hyperextensibility of joints, scoliosis**
- **lung dysfunction, renal abnormalities thrombocytopenia, dermatitis, eczema.**
- **Fatal outcome during between neonatal to childhood**

Defective acute phase response.

Complete unresponsiveness to IL-6 family cytokines (IL-6, IL-11, IL-27, OSM, LIF)

Genetic syndrome caused by the complete lack of signalling of a whole family of GP130-dependent cytokines in humans and highlights the importance of the LIF signalling pathway in pre- and perinatal development.

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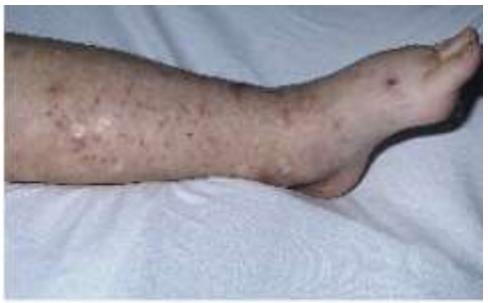
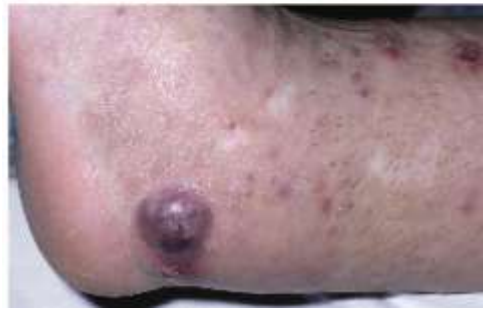
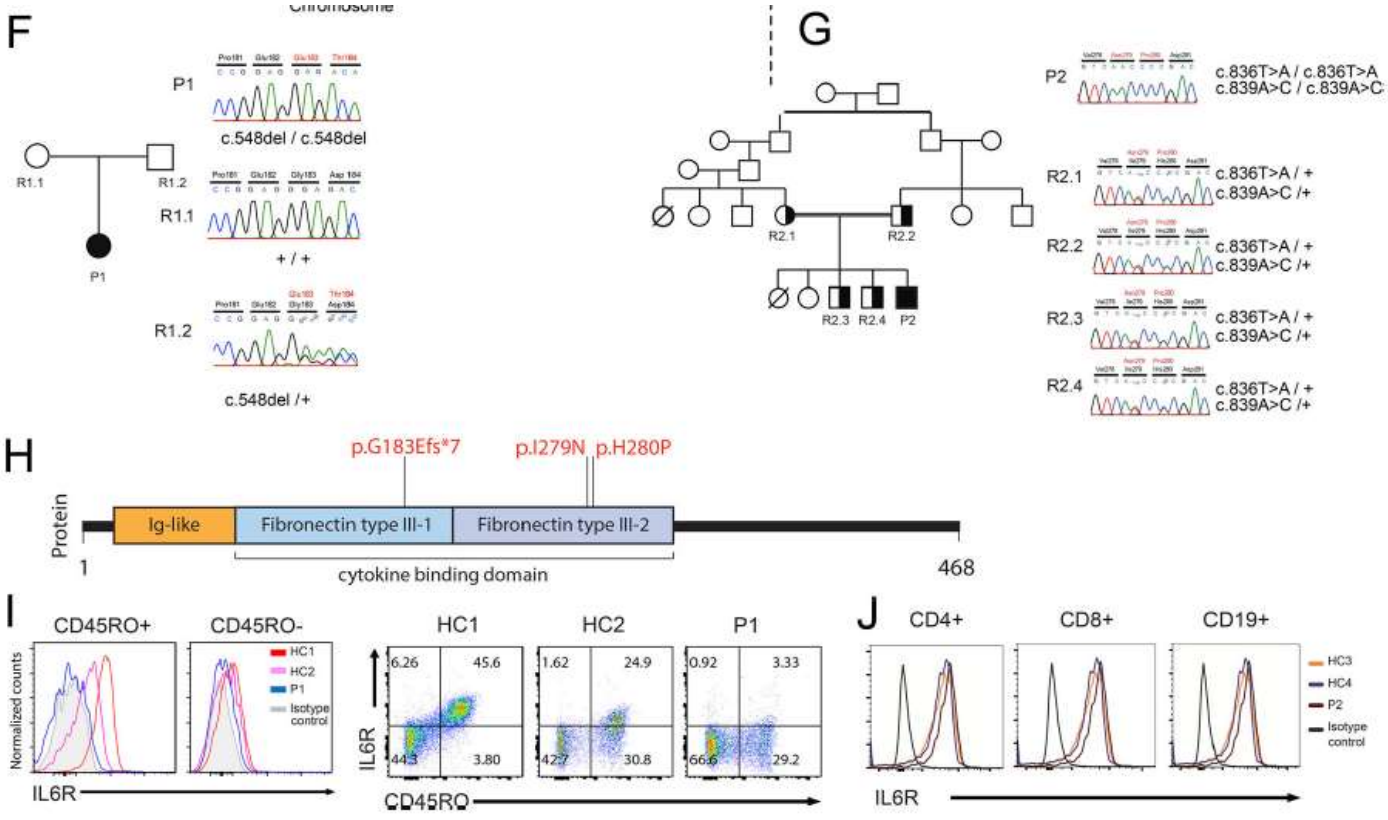
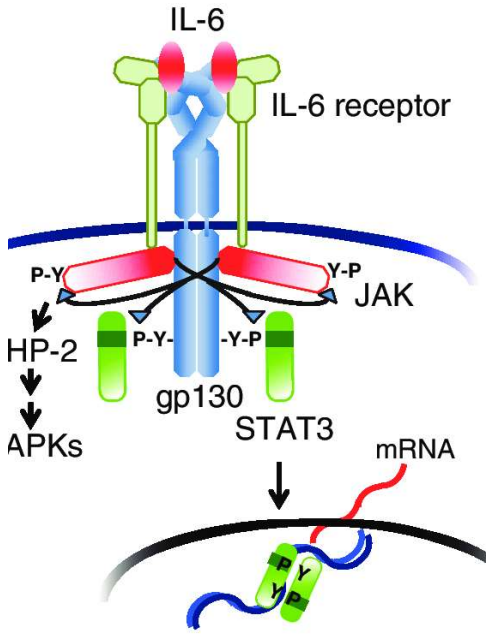
AR *IL6R* deficiency – AR HIES

Loss of the interleukin-6 receptor causes immunodeficiency, atopy, and abnormal inflammatory responses (Spencer et al, JEM 2019)









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Impaired IL-6 immunity and HIES

The nature of human IL-6

Anne Puel[1,2] and Jean-Laurent Casanova[1,2,3,4,5]

JEM 2019

AD ; AR HIES

Gene defect	High IgE	Eczema	Staphylococcal disease	Inflammation	Extra-hematopoietic features	IL-6 response	References
TYK2$^{-/-}$ (Japanese patient) AR	+	+	+	ND	–	–	Minegishi et al., 2006
TYK2$^{-/-}$ (other patients)	–	–	–	+	–	+	Kreins et al., 2015
TYK2$^{P1104A/P1104A}$	–	–	–	+	–	+	Boisson-Dupuis et al., 2018
STAT3$^{+/-}$ AD	+	+	+	–	+	–	Minegishi et al., 2007
ZNF341$^{-/-}$ AR	+	+	+	+/–	+/–	–	Béziat et al., 2018; Frey-Jakobs et al., 2018
IL6ST$^{-/-a}$ AR/AD	+	+	+	–	+	–	Schwerd et al., 2017
IL6R$^{-/-}$ AR	+	+	+	–	–	–	Spencer et al., 2019
Anti–IL-6 autoantibodies	–	–	+	–	–	–	Puel et al., 2008
Erbin+/- AD	+	+	+	-	+	-	Lyons et al., 2014

Beziat et al. 2020

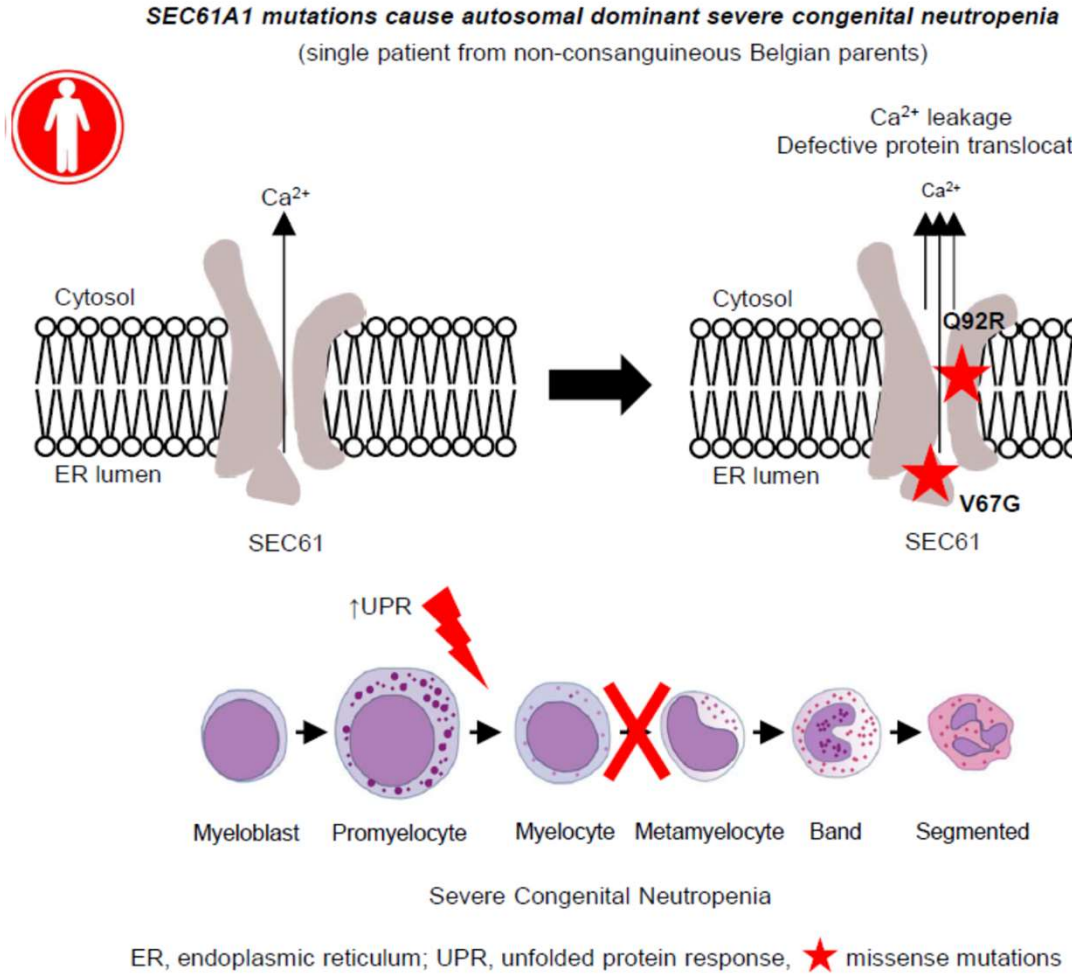
HyperIgE phenotype: eczema, recurrent infections and elevated serum IgE:

***STAT3* (AD), *ERBB2IP* (Erbin AD), *IL6ST* (AR, AD), *CARD11* (AD), *IL6R* (AR), *ZNF341* (AR), *DOCK8* (AR), *PGM3* (AR)**

AD Sec61α1 deficiency (AD-SCN)

Defective SEC61α1 underlies a novel cause of autosomal dominant severe congenital neutropenia (Van Nieuwenhove et al. JACI 2020): gene *SEC61A1*

c.A275G;p.Q92R (haploinsufficiency)



1 pt with classical clinical manifestations of severe congenital neutropenia (SCN)

Neutrophil counts <0.5 giga/L but responsive to G-CSF ttt

Normal B cell count with hyperγ, ↑ plasmablastes

Specific mutations in *SEC61A1* cause SCN through dysregulation of the unfolded protein response (UPR).

C. Picard 11/12/2020

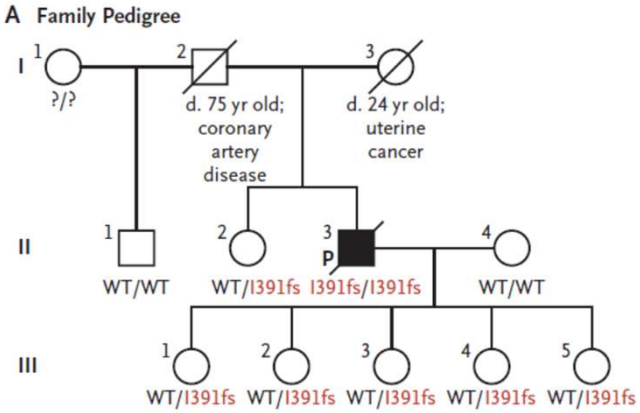
AR *NOS2* deficiency (AR-CMV)

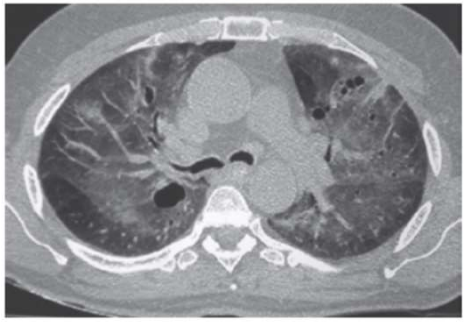
c.1436_1437insT
p.Ile391IlefsTer26

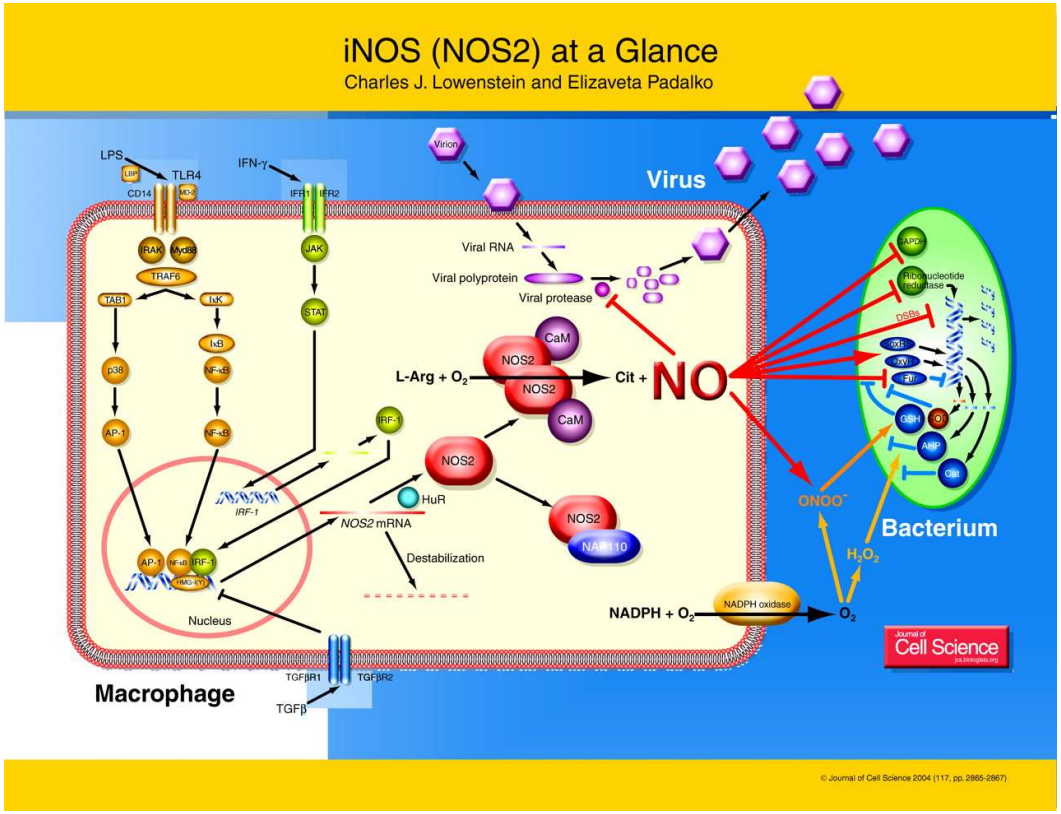
Fatal Cytomegalovirus Infection in an Adult with Inherited NOS2 Deficiency.
(Drutman SB et al. N Engl J Med. 2020)

Severe susceptibility to CMV-induced disease, previously healthy man (51 yo) who after acute CMV infection had an onset of progressive CMV disease that led to his death 29 months later.

↓ CD4+ T cells; ↓ NK cells, normal CD8+ T, ↓ B cells







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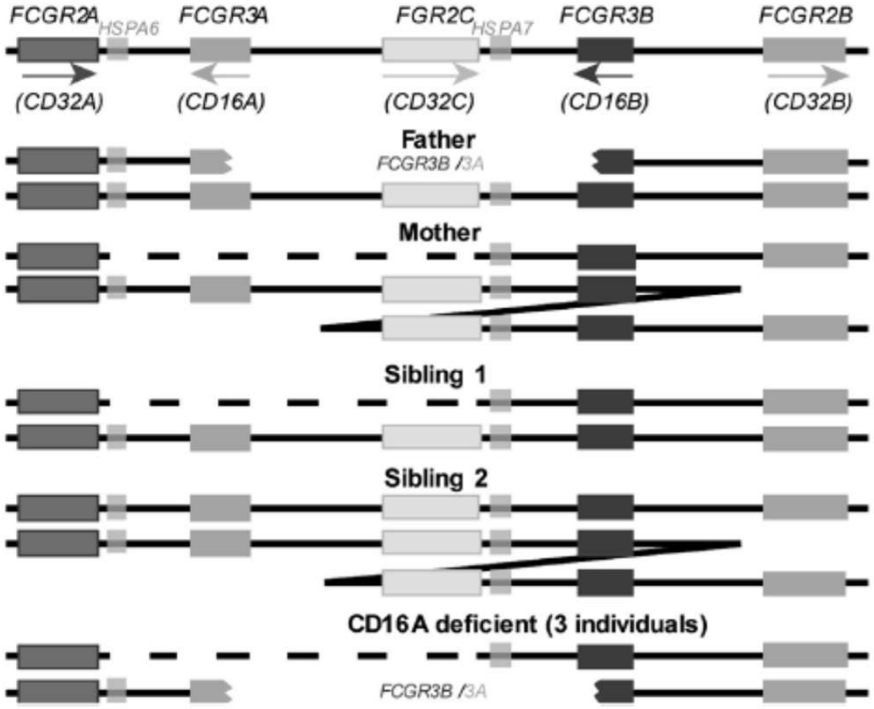
AR CD16A deficiency (AR-EBV)

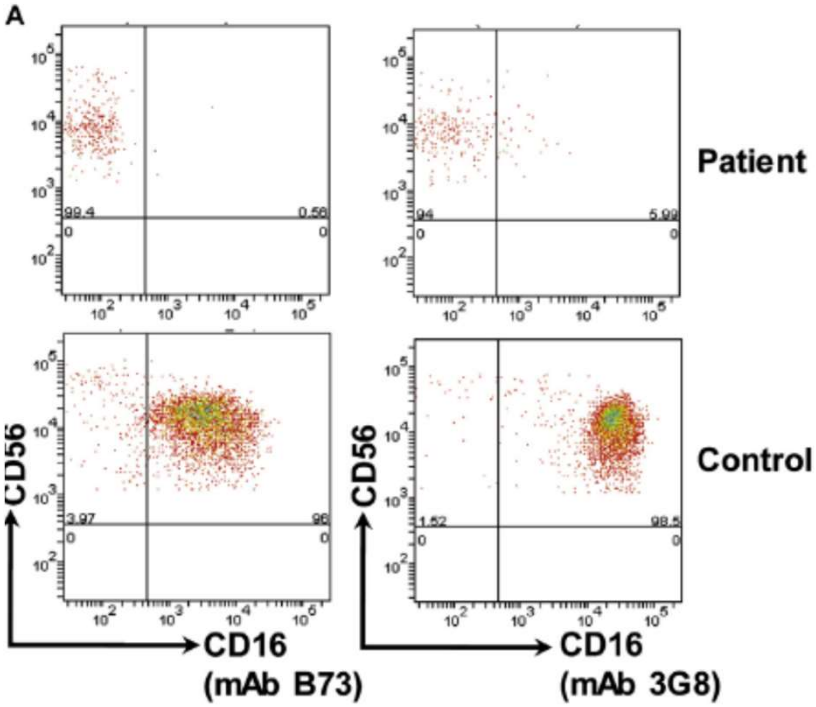
Identification of the first cases of complete CD16A deficiency: Association with persistent EBV infection (A. Perez-Portilla et al. JACI 2020)

1 pt 11 yo and an extended workup revealed persistently high levels of EBER DNA in peripheral blood an multiple-organ infiltration with EBV-positive T lymphocytes including an IgA- and EBV-positive interstitial nephritis (CAEBV)

Normal NK cell numbers but , ↓ adaptive NK ($CD56^{dim}CD57^{hi}$); Impaired NK cell ADCC

2 mutated asymptomatic siblings





The CD16A-deficient individuals had inherited a maternal chromosome where the FCGR3A gene with deletion and a paternal chromosome that encoded a hybrid FCGR3B/A gene

C. Picard 11/12/2020

AR *DEF6* deficiency (AR-EBV)

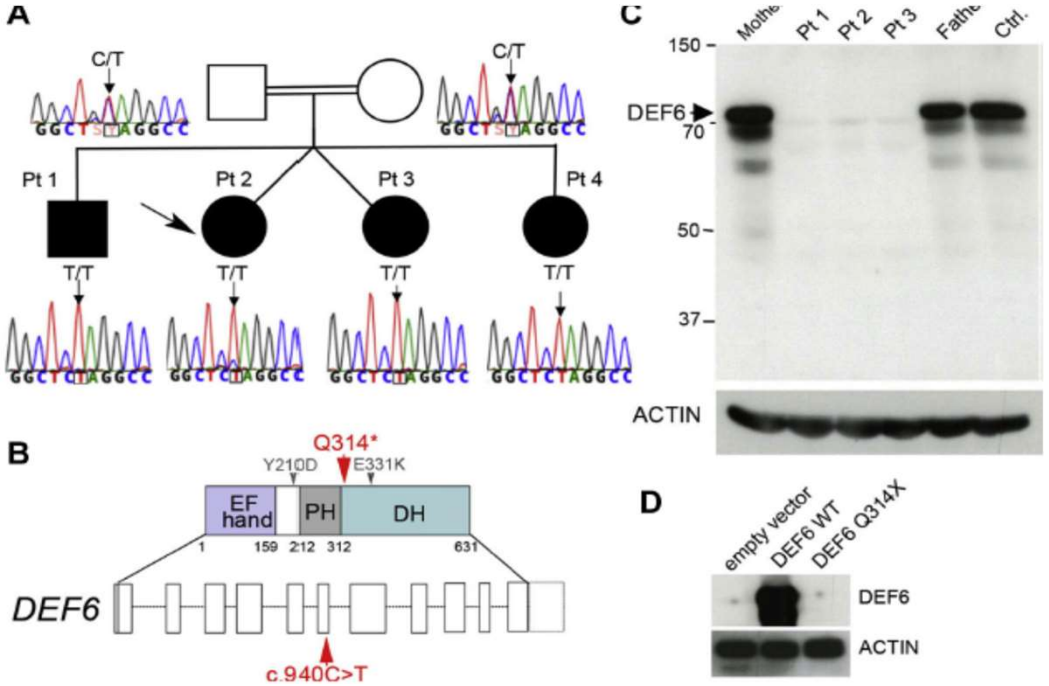
DEF6 deficiency, a mendelian susceptibility to EBV infection, lymphoma and autoimmunity

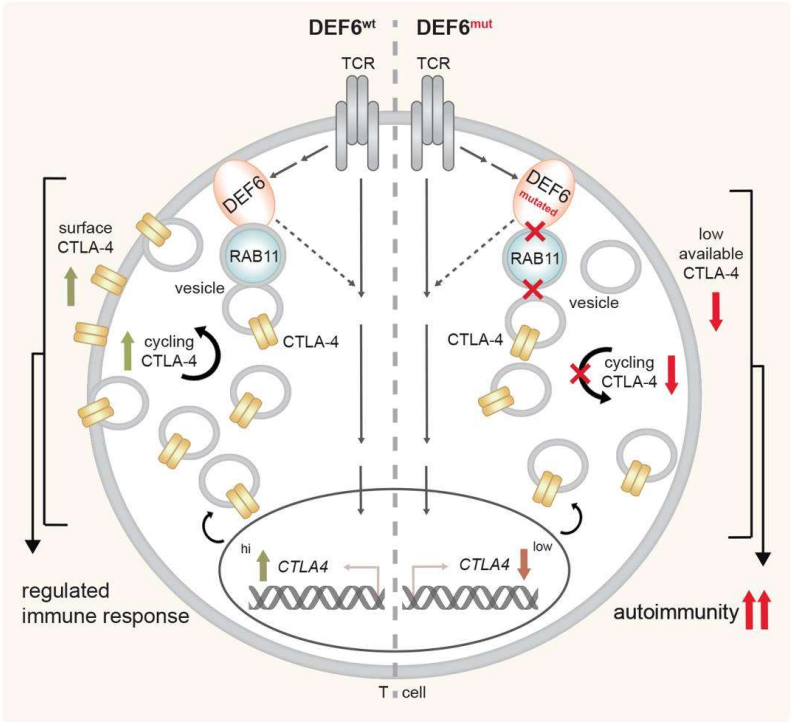
(B. Fournier, JACI 2020)

DEF6 is a specific guanine nucleotide exchange factor for the Rho GTPase Cdc42 and Rac1.
DEF6 is involved in TCR signalling through its recruitment to the immune synapse.

A homozygous mutation in *DEF6* (WES): c.940C>, p.Q314* in 4 members of a CS family with autoimmunity and susceptibility to EBV (EBV-associated lymphoproliferation and lymphoma) without extra-hematopoietic manifestations.

No Def6 protein expression





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AD *CD48* deficiency (AD-EBV)

Recurrent inflammatory disease caused by a heterozygous mutation in *CD48* (Volkmer B, JACI 2019)

1 pt age of 9 mths onward in a patient now 24yo fever, polymorphic rashes, SMG, Pancytopenia, ↑ ferritinemia, ↑TG, HLH-like, partial cytotoxic defect (T/NK cells)

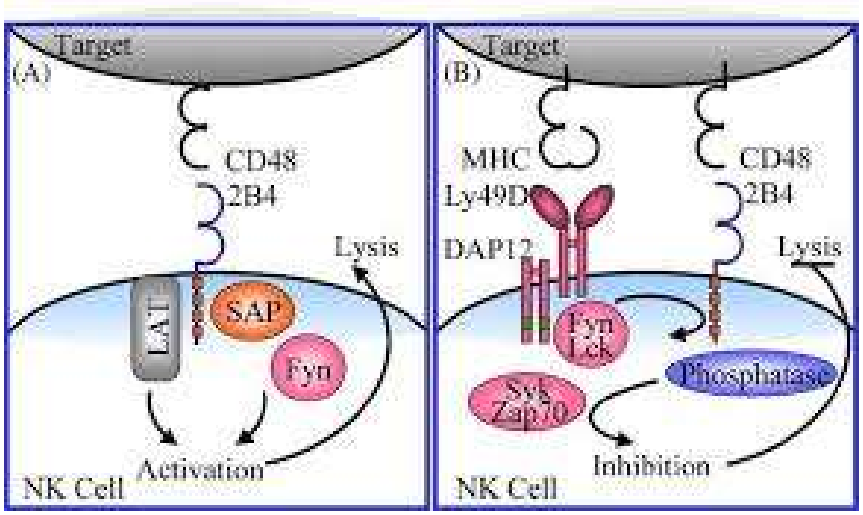
↑↑HLA-DR+ CD8 T cells; Mild ↓ CD4, T cells;

↑ immature Nkbright / ↓ mature NK cells,

Hemophagocytosis in the bone marrow

***CD48* : c.659C>A, p.S220Y (haploinsufficiency)**

NK receptor 2B4 bound to CD48

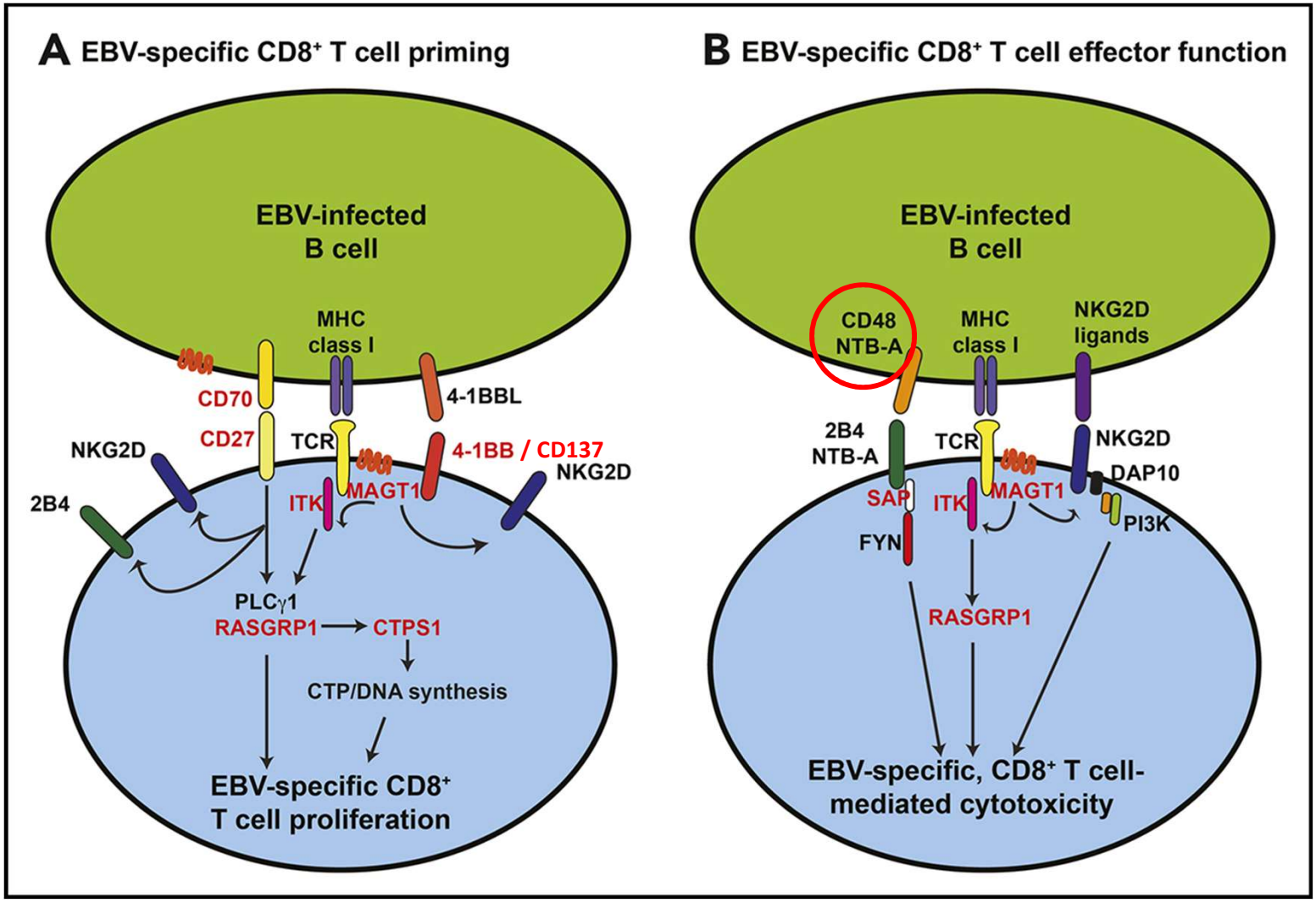


The patient recovered spontaneously from these episodes (4 to 7 days); mild SMG and CD4 lymphopenia between episodes

CD48 expression is needed to :
(1) Control inflammation,
(2) ensure correct NK cell maturation and function,
(3) regulate target cell susceptibility to cytotoxicity.

C. Picard 11/12/2020

PID reveal the molecular requirements for effective host defense against EBV infection

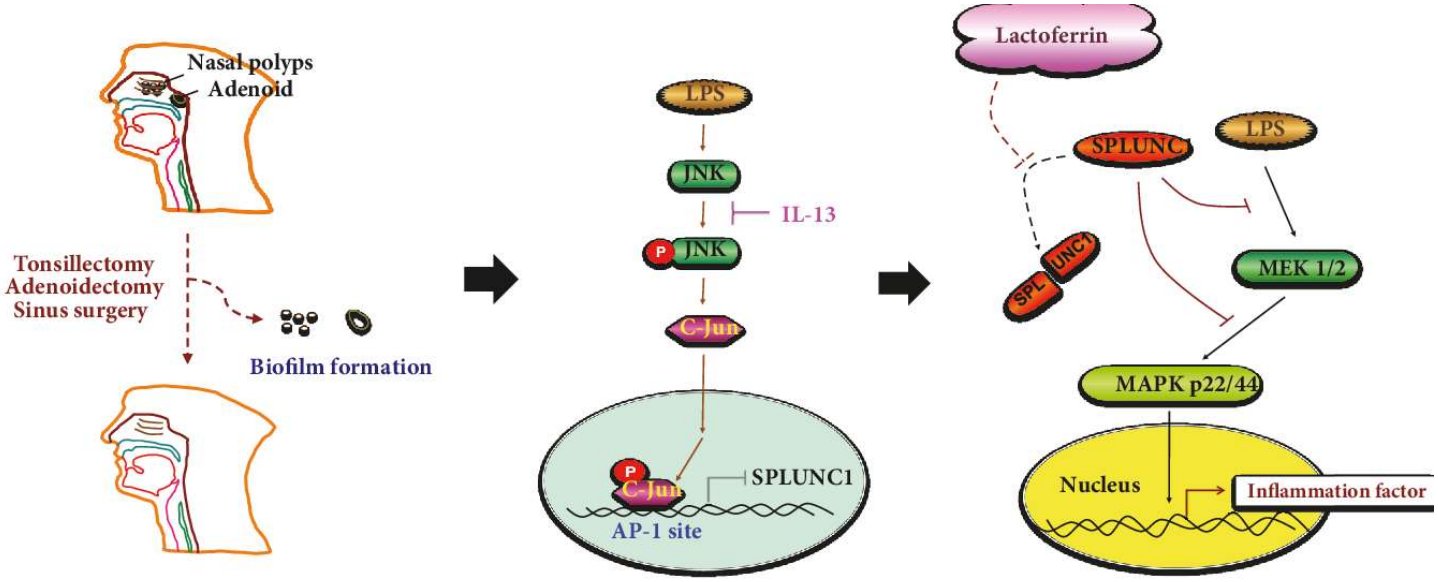


Stuart G. Tangye, Sylvain Latour, Primary immunodeficiencies reveal the molecular requirements for effective host defense against EBV infection, Blood, 2020,

AD *BPIFA1*/SPLUNC1 (AD-DN: Meningo)

A Rare Mutation in SPLUNC1 Affects Bacterial Adherence and Invasion in Meningococcal disease.
(Mashbat B et al. Clin Infect Dis. 2020)

- **3 pts from 2 kindreds: Invasive meningococcal disease (*Neisseria meningitidis*) and heterozygous *BPIFA1 mutation:* c.65G>A, p.(Gly22Glu)**
- **The dominant negative (DN) mutant recombinant *BPIFA1* (p.Gly22Glu) showed reduced antibiofilm activity, increased meningococcal adhesion, and increased invasion of cells, compared with WT *BPIFA1* cells.**



Conclusions: A mutation in *BPIFA1* affecting mucosal attachment, biofilm formation, and invasion of mucosal epithelial cells is a new genetic cause of meningococcal disease.

AR *IFNG* deficiency (AR-MSMD)

Inherited human IFNgamma deficiency underlies mycobacterial disease.
(Kerner G, Rosain J et al. J Clin Invest. 2020)

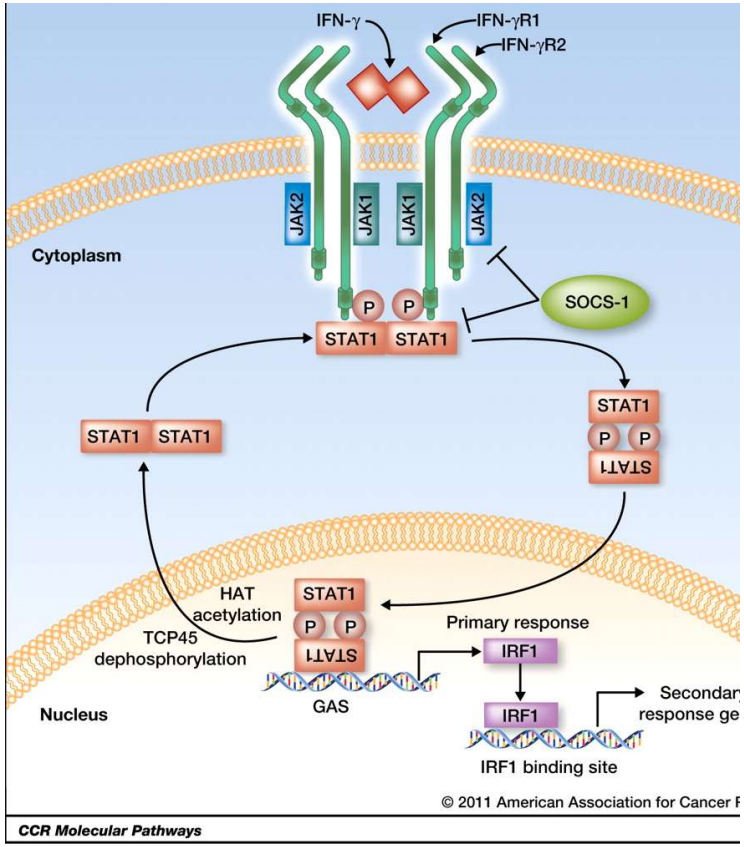
2 cousins: disseminated mycobacterial disease (BCGosis) homozygous mutation in *IFNG* gene:

c.354_357del; p.(T119Ifs4*), Loss of expression and loss of function.

Patients T and NK cells from also failed to produce and secrete detectable amounts of IFN-γ

The patients' herpesvirus Saimiri–immortalized T lymphocytes: No IFN-γ production

Biological phenotype rescued by retrotransduction with WT *IFNG* cDNA.



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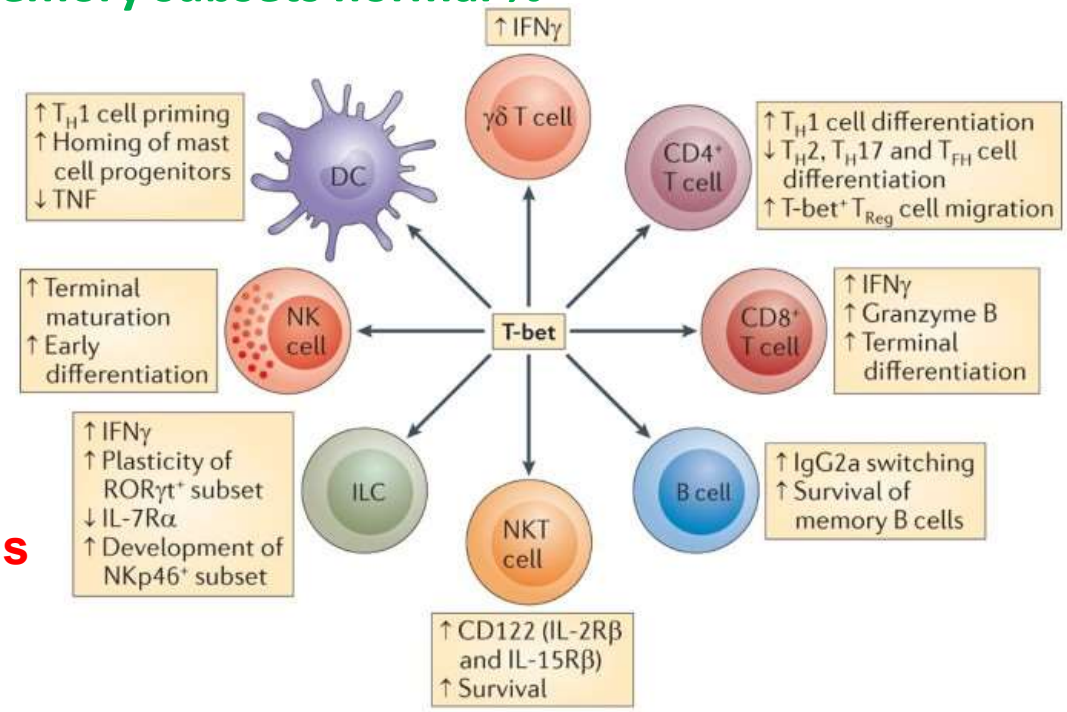
AR *TBX21* (Tbet) deficiency (AR-MSMSD)

Human T-bet governs innate and innate-like adaptive IFN-γ immunity against mycobacteria.
(Yang R //Casanova JL. Cell. 2020)

- **1 MSMD patient : p.Glu156_Met157delins homozygote; ↓ IFN-γ producing T cells**
- **CD4 and CD8 T cells, naïve and memory subsets normal %**
- **↓ CXCR3⁺ Th1 cells,**
- **↑ immature NK, ↓ mature NK**
- **↓ NKT, ↓ MAIT, Vδ2⁺ γδ T cells**



Impairment of development and fonction:
T CD4, NK, NKT, MAIT, γ/δ2, γ/δ T cells
No IFNγ production by T cells

The T-box transcription factor T-bet (Tbx21) is a key regulator of type 1-like immunity, playing critical roles in the establishment and/or maintenance of effector cell fates in T and B lymphocytes, as well as DC and NK cells.

C. Picard 11/12/2020

AR *SNORA31* deficiency (AR-HSE)

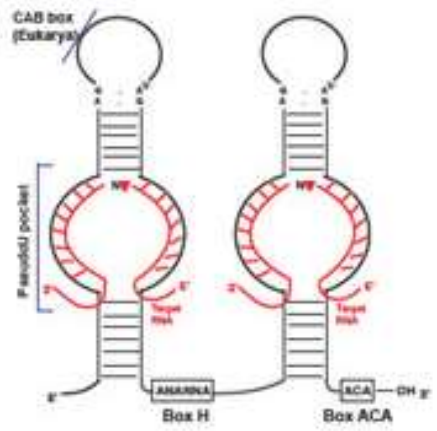
Human SNORA31 variations impair cortical neuron-intrinsic immunity to HSV-1 and underlie herpes simplex encephalitis (Lafaille FG, et al. Nat Med. 2019)

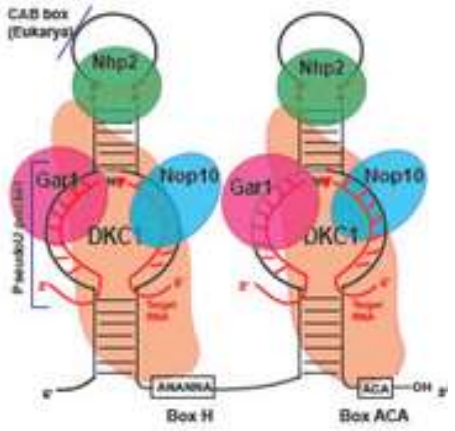
***SNORA31*, encoding a small nucleolar RNA of the H/ACA class**

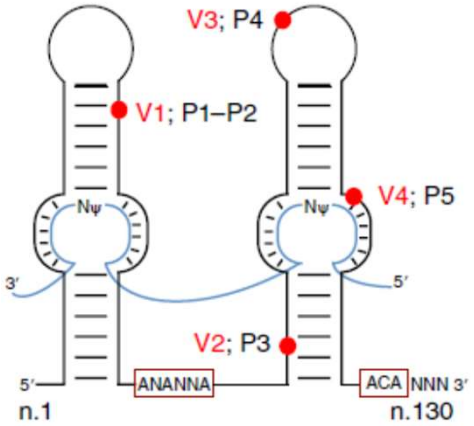
snoRNA31 function: a guide RNA directing the chemical modification of target uridine residues into pseudouridine in rRNA and small nuclear RNA28

5 patients with Herpes Simplex Encephalitis (HSE): n.36T>C, n.75C>G, n.96T>G, n.111T>C

Transcriptome analysis of SNORA31-mutated neurons revealed normal responses to TLR3 and IFN-α/β stimulation but abnormal responses to HSV-1







Deficient *SNORA31* iPSC's cortical neurons are susceptible to HSV1 infection.

It is a new genetic aetiology and immunological mechanism of HSE, involving a disruption of CNS cortical neuron intrinsic immunity to HSV-1 with maintenance of the TLR3 and IFNAR1/IFNAR2 response pathways.

C. Picard 11/12/2020

AD *MAPK8* deficiency (AD-CMC)

Chronic mucocutaneous candidiasis and connective tissue disorder in humans with impaired JNK1-dependent responses to IL-17A/F and TGF-beta

(Li J, Ritelli M,// Puel A et al. Sci Immunol. 2019)

Chronic Mucocutaneous Candidiasis (CMC) and connective tissue disorder (similar to Ehlers-Danlos syndrome)

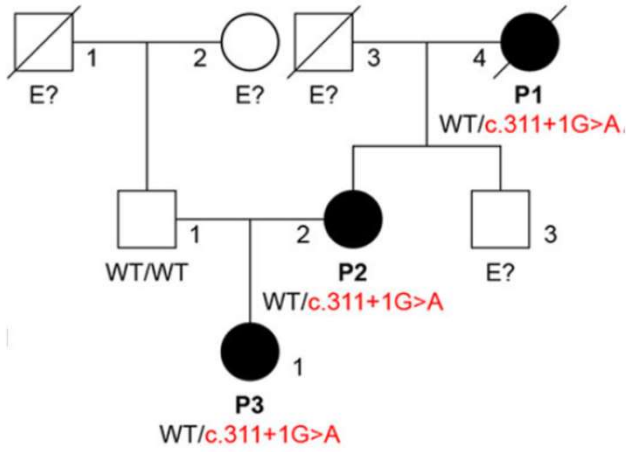
AD mutation in *MAPK8* gene (haploinsufficiency): c.311+1G>A, 3 pts

***MAPK8* gene encodes JNK1, one of the 3 members of the JNK family. This protein is a component of the mitogen-activated protein kinase (MAPK) pathway**

↓ functional Th17 cells *ex vivo, in vitro*

↓ responses of fibroblasts to IL-17A, IL-17F

↓ TGFβ signalling



The integrity of the human JNK1 pathway is essential for IL-17A/F-dependent mucocutaneous immunity to Candida and for the TGF-β-dependent homeostasis of connective tissues.

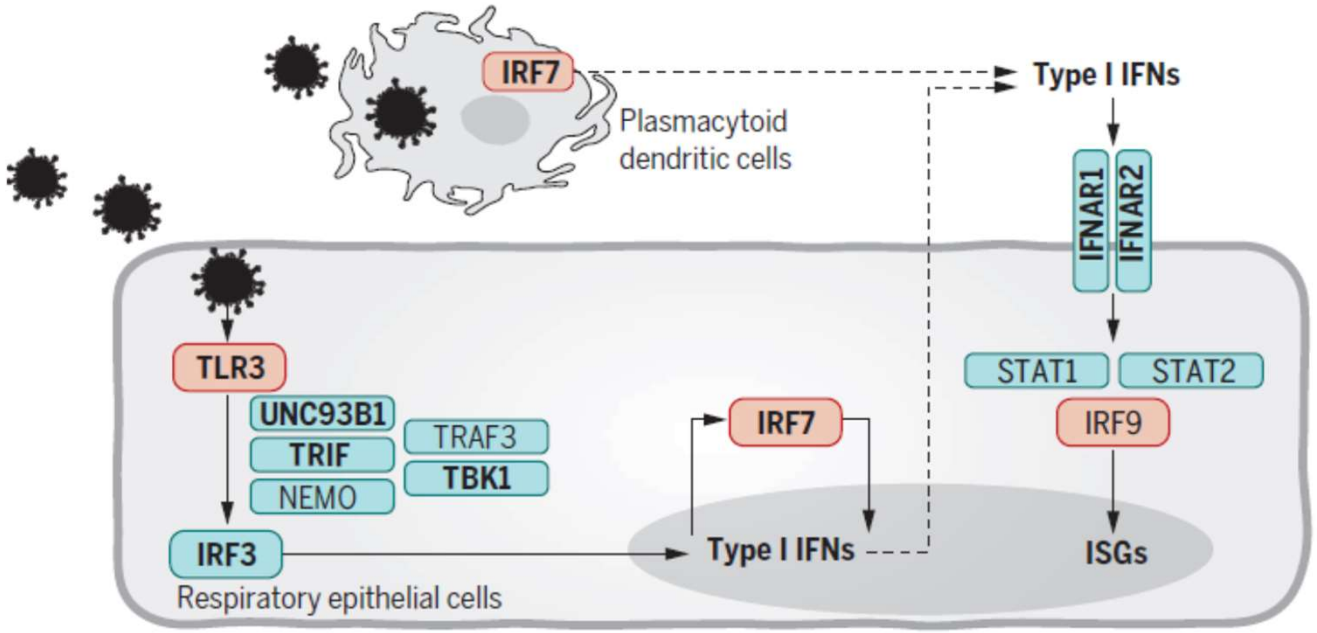
Susceptibility to COVID-19:

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19 (Zhang et al., Science 2020)

3.5% of patients with life threatening COVID-19 pneumonia had :

- known: AR *IRF7* and *IFNAR1* deficiencies or AD *TLR3, TICAM1, TBK1* and *IRF3* deficiencies
- or new AD *UNC93B1, IRF7, IFNAR1*, and *IFNAR2* deficiencies genetic defects (Haplo, 1 DN)

Genes involved in the TLR3- and IRF7-dependent induction and amplification of type I IFNs



This discovery reveals essential roles for both the double-stranded RNA sensor TLR3 and type I IFN cell-intrinsic immunity in the control of SARS-CoV-2 infection.

C. Picard 11/12/2020

Table 1. Disease-causing variants identified in patients with life-threatening COVID-19.

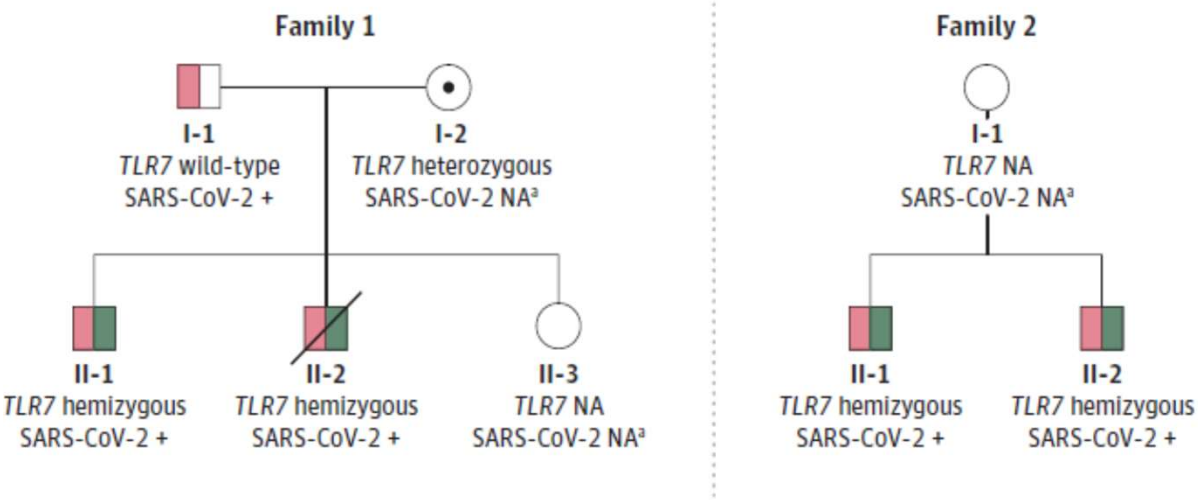
Gene	Inheritance	Genetic form	Genotype	Gender	Age [years]	Ancestry/residence	Outcome
TLR3	AD	Known	p.Ser339fs/WT	M	40	Spain	Survived
TLR3	AD	Known	p.Pro554Ser/WT	M	68	Italy	Survived
TLR3	AD	Known	p.Trp769*/WT	M	77	Italy	Survived
TLR3	AD	Known	p.Met870Val/WT	M	56	Colombia/Spain	Survived
UNC93B1	AD	New	p.Glu96*/WT	M	48	Venezuela/Spain	Survived
TICAM1	AD	Known	p.Thr4Ile/WT	M	49	Italy	Survived
TICAM1	AD	Known	p.Ser60Cys/WT	F	61	Vietnam/France	Survived
TICAM1	AD	Known	p.Gln392Lys/WT	F	71	Italy	Deceased
TBK1	AD	Known	p.Phe24Ser/WT	F	46	Venezuela/Spain	Survived
TBK1	AD	Known	p.Arg308*/WT	M	17	Turkey	Survived
IRF3	AD	Known	p.Glu49del/WT	F	23	Bolivia/Spain	Survived
IRF3	AD	Known	p.Asn146Lys/WT	F	60	Italy	Survived
IRF7	AR	Known	p.Pro364fs/p.Pro364fs	F	49	Italy/Belgium	Survived
IRF7	AR	Known	p.Met371Val/p.Asp117Asn	M	50	Turkey	Survived
IRF7	AD	New	p.Arg7fs/WT	M	60	Italy	Survived
IRF7	AD	New	p.Gln185*/WT	M	44	France	Survived
IRF7	AD	New	p.Pro246fs/WT	M	41	Spain	Survived
IRF7	AD	New	p.Arg369Gln/WT	M	69	Italy	Survived
IRF7	AD	New	p.Phe95Ser/WT	M	37	Turkey	Survived
IFNAR1	AR	Known	p.Trp73Cys/Trp73Cys	M	38	Turkey	Survived
IFNAR1	AR	Known	p.Ser422Arg/Ser422Arg	M	26	Pakistan/Saudi Arabia	Deceased
IFNAR1	AD	New	p.Pro335del/WT	F	23	China/Italy	Survived
IFNAR2	AD	New	p.Glu140fs/WT	F	54	Belgium	Survived

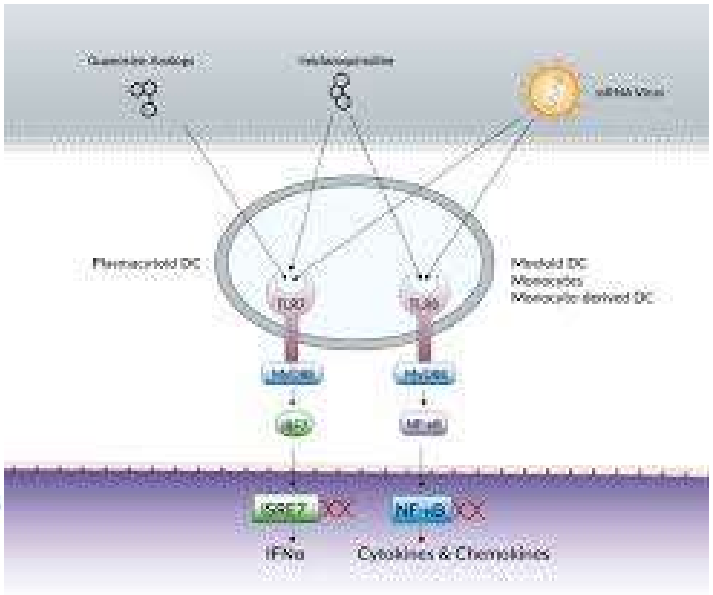
(Zhang et al., Science 2020)

XL-TLR7 deficiency (XL-Covid19)

Presence of Genetic Variants Among Young Men With Severe COVID-19

(van der Made CI, et al. JAMA. 2020)





The 4 male patients mean age of 26 years (range: 21-32), with severe COVID-19 infection, requiring mechanical ventilation.

WES : loss-of-function hemizygous variants of the X-chromosomal *TLR7* gene*:*

F1:c.2129_2132del; p.[Gln710Argfs*18] ; F2 (c.2383G>T; p.[Val795Phe].

Primary peripheral blood mononuclear cells from the patients, significantly decreased mRNA expression of *IRF7*, *IFNB1*, and *ISG15* on stimulation with the TLR7 agonist imiquimod

The production of IFN-γ was decreased in patients in response to stimulation with imiquimod.

= IFN-γ production defect

C. Picard 11/12/2020

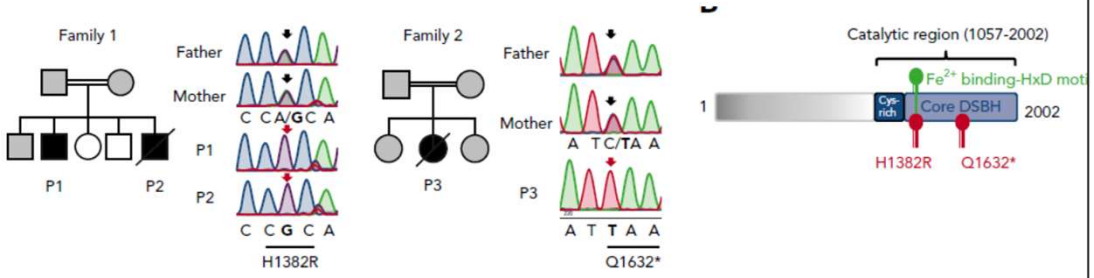
AR *TET2* deficiency (AR-ALPS-like)

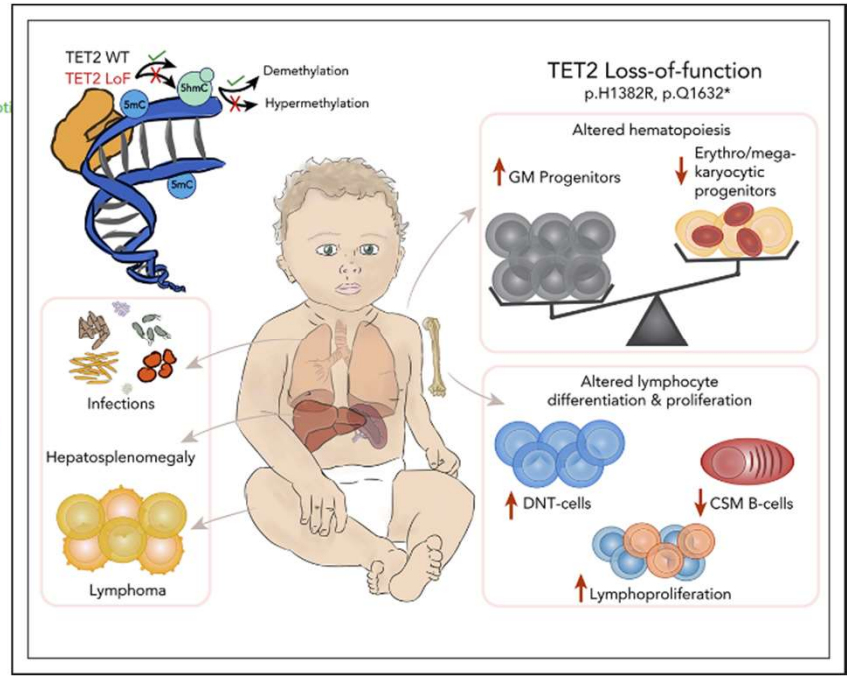
Germline *TET2* loss of function causes childhood immunodeficiency and lymphoma.

(Stremenova Spegarova J, et al. Blood. 2020)

3 children with an immune dysregulation syndrome, susceptibility to infection: lymphadenopathy, HSMG, developmental delay, autoimmunity (cytopenia), lymphoma of B-cell (n:2, 1 EBV) or T-cell (n:1) .

All 3 showed early autologous T-cell reconstitution after HSCT.





Circulating T cells showed an abnormal immunoph.:

- **↑T DN,↓Th1 & Th17 ↑Th2, Th follicular~0;**

↓ B cells class-switched memory

- **Impaired Fas-dependent apoptosis in 2 pts.**

Mutated TET2 protein was absent or enzymatically defective for 5-hydroxymethylating activity, resulting in whole-blood DNA hypermethylation.

C. Picard 11/12/2020

AD *SOCS1* deficiency (AD autoimmunity)

Early-onset autoimmunity associated with SOCS1 haploinsufficiency

(Hadjadj et al. Nature Com 2020) and several others reports

c.368C>G,p.(P123R);
c.24delA,p.(A9fs*76);
c.64C>T, p.(R22W);
c.460T>C, p.(Y154H
c.476_480dupGCCGC,p.M161fs*46

10 patients (5 families) with early onset autoimmune manifestations: heterozygous (AD) germline loss-of-function mutations in the *SOCS1* gene (incomplete penetrance)

Early onset severe multisystemic autoimmunity (flared in context of infection-induced inflammation):

- ITP, AIHA, Evan's syndrome
- SLE, GN, psoriasis, arthritis, thyroiditis…..
- Lymphoma, syndrome lymphoproliferatif
- Recurrent bacterial infections,

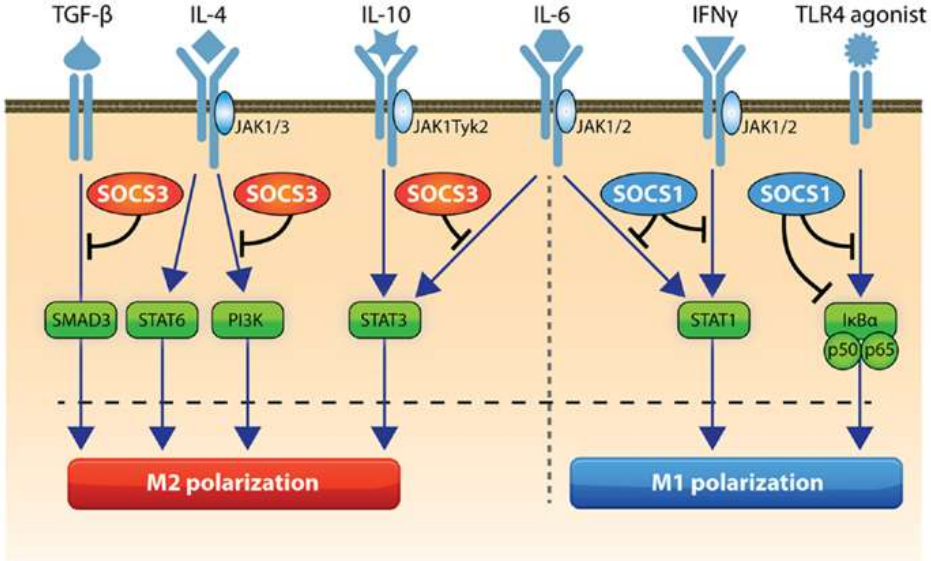
↓ marginal zone B cells

↓ switched memory B cell

↑ CD21low CD38low B-cell

↑plasma B-cell activating factor (BAFF) levels

Auto-antibodies,↓ Treg and suppressive fct



The intracellular protein SOCS1 downregulate cytokine signalling by inhibiting the JAK-STAT pathway

SOCS1 insufficiency provide mechanistic insight into the development of autoimmunity induced by cytokine hypersensitivity in immune cells following the loss of a downregulatory element.

C. Picard 11/12/2020

AR GIMAP5 and GIMAP6 deficiencies (AR autoimmunity)

Loss of GTPase of immunity-associated protein 5 (Gimap5) promotes pathogenic CD41 T-cell development and allergic airway disease

(Patersson et al. JACI 2019)

A young adult patient with history of impaired viral immunity, auto-immunity. SMG

Progressive T-cell lymphopenia (CD4 > CD8) loss of naïve T-cells, particularly CD4 T-cell
Abnormal T-cell function *in vitro*.

WES a homozygous mutation Leu204Pro in gene encoding GTPase IMAP Family Member 5 (*GIMAP5*)
Absent protein expression in T-cells. Impaired survival of T-cells that partially could be rescued *in vitro* by lithium.

GIMAP-5 deficiency is a disorder of immunodysregulation/immune-senescence.

A Human Case of GIMAP6 Deficiency: A Novel Primary Immune Deficiency.

(Shadur B, et al. Eur J Hum Genet. In press)

2 siblings with sinopulmonary infections mild hepatosplenomegaly, Patient with a lupus-like PID, SMG Autoimmunity.

~near normal T cells and subsets
- ↑ DN ab T cells
- ↑ T cell apoptosis

~near normal B cells/subsets
↑ CD21low B cells, Normal Ig (GAM)

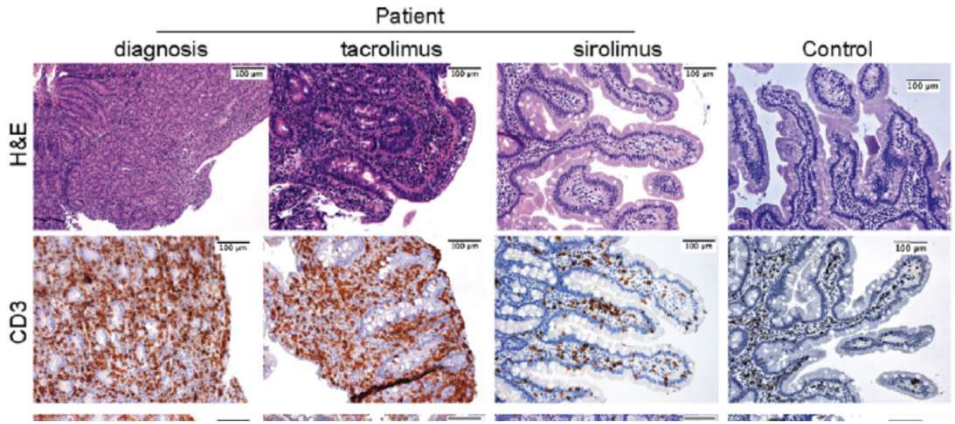
GIMAP6 is a novel PID-associated gene
= cell-specific regulator of autophagy.

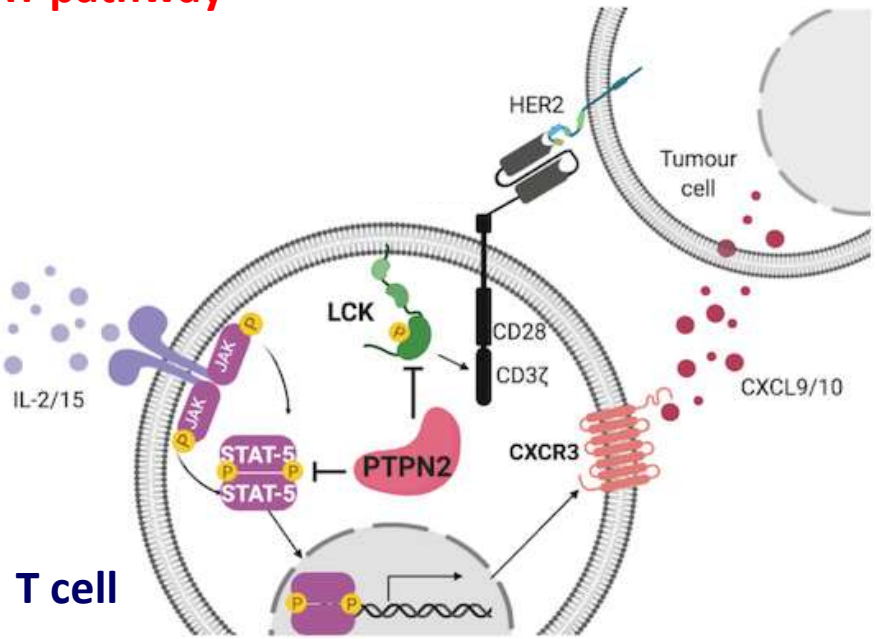
(GIMAPs) GTPase of the immunity associated protein family are a protein family small GTPases. Immunological functions, such as thymocyte development, apoptosis of peripheral lymph. and T helper cell differentiation

AD PTPN2 Deficiency in Early-Onset Intestinal Autoimmunity

Loss-of-Function Mutation in PTPN2 Causes Aberrant Activation of JAK Signaling Via STAT and Very Early Onset Intestinal Inflammation. (Parlato M, et al. Gastroenterology. 2020)

- **a 3-year-old girl (P1) born from healthy non-consanguineous parents presented with severe chronic secretory diarrhea and eczema since the age of 3 months.**
- **De novo a heterozygous missense variant in *PTPN2* gene: c.646T>G, p. Cyst216Gly, haploinsufficiency**
- **PTPN2 encodes an ubiquitous non-receptor protein tyrosine phosphatase that exerts a negative feedback on the JAK-STAT pathway**





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AD *RIPK1* deficiency (AD CID-autoinflammation)

A dominant autoinflammatory disease caused by non-cleavable variants of RIPK1.
(Tao P et al. Nature. 2020)
Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease.
(Lalaoui N et al. Nature. 2020)

RIPK1 is a key regulator of innate immune signalling pathways = CRIA syndrome

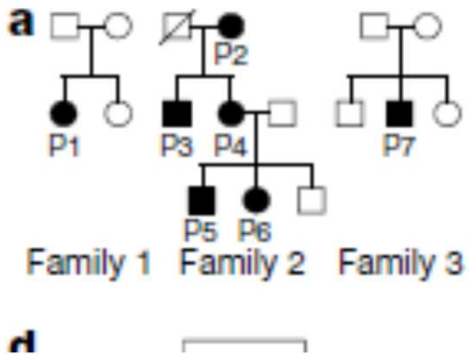
Heterozygous missense mutations D324N, D324H, D324V, D324Y, D138N (DN)
⇒ prevent caspase cleavage of RIPK1 in humans

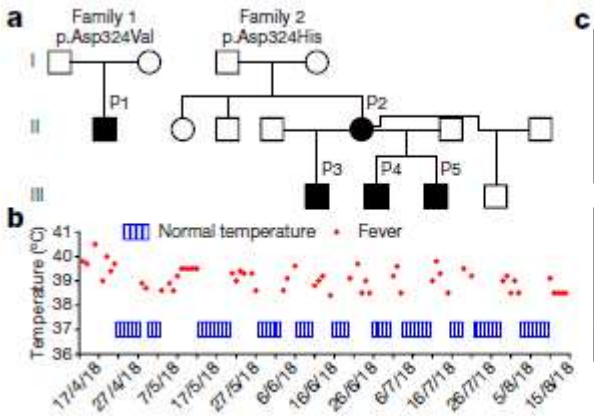
- **Early onset (<1month): 12 pts from 5 kindreds: early-onset periodic fever syndrome (3-5days) and severe intermittent lymphadenopathy, HSMG, ulcers, tonsillitis, arthralgia, GI features,**

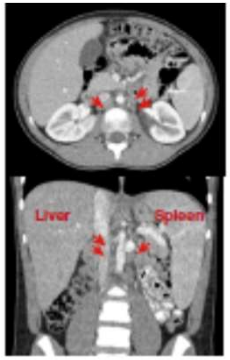
- ↑inflamm markers, ↑ pro-inflamm cytokines/gene signature;

with responsive to Tocilizumab (IL-6 inhibitor), not to IL1/TNF blockade.

↑ counts of both double-negative T cells and naive B cells. ↓ T CD4 naïf and T CD8







C. Picard 11/12/2020

AD *CDC42* deficiency (AD-auto-inflammation)

A novel disorder involving dyshematopoiesis, inflammation, and HLH due to aberrant CDC42 function ((Tam et al. JEM 2019), + several others reports…..)

c.556C>T ; (p.R186C),
c.563G>A; (p.C188Y),
c.576A>C; (p.*192C*24),
c.242G>A; p.Cys81Tyr

Neonatal onset: pancytopenia, fever, rash, HSMG, HLH, myelofibrosis, multisystemic inflammatory disease

> 15 patients

Recurrent infections; enterocolitis, diarrhea with intestinal bleedings, neurodevelopmental delay (+/-).

Treated: Anakinra/IFNγ mAb (IL-1 and IFNγ neutralization) and HSCT.

Mutations haplo-insuf. affects actin function. The mutated protein impaired interaction with regulators and effectors, (RhoGDI, IQGAP1, WASP), leading to aberrant subcellular localization, actin cytoskeleton rearrangement, and reduced migration.

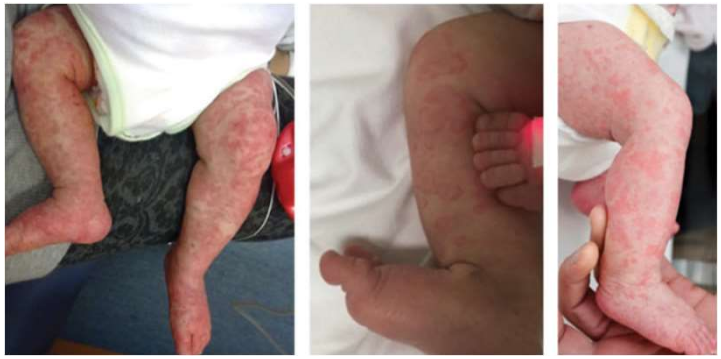
↑Serum levels of IL-1, IL-18, IFNγ, ferritin, sCD25, CRP

↓ NK function (cytox),

↑ central memory CD4+ cells with ↓ T naive CD31+ cells,
↑ Tregs with high memory phenotype

↑ B cell switched memory cells, plasma cells and autoreactive B cells; and ↓ transitional B cells,

↓ PN, DC and monocytes



Autoinflammatory syndrome : CDC42 cause a novel IL-1 inhibition – responsive

CDC42 encodes a small Rho family GTPase that regulates multiple signalling pathways controlling cell polarity and migration, actin polarization, cytoskeletal architecture, endocytosis, and cell-cycle progression.

C. Picard 11/12/2020

AR *HEM1/NCKAPL1* deficiency (AR auto-inflammation)

HEM1 deficiency disrupts mTORC2 and F-actin control in inherited immunodysregulatory disease

(Cook et al., Science 369, 202–207 2020); and several other reports

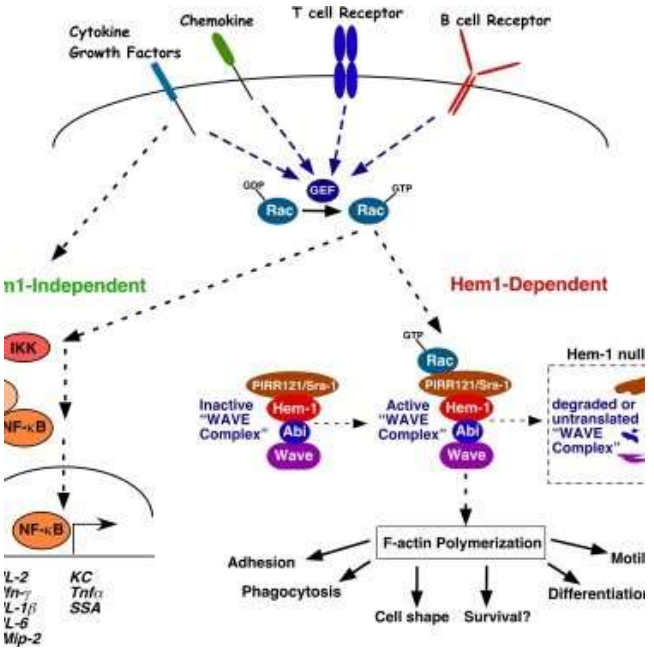
***NCKALP1* homozygous mutation:**
p.P359L, p.M371V, p.V519L, p.R258L, c.385C>T, p.R129W

>10 pts from 8 families :

PID with atopy, lymphoproliferation, hyperinflammation

Recurrent URTI, skin rashes /abscesses, ulcers, SLE-like, lymphadenopathy, fever, HLH-like

Normal T cell numbers , ↑T_{CM}, exhausted cells;
↓ T cell proliferation,
Normal B cells and naïve/memory subsets;
↑ $CD21^{low}$ cells, Normal/ ↓ Ig levels , ↑IgE autoAbs, cytoskeletal defects; immature NK cells but intact function,
Cytokine overproduction (Th1) anti-dsDNA Abs,



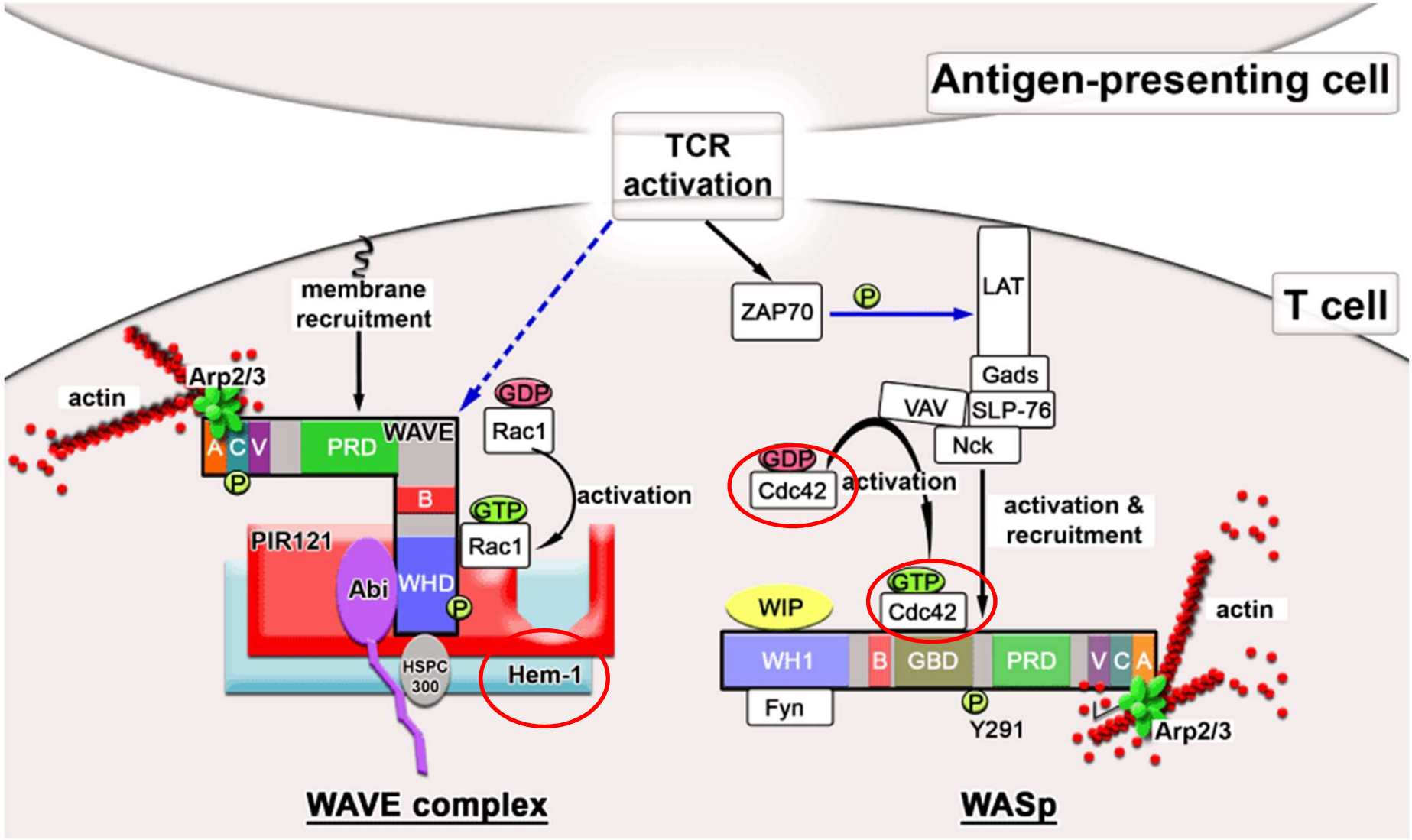
WAVE regulatory complex (WRC)

Human patients with immunodeficiency and immune hyperactivation with LOF mutations in *NCKAP1L,* the gene encoding HEM1, disrupt WRC-mediated actin polymerization and abrogate mTORC2 activation of AKT.

WRC deficiency caused by the absence of the WRC hematopoietic cell–specific subunit HEM1 results in a human disorder with severe immune dysregulation and recurrent infections.

C. Picard 11/12/2020

Inborns errors of immunity affecting the actin cytoskeleton

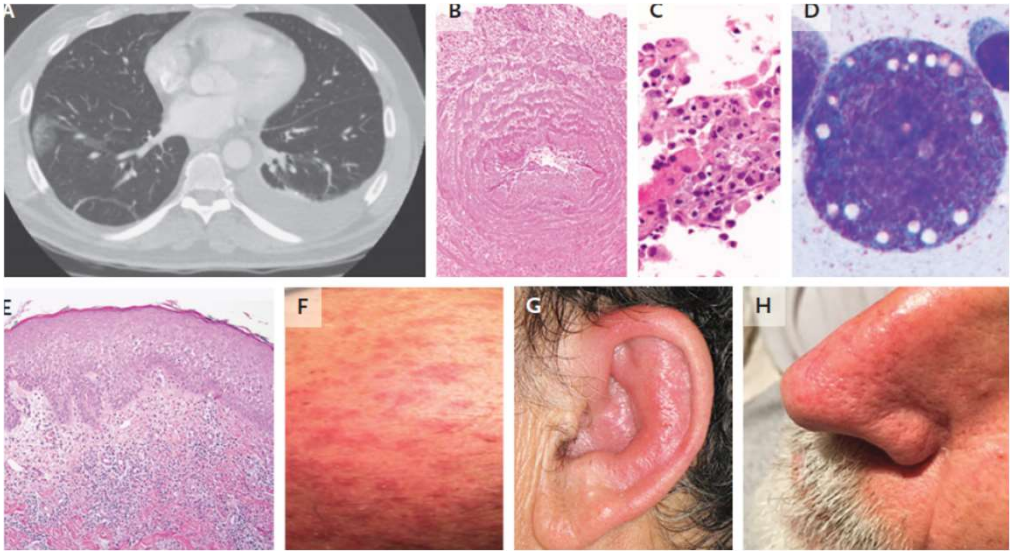


XL-*UBA1* (XL somatic mutation - autoinflammation)

Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease.

(Beck DB et al. N Engl J Med. 2020)

- 25 male patients 64yo (45-80) with adult onset treatment-refractory inflammatory synd.
- Fevers, cytopenias, dysplastic bone marrow, neutrophilic cutaneous and pulmonary inflammation
- Inflammatory syndrome (relapsing polychondritis, Sweet's syndrome, polyarteritis nodosa, giant-cell arteritis) or a hematologic condition (MDS, multiple myeloma)
- Often fatal



(Met41Val, Met41Thr, Met41Leu)
Mutations > half the hematopoietic stem cells, including peripheral-blood myeloid cells but not lymphocytes or fibroblaste

VEXAS syndrome
Vacuoles,
E1 enzyme,
X-linked,
Autoinflammatory,
Somatic

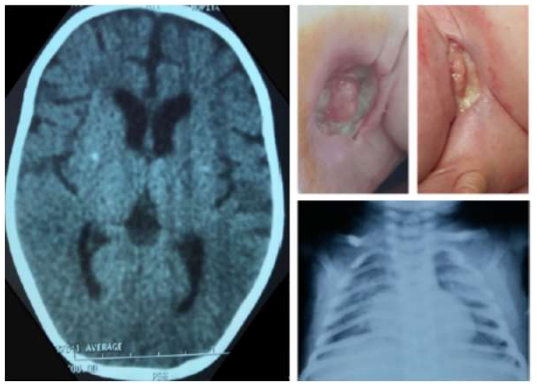
Mutant peripheral-blood cells ↓ ubiquitylation and activated innate immune pathways.

C. Picard 11/12/2020

AR STAT2 GOF

c.443G>A, p.R148Q

Homozygous STAT2 gain-of-function mutation by loss of USP18 activity in a patient with type I interferonopathy (Gruber et al. JEM 2020)

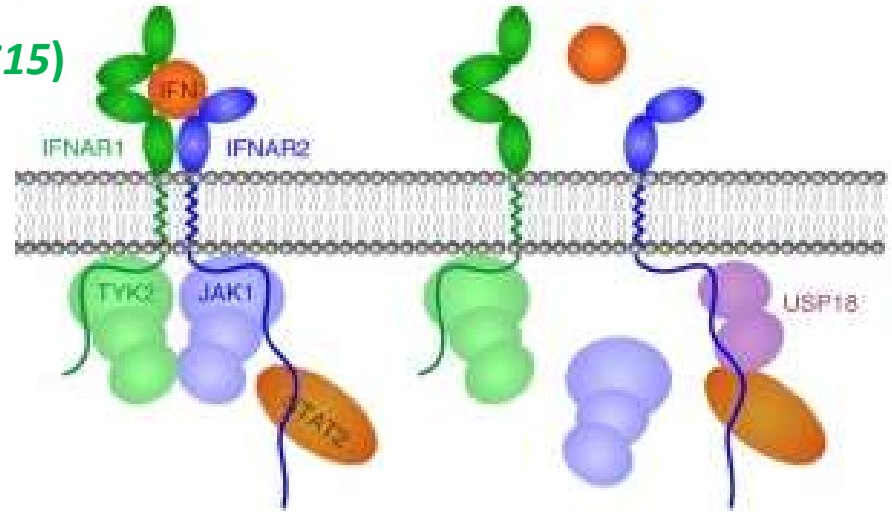


1 patient from CS parents with early-onset, severe autoinflammation evocative of severe type I interferonopathy. Skin ulcerations, seizures, cerebral calcifications, and ultimately respiratory failure and death

less myeloid and NK cells and more B and T cells,

mRNA levels of four ISGs (*IFIT1, IFI27, RSAD2, ISG15*) all were elevated >1000-fold / healthy donor

The defect in USP18 trafficking to the receptor and explains both the GOF and recessive inheritance of STAT2 R148Q



USP18 negative regulator of STAT2

C. Picard 11/12/2020

AR *RCH1* deficiency (AR-autoinflammation - HLH)

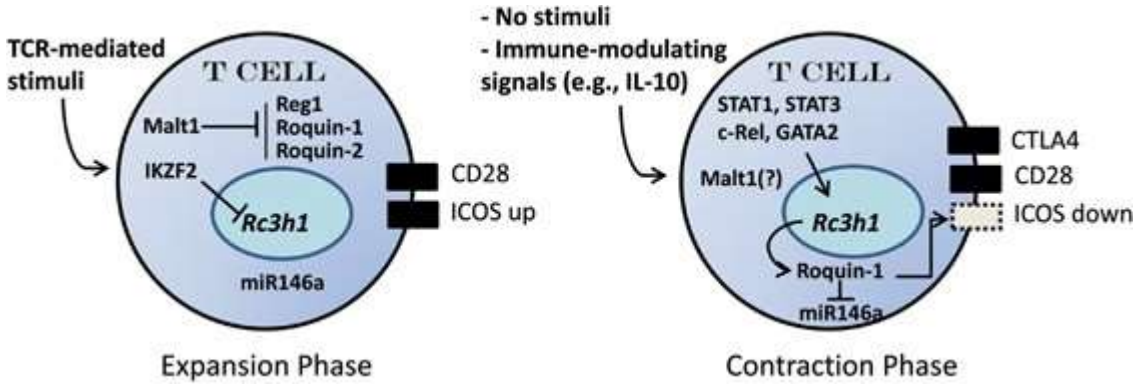
A human immune dysregulation syndrome characterized by severe hyperinflammation with a homozygous nonsense Roquin-1 mutation. (Tavernier SJ, et al. Nat com 2019)

One patient 18-year-old male, who was referred at age 11 suffering from hyperinflammation clinically ~ hemophagocytic lymphohistiocytosis (HLH)

WES : a homozygous nonsense R688X *RC3H1* mutation

RC3H1 encodes Roquin-1 a post-transcriptional repressor of immune-regulatory proteins such as ICOS, OX40, CTLA4, Rel and TNF.

The R688X variant reveals a phenotypic immune cell activation, hypercytokinemia and disease development (similar mice model)



R688X Roquin-1 fails to localize to P-bodies and interact with the CCR4-NOT deadenylation complex, impeding mRNA decay and dysregulating cytokine production.

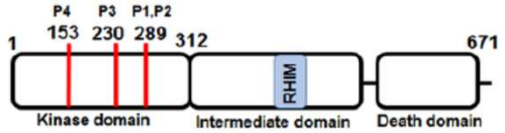
The results suggest that impaired Roquin-1 function provokes hyperinflammation by a failure to quench immune activation.

Biallelic *RIPK1* mutations in humans cause severe immunodeficiency, arthritis, and intestinal inflammation

Delphine Cuchet-Lourenço[1*], Davide Eletto[1*], Changxin Wu[1*†], Vincent Plagnol[2], Olivier Papapietro[1], James Curtis[1], Lourdes Ceron-Gutierrez[3], Chris M. Bacon[4,5], Scott Hackett[6], Badr Alsaleem[7], Mailis Maes[1], Miguel Gaspar[1], Ali Alisaac[1,8], Emma Goss[1], Eman AlIdrissi[9], Daniela Siegmund[10], Harald Wajant[10], Dinakantha Kumararatne[3], Mofareh S. AlZahrani[9], Peter D. Arkwright[11], Mario Abinun[12], Rainer Doffinger[3], Sergey Nejentsev[1‡]

Science 2018

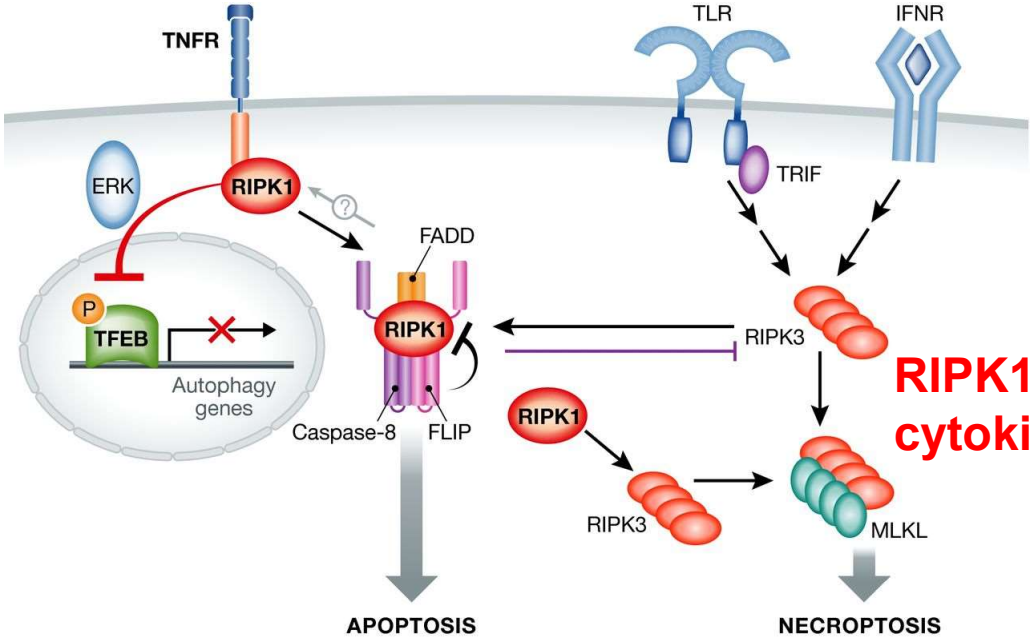
AR-CID



p.Y289X,
p.N230MfsX8,
Deletion ex 4

- Receptor Interacting Serine/Threonine Kinase 1 (RIPK1) = master regulator of signaling pathways leading to inflammation + cell death

- 4 pts from 3 kindreds: homozygous (AR) mutations *RIPK1*: 1st month onset
- Recurrent infections (CMV, VZV, RSV, *M.avium*, bacteria, Aspergillus),
- Chronic lung disease DDB, Early-onset severe IBD and progressive polyarthritis.
- Lymphopenia (T CD4, T CD8, NK), pro-inflammatory cytokines production ↓↓



HSCT reversed cytokine production defects and resolved clinical symptoms in 1 patient

RIPK1-deficient cells ↓ MAPK activation, cytokine secretion and prone to necroptosis.

C. Picard 14/12/2018

Actualités 2020

Combined immunodeficiency (CID):

- AR *PAX1* deficiency (SCIDT-B+NK+)
- AR ITPKB deficiency (SCIDT-B+NK+)
- AR SLP76 (SCIDT-B+NK+, PN and platelets dysfunction)
- AR *CDH17* deficiency (CID T-B-NK+)
- AR MAN2B2 deficiency (CID-CDG)
- AR POLR3E deficiency (CID-virus)
- AR *IL7* deficiency (CID-HPV)
- AR *MCM10* deficiency (CID-HPV)
- AR *CD4* deficiency (CID-HPV)
- AR *MR1* deficiency (CID-HPV)
- AR *NFKB1* deficiency (CID)

B cell deficiency (PAD):

- AR *TNFSF13* deficiency (APRIL, CVID)
- AR *CTNNBL1* deficiency (CIVD)
- AR FNIP1 deficiency (PAD, WPW)

HyperIgE syndrome :

- AD (DN) *IL6ST* deficiency (partial gp130 def.)
- AR *IL6ST* deficiency (complete gp130 def.)

Phagocytes deficiency :

- AD (HI) Sec61α1 deficiency (SCN)
-

Mendelian predisposition:

- AR *NOS2* deficiency (CMV)
- AR CD16A deficiency (EBV)
- AR DEF6 deficiency (EBV)
- AD (HI) *CD48* deficiency (EBV)
- AD (DN) *BPIFA1/SPLUNC1 (Neisseria)*
- AR *IFNG* deficiency (vaccin: BCG, MSMD)
- AR TBX21 (Tbet) deficiency (MSMSD)
- AR *SNORA31* deficiency (HSE)
- AD (HI) MAPK8 deficiency (CMC

Susceptibility to COVID 19:

- AD (HI) UNC93B1 deficiency
- AD (HI) IRF7 deficiency
- AD (HI/ DN) INFAR1 deficiency
- AD (HI) IFNAR2 deficiency
- XL *TLR7* deficiency

C. Picard 11/12/2020

Actualités 2020 suite

Autoimmunity:

- AR *TET2* deficiency (ALPS-like)
- AD (HI) SOCS1 deficiency
- AR *GIMAP5* deficiency
- AR *GIMAP6* deficiency
- AD (HI) PTPN2 deficiency

Autoinflammation:

- AD (HI) *CDC42* deficiency
- AR *HEM1/NCKAPL1* deficiency
- XL UBA1 (somatic mutation)
- *AR STAT2 GOF*
- AR *RCH1 deficiency*
- AD (DN) *RIPK1* deficiency

ESID 2020

19TH BIENNIAL MEETING OF
THE EUROPEAN SOCIETY
FOR IMMUNODEFICIENCIES
ONLINE MEETING | 14-17 OCTOBER 2020

Combined immunodeficiency (CID):

- *XL SASH3* deficiency (ENT, VZV, HSV, HPV,DID, NHL)
- AR *ITPR3* deficiency (CID EBV)

B cell deficiency (PAD):

- AR BOB1 (*POUZAF1)* deficiency (agamma)

Phagocytes deficiency :

- AR *DBF4* deficiency (SCN)

Dysregulation:

- AR *RHOG* deficiency (FHL)
- AD *TRAF3* (haploInf) lymphoïde hyperplasia

Autoinflammation:

- AD NLRP6
- XL *TLR8 GOF (mosaic)*

C. Picard 11/12/2020

XL SASH3 deficiency (XL-CID)

SASH3 : SAM and SH3 domain containing 3
May function as a signaling adapter protein in lymphocytes

19TH BIENNIAL MEETING OF
THE EUROPEAN SOCIETY
FOR IMMUNODEFICIENCIES
ONLINE MEETING | 14-17 OCTOBER 2020

- **11 patients from 10 kindreds (p.R245X, p.R288X, p.R347C, p.I1227T…)**
- **CID: - ENT, Viral infections: severe VZV (recurrent), HSV (chronic), HPV,**
  - Autoimmunity : DID; thyroïde, cytopenia….
  - Eczema; inflammatory, granuloma, Lymphoma NHL

- **Lymphopenia**
- **↓CD4 and CD8 naïfs, ↓B, ↓NK, ↓ TTL, abnormal T cell repertory**
- **↓ TCR signalling (phospho)**

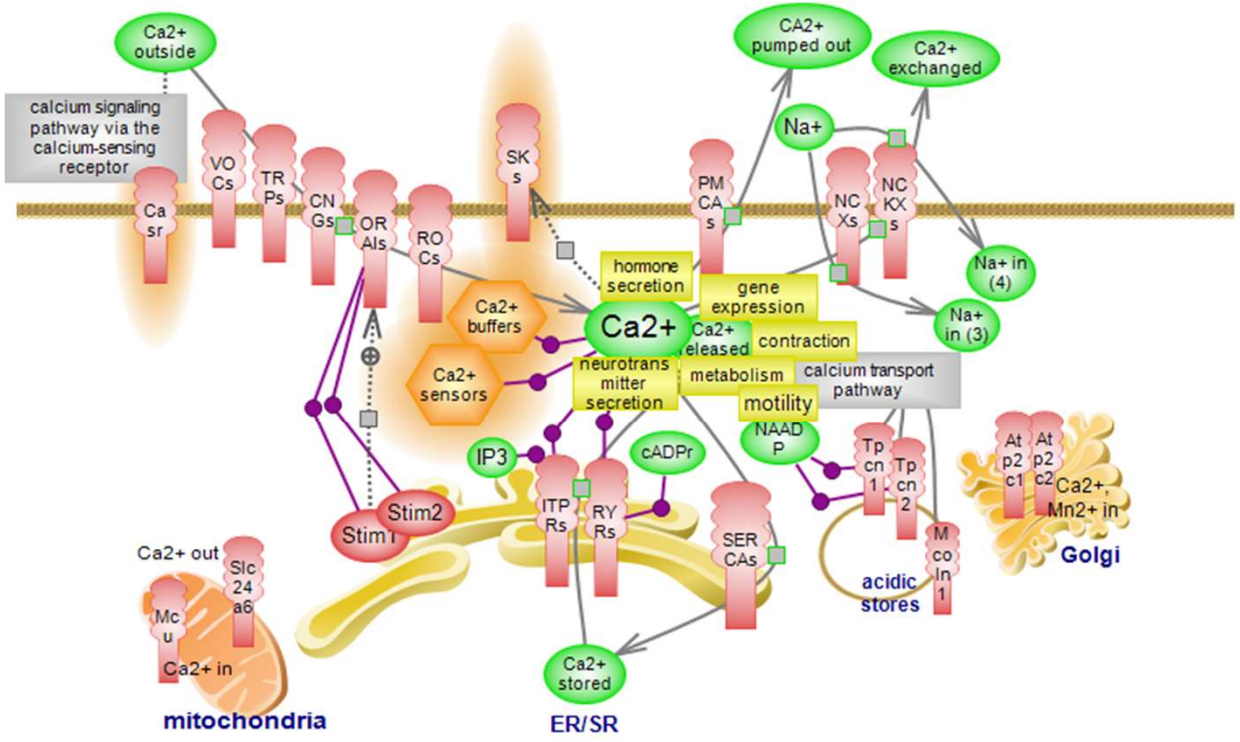
Hemizygous mutation caused Impairement of TCR signalling pathway (prolif ↓ ,↑ apoptosis).

- **SASH3, also called SLY/SLY1 (SH3-domain containing protein expressed in lymphocytes), is expressed exclusively in lymphocytes and is essential in the full activation of adaptive immunity**

AR *ITPR3* deficiency (AR-CID)

the type 3 isoform of the inositol 1, 4, 5-trisphosphate receptor (ITPR3)

- **3 patients CID Infections, Leyomosarcome EBV (1), inflammation, granuloma**
- **Arg1850, Tyr2033, Arg2524Cys, Phe1618**
- **↓ calcic flux, with the exception of one patient with stop gain mutation ↑ calcic flux**



ITPR3 (or IP3R3) is a Ca^{2+} channel enriched at ER-mitochondria contact sites where it provides Ca^{2+} for transport into the mitochondria

ARIADNE

C. Picard 11/12/2020

AR BOB1 (*POUZAF1*) deficiency (AR agamma)

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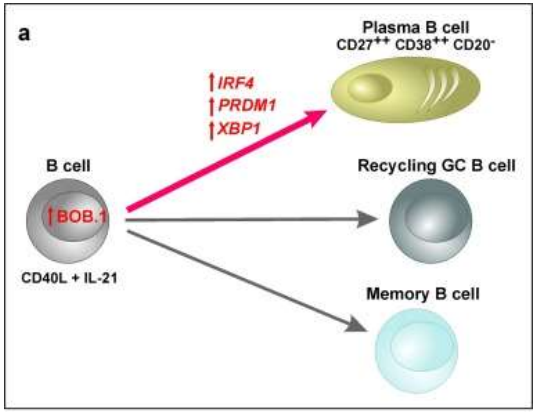
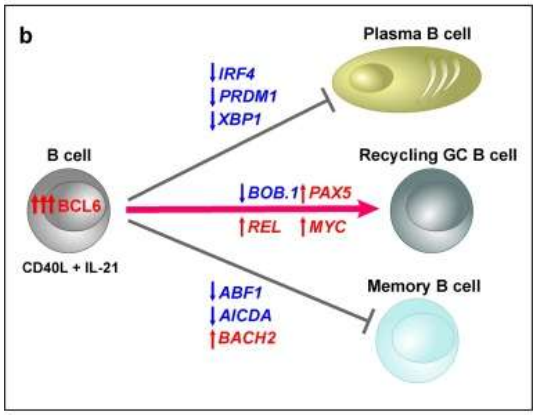
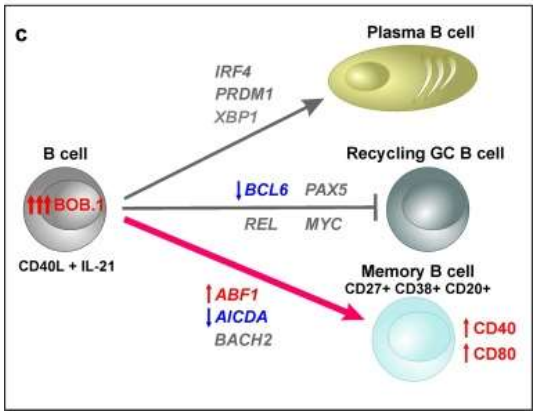






Patient from consanguinous kindred with homozygous null mutation in *POUZAF1* gene:

Infection (lung),

neurologic disaese with ↓ myelinisation white matter and ↑ cells in CSF

- **B cells normal count , but ↓ ↓B CD27+ cells**
- **No plasmablasts**
- **Agammaglobulinemia**
- **Defect production of specific Abs**

BCR impairment and defective class switch

Mice lacking the lymphocyte-specific transcription factor Bob1 fail to generate germinal centers and a robust Ig responses.

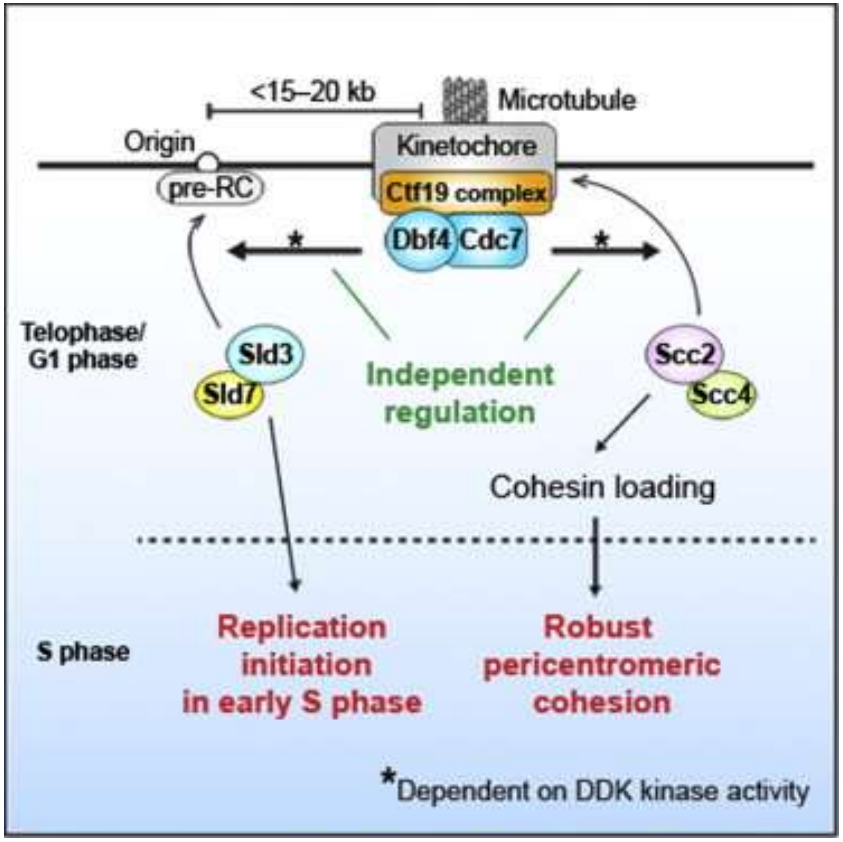
C. Picard 11/12/2020

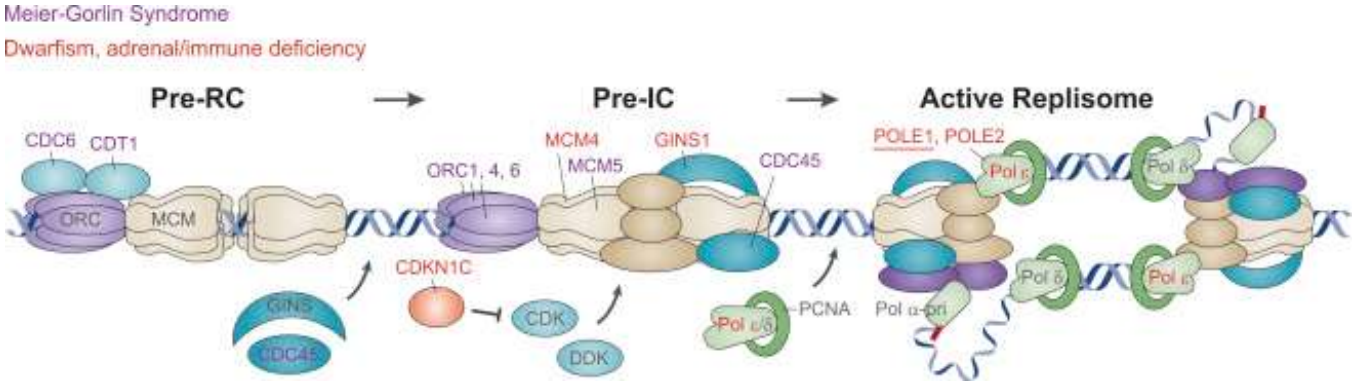
AR *DBF4* deficiency (AR-SCN)

19TH BIENNIAL MEETING OF
THE EUROPEAN SOCIETY
FOR IMMUNODEFICIENCIES
ONLINE MEETING | 14-17 OCTOBER 2020

- 1 patient c.627A>C; p. Lys209Asn homozygote
- Infections, dysmorphia, Neutropenia
- BOM: Arrest at promyelocytes stage
- DDK deficiency

CDC7-DBF4 kinase (DDK) initiates DNA replication in eukaryotes by activating the replicative MCM helicase



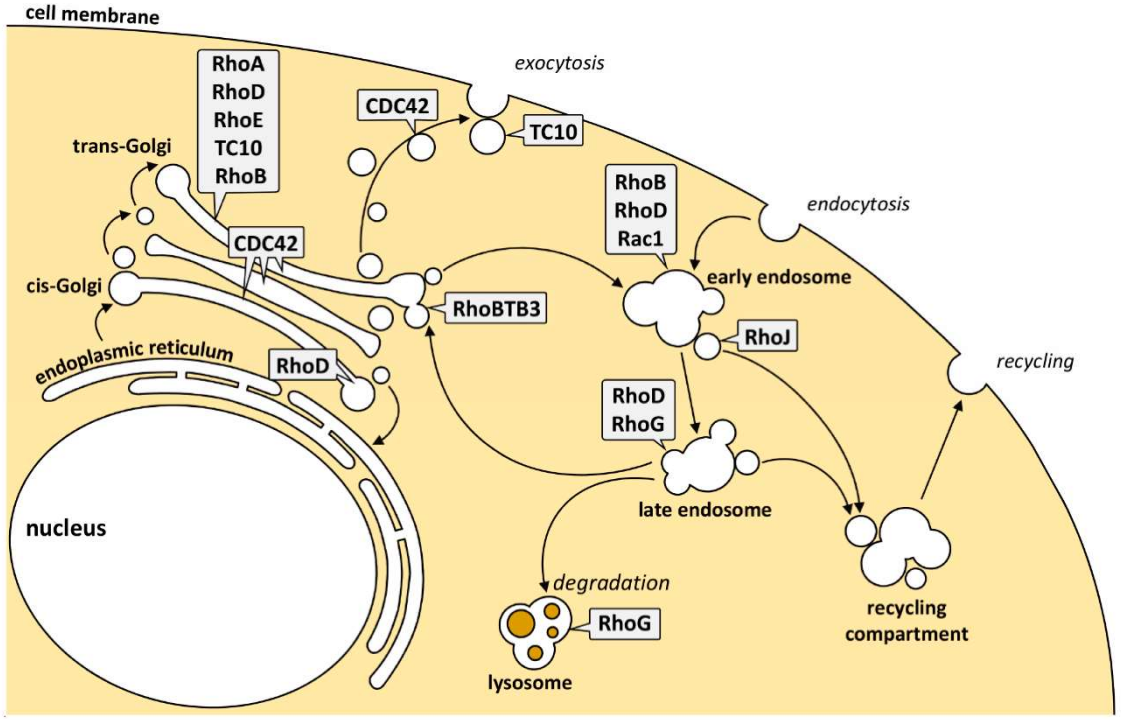


AR *RHOG* deficiency , HLH

RhoG regulates gene expression and the actin cytoskeleton in lymphocytes

Patients with HLH manifestations with biallelic mutations in *RHOG* gene that caused abnormalities of cytotoxic vesicles for the membrane docking

RhoG has a role for the Munc13-4 docking at cellular membrane



RhoG (Ras homology Growth-related) (or ARGH) is a small (~21 kDa) monomeric GTP-binding protein (G protein), and is an important component of many intracellular signalling pathways.

XL *TLR8* GOF (mosaic)

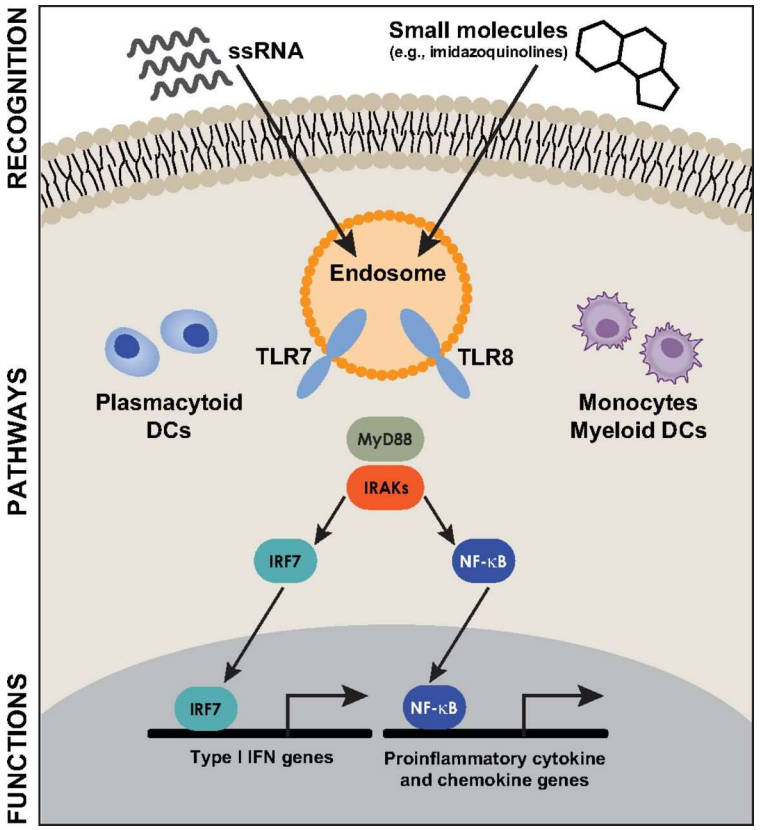
- 6 male patients with hyper inflammation, infections, syndrome Lympho-Proliferatif
- Hemizygous mutations in *TLR8* gene: P432L, F494L in 30% of cells = Mosaicism

Neutropenia, B cell defect

↑CD8 and T_{Temra}, exhausted cells,

↓ B cells and ↓↓ B memory ;

Hypogammaglobulinemia, ↑pro-inflammatory cytokines



ESID 2024: Marseille

AD *TRAF3* (haploInf) lymphoïde hyperplasia: Hyperplasia tonsilar, tongue

AD NLRP6 p.R653G: skin and liver inflammation with increased IL-1b , IL-18, NFKB activation

SHARPIN c.220dupC; p.L174PfsX86: Polyarthritis, colitis, hepatic glycogenolysis