



**HAL**  
open science

## Break down the barriers of auto-inflammation: how to deal with a monogenic auto-inflammatory disease and immuno-hematological features in 2022?

Hélène Vergneault, Capucine Picard, Sophie Georgin-lavialle

### ► To cite this version:

Hélène Vergneault, Capucine Picard, Sophie Georgin-lavialle. Break down the barriers of auto-inflammation: how to deal with a monogenic auto-inflammatory disease and immuno-hematological features in 2022?. Immunology, In press, 10.1111/imm.13579 . hal-03790002

**HAL Id: hal-03790002**

<https://hal.sorbonne-universite.fr/hal-03790002v1>

Submitted on 27 Sep 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

MERCK

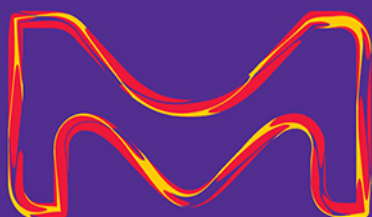
# SPEND LESS. DISCOVER MORE.

Get 50% off when you try  
ColorWheel® flow cytometry  
antibodies and dyes

Our innovative technology gives you the power to control your multicolor flow cytometry analysis with easy mix and match of any ColorWheel® antibody to any ColorWheel® dye, providing maximum flexibility.

Discover how ColorWheel® antibodies and dyes can streamline your flow cytometry workflow with this trial offer for a **50% discount on your first order.**

Get your offer at  
[SigmaAldrich.com/cwoffer](https://SigmaAldrich.com/cwoffer)



© 2022 Merck KGaA, Darmstadt, Germany and/or its affiliates. All Rights Reserved. Merck, the vibrant M, Sigma-Aldrich, and ColorWheel are trademarks of Merck KGaA, Darmstadt, Germany or its affiliates. All other trademarks are the property of their respective owners. Detailed information on trademarks is available via publicly accessible resources. 43578 08/2022



The Life Science  
business of Merck  
operates as  
MilliporeSigma in the  
U.S. and Canada.

**Sigma-Aldrich®**  
Lab & Production Materials

## **Break down the barriers of auto-inflammation: how to deal with a monogenic auto-inflammatory disease and immuno-hematological features in 2022?**

### **Authors**

Hélène Vergneault<sup>1</sup>, Capucine Picard<sup>2,3</sup>, Sophie Georgin-Lavialle<sup>1</sup>

### **Affiliations**

1. Sorbonne University, Internal Medicine Department, APHP, Tenon Hospital, Paris, France. National Reference Center for Autoinflammatory Diseases and Inflammatory Amyloidosis (CEREMAIA)
2. Study Center for Primary Immunodeficiencies, Necker Hospital for Sick Children, APHP, Université de Paris, Paris, France.
3. Laboratory of Lymphocyte Activation and Susceptibility to EBV, INSERM UMR1163, Imagine Institute, Necker Hospital for Sick Children, Université de Paris, Paris, France.

### **Corresponding author**

Dr Hélène Vergneault, MD

Sorbonne University, Department of Internal Medicine

Assistance Publique - Hôpitaux de Paris, Hôpital Tenon

4, rue de la Chine, 75020, Paris, France

Email: [helene.vglt@gmail.com](mailto:helene.vglt@gmail.com)

Co-authors e-mail : [sophie.georgin-lavialle@aphp.fr](mailto:sophie.georgin-lavialle@aphp.fr) ; [capucine.picard@aphp.fr](mailto:capucine.picard@aphp.fr)

**Abstract word count:** 179

**Manuscript word count:** 5375

**Reference number:** 73

**Data availability statement :** Data sharing is not applicable to this article as no new data were created or analyzed in this study

**Competing interests:** None

**Financial support:** None for this work

**Ethic approval and patient consent statement :** not applicable

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/imm.13579](https://doi.org/10.1111/imm.13579)

## Abstract

In the past few years, the spectrum of monogenic systemic auto-inflammatory diseases (MSAID) has widely expanded beyond the typical recurrent fever. Immuno-hematological features, as cytopenias, hypogammaglobulinemia, hypereosinophilia, lymphoproliferation and immunodeficiency, have been described in association of several MSAID. The objective of this review was to describe these particular MSAID.

MSAID must be suspected in front of immuno-hematological features associated with non-infectious recurrent fever, chronic systemic inflammation, inflammatory cutaneous manifestations, arthritis or inflammatory bowel disease. Genes and cellular mechanisms involved are various but some of them are of special interest. Defects in actine regulation pathway are notably associated with cytopenia and immune deficiency. Because of their frequency, ADA2 deficiency and Vacuoles, E1-Enzyme, X-linked, auto-inflammatory, Somatic (VEXAS) syndrome deserves to be noticed. ADA2 deficiency results in polyarteritis nodosa-like presentation with a wide panel of manifestations including cytopenia(s), lymphoproliferation and immune deficiency. Neutrophilic dermatosis or chondritis associated with macrocytic anemia or myelodysplasia should lead to screen for VEXAS. Of note, most of MSAID are associated with inflammatory anemia.

We proposed here a clinical and pragmatic approach of MSAID associated with immuno-hematological features.

**Keywords:** autoinflammation, anemia, thrombocytopenia, hypogammaglobulinemia, immunodeficiency, VEXAS.

## Introduction

Monogenic systemic auto-inflammatory diseases (MSAID) are a distinct group of diseases caused by errors of the innate inflammatory response. They are classically associated with abnormal systemic inflammation in the absence of infection or auto-immunity. Since the identification of *MEFV* mutation responsible for Familial Mediterranean Fever (FMF) and the further description of the other historic periodic fevers due to mutation of *TNFRSF1A* (Tumor necrosis factor-Receptor-Associated Periodic Syndrome), *MVK* (mevalonate kinase deficiency) and *NLRP3* (cryopyrinopathy), the spectrum of MSAID has broadened with actually 50 or more genes involved. Main pathophysiological pathways affect respectively inflammasomes, downstream TNFR1 pathway, reticulum endoplasmic stress, interferon pathway, actin polymerization regulation or the production of endogenous interleukin antagonists.

MSAID are usually suspected in front of recurrent attack of fever or chronic systemic inflammation associated with cutaneous manifestations (urticaria, aseptic abscess, aphthous), arthritis or inflammatory bowel disease (IBD). However, the diagnosis of MSAID can also be made in the presence of other manifestations such as cytopenia and lymphoproliferation. The dichotomous view of innate immunity defects classifying on the one side MSAID and on the other primary immune deficiency (PID), has been shattered by recent identification of defective regulation of cellular pathways leading to autoinflammation and susceptibility to infections and/or hypogammaglobulinemia. In clinical practice, the hypothesis of MSAID is first evoked by integrating a set of elements including the presence of an inflammatory syndrome, the age and a familial context suggesting a genetic transmission. In a second time, the presence of specific clinical or biological features drives the diagnosis towards a specific disease.

Our objective was to review MSAID associated with immuno-hematological features and to propose a pragmatic and clinical approach for clinicians.

## Materials and methods

A literature review was performed to identify MSAID associated with immuno-hematological features. We focused on hemogram abnormalities including cytopenias and hypereosinophilia, lymphoproliferation, hypogammaglobulinemia and immunodeficiency. The database Medline (Pubmed) was screened by 3 investigators from 1997 to 2021. The search involved the terms « autoinflammation », « inborn errors of immunity », « cytopenia », « anemia », « thrombopenia », « neutropenia », « hypereosinophilia », « hemophagocytosis lymphohistiocytosis », « hypogammaglobulinemia », « antibody deficiency », « immuno deficiency ». After a screening of 220 references, 37 MSAID were identified. Their description was based on the following features cytopenias (anemia, thrombopenia, neutropenia, hemophagocytosis lymphohistiocytosis), hypereosinophilia, hypogammaglobulinemia, primary immunodeficiency (Table 1).

## Results

### 1-Cytopenias

#### 1) Anemia

Anemia is a frequent cytopenia associated with MSAID. It is necessary to specify the characteristics of this anemia to orient the diagnosis (Figure 1).

Microcytic anemia is the most frequent. It can occur in any MSAID because of the systemic inflammation.

Microcytic anemia, due to congenital dyserythropoiesis, associated with chronic recurrent multifocal osteomyelitis and recurrent fever occurring in the first years of life is highly evocative of Majeed syndrome, which include neutrophilic dermatosis in less than 25% of cases (1). Majeed syndrome is due to homozygous LOF mutations in *LPIN2* which encodes LIPIN2 (2). This phosphatidic acid phosphatase is implicated in triglyceride synthesis and probably in inflammation through its interaction with NLRP3 inflammasome (3).

Microcytic anemia is especially frequent in the course of **TANK binding kinase 1 (*TBK1*)** deficiency characterized by fever, polyarthritis beginning in the first year of life, cutaneous vasculitis and seizures (4). *TBK1* homozygous loss of function (LOF) mutation has been described in four patients from three unrelated families. *TBK1* is a crucial regulator of *RIPK1* (Figure 2). It steers TNF receptor engagement through phosphorylation of *RIPK1* and inhibition of the deubiquitinase *CYDL*. In absence of *TBK1*, *RIPK1* can dissociates from *TNFR1* and induces cell-death trough caspase 8 and *RIPK3* pathways.

In context of auto-inflammation, macrocytic anemia is highly suggestive of **Vacuoles, E1-Enzyme, X-linked, auto-inflammatory, Somatic (VEXAS) syndrome**. VEXAS syndrome is a late-onset inflammatory syndrome described for the first time in 2020; it affects mostly males

and is characterized by recurrent fever, asthenia, cutaneous features such as neutrophilic dermatosis or cutaneous vasculitis, chondritis and pulmonary infiltration in a context of chronic peripheral inflammation (5). Patients display macrocytic anemia with lipid vacuoles in bone marrow and between 26 and 50 % of patients have myelodysplasia (6,7). VEXAS syndrome is associated with somatic mutations in *UBA1* lying on the X chromosome and encoding the ubiquitin-activating enzyme-1 (6). *UBA1* is expressed in hematopoietic stem cells and myeloid lineage cells; most mutations are in exon 3 and promote the production of an impaired isoform of UBA1. This leads to the reduction of cytoplasmic UBA1 function and therefore to the decrease of ubiquitylation and innate immune pathways activation.

Sideroblastic anemia is characteristic of **SIFD syndrome: Sideroblastic anemia, Immunodeficiency, Fever, Developmental delay**. Manifestations of SIFD occur in two-third of cases in neonatal period generally by non-infectious periodic attacks of fever with elevated inflammatory markers (8), vomiting and diarrhea, oral ulcers, skin cellulitis, arthralgia or arthritis (9). Patients suffered from congenital sideroblastic anemia and immune deficiency manifested by sinopulmonary bacterial infections secondary to B-cell lymphopenia and hypogammagobulinemia (8). Affected children also display development delay characterized by impaired motricity, comprehension and communication. Other neurological manifestations may occur as seizure, cerebellar ataxia, cerebral atrophy on neuroimaging, sensorineural hearing loss. Exact physiopathology of SFID remains to be clarified. It is caused by bi-allelic LOF mutations in *TRNT1* which encodes the CCA-adding enzyme, an essential molecule for tRNAs maturation. TRNT1 deficiency is responsible for impaired maturation of mitochondrial and cytosolic tRNAs (9) and increased reactive oxygen species production leading to enhanced IL-1 $\beta$  secretion.



Haemolytic anemia secondary to paroxysmal nocturnal hemoglobinuria with neutrophilic urticaria, arthralgia, fever and aseptic meningitis has been described in four patients with **mutations of *PIGT*** which encodes a GPI-anchor. Its results from biallelic mutation including a germline heterozygous mutation and a somatic mutation occurring in hematopoietic stem cells, leading to the expression on cell surface of a defective GPI-anchor which is enabled to interact with proteins (10). Free GPI is responsible of increased IL-1 $\beta$  secretion, activation of the lectin pathway of complement and generation of C5b-9 complexes.

## 2) Thrombocytopenia

Thrombocytopenia was found to be associated with a subgroup of MSAID called actinopathies where mutations in genes involved in actin polymerization regulation were detected. The complete clinical picture of the following two MSAID includes immune deficiency:

- **Periodic Fever with Immunodeficiency and Thrombocytopenia (PFIT)** is characterized by periodic fever attacks arising from the first week of life and lasting 3 to 7 days with increased inflammatory markers. Recurrent oral inflammation and recurrent perianal ulcerations are associated as well as recurrent severe bacterial infections due to impaired neutrophil function (11). Half patients display thrombocytopenia. PFIT is caused by homozygous mutation in *WDR1* which encodes a protein promoting the disassembly of actin filaments. This was found to induce increased caspase-1 cleavage and excessive IL-18 production by monocytes (12).

-The association of autoinflammation and thrombopenia to atopy, lymphadenopathy and combined immune deficiency can evoke mutation in *ARPC1B* gene (13). Clinical manifestations appear in the first months of life. Patients are stunted and present extensive eczema and allergies, skin vasculitis, hemorrhagic colitis and less frequently arthritis. Patients present recurrent respiratory tract infections and skin infections including bacterial infections,

molluscum and warts. Thrombocytopenia is characterized by microthrombocytes with dense granule deficiency and is responsible of gastric hemorrhage (14). T-cells are low, and levels of immunoglobulin E (IgE) and IgA are increased. Hemophagocytotic lymphohistiocytosis (HLH) has been reported (13). ARPC1B is a hematological linear cells isoform of ARPC1, a component of actin-related protein 2/3 complex (Arp2/3) which plays a key role for actin polymerization (13,14). ARPC1B deficiency due to homozygous LOF mutation is responsible for impaired cytoskeleton rearrangement leading to alteration of chemotaxis, endocytosis and immunological synapse formation in neutrophils, NK-cells and Treg.

Thrombocytopenia was also described in one third patients suffering from CANDLE-like syndrome due to **LRBA deficiency** and **IKBK~~G~~-deleted exon 5 auto-inflammatory syndrome**, we will detailed further (15).

Early-onset immune thrombocytopenia, sometimes as part of Evans syndrome or accompanied by lymphoproliferative manifestations, can be due to **SOCS1 haploinsufficiency** (16). The protein SOCS1 is a downregulator of the JAK-STAT pathway. SOCS1 haploinsufficiency leads to cytokine hypersensitivity of monocytes, T- and B-cells which is responsible of auto-immune manifestations as auto-immune cytopenias or systemic lupus erythematosus (16).

### 3) Neutropenia

The association of neutropenia and inflammatory manifestations is suggestive of **Glucose-6-phosphatase (G6PC3) deficiency**. This heterogeneous syndrome associates congenital neutropenia with cardiac and urogenital developmental defects. In some cases, it associates with inflammatory bowel disease presenting as Crohn-like disease but without granuloma on biopsy (17). G6PC3 is an ubiquitous enzyme that regulates cytoplasmic glucose availability through

hydrolysis of glucose-6-phosphate during glycolysis and glycogenolysis. Neutrophils deficient in G6PC3, due to bi-allelic LOF mutations, display higher levels of activation markers, excessive IL-8 and reactive oxygen species, and increased apoptosis (18).

#### 4) Pancytopenia and hemophagocytic lymphohistiocytosis (HLH)

Pancytopenia in context of susceptibility to HLH occurs in three MSAID: somatic mutations of *NLR4*, X-linked lymphoproliferative syndrome type 2 (*XIAP* gene) and NOCARH syndrome (*CDC42* gene).

- ***NLR4* mutations** cause a constitutive activation of NLR4 inflammasome leading to enhanced production of cytokines IL-1 $\beta$  and IL-18. Heterozygous gain of function (GOF) mutations of *NLR4* are associated with two phenotype (19). Familial mutations manifest by familial cold urticaria associated with recurrent fever in only half of cases. Sporadic mutations are responsible of severe disease occurring earlier, in first months of life, with recurrent fever, severe inflammatory bowel disease, pulmonary or neurological involvement in some cases and HLH (20).

-**X-linked lymphoproliferative syndrome type 2 (XLP2)** due to ***XIAP* deficiency** is a X-linked disorder characterized by pediatric-onset Crohn-like inflammatory bowel disease, recurrent splenomegaly and susceptibility to develop HLH frequently triggered by Epstein Barr virus (EBV)(21,22). There is individual variability: in a same family, dominant phenotype (IBD, lymphoproliferation, HLH) and severity differ from one individual to another. Some patients also display hypogammaglobulinemia or other inflammatory manifestations like

arthritis, cutaneous abscesses, erythema nodosum, uveitis and nephritis. XLP2 is caused by mutation in *XIAP* gene located on X chromosome (21). XIAP is an ubiquitous anti-apoptotic protein. Through its ubiquitinase activity, it is also involved in many intra-cellular pathways including activation of NF- $\kappa$ B and MAP-kinases pathways. XIAP plays a role in innate and adaptative immunity. It participates in signaling pathway of the pattern recognition receptor NOD2 and inhibits caspase in activated T lymphocytes promoting their survival. XIAP-deficiency leads to pathogen clearance defect, uncontrolled activation of inflammasomes accumulation of the pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$  and IL-18.

-Neonatal Onset of Cytopenia, Autoinflammation, Rash, and HLH define **NOCARH syndrome**. From the first day of life, patients present recurrent fever associated with chronically elevated inflammatory markers, psoriasiform skin rash, pancytopenia, hepatomegaly with frequent cytolysis, splenomegaly and predisposition to hemophagocytic lymphohistiocytosis (23,24). All patient display failure to thrive and some of them display facial dysmorphism (24). NOCARH syndrome was described associated to *CDC42* heterozygous mutation which belongs to Rho GTPase family and regulates multiple intracellular signaling pathways including polarization and migration of the cell via actin filaments, cytoskeleton architecture, endocytosis and progression through the cell cycle. It regulates actin polymerization by binding to Wiskott-Aldrich protein (WASp), which subsequently activates Arp2/3 complex. De novo heterozygous mutation in the C-terminal region of CDC42 is responsible for impaired active/inactive cycling of Cdc42 leading to defects in actin polymerization and hyperactivating of NF- $\kappa$ B signaling (25). IL-1b and anti-IL18 production are increased as well as INF $\gamma$  (23).

Accepted Article

A pancytopenia in context of arthritis and skin inflammation including pyoderma gangrenosum and other ulcerative lesion, pustular lesion, abscesses and acne suggest **PAMI syndrome** (*PSTPIP1*-associated myeloid-related-proteinemia inflammatory syndrome) also known as hypercalprotectinemia and hyperzincemia syndrome (26). PAMI syndrome is characterized by chronic inflammatory syndrome and high levels of calprotectinemia and zincemia. Anemia and neutropenia are almost systematically present while thrombocytopenia occurs in half of cases (26). Hepatosplenomegaly and less frequently lymphadenopathy are associated. PAMI syndrome is caused by a heterozygous mutation of *PSTPIP1* distinct from those responsible of PAPA (pyogenic arthritis, pyoderma gangrenosum, acne) syndrome (27). *PSTPIP1* encodes a cytoskeleton-associated adaptor protein implicated in cytoskeletal organization and T-cell activation. p.E250K and p.E257K mutants are associated with an enhanced binding to pyrin and increased levels of calprotectin which is composed by the two alarmin MRP8 and MRP14.

Unexplained cytopenia(s) can also be a way to evoke a **deficiency in adenosine deaminase 2 (ADA2)** which we will describe below. Anemia and thrombocytopenia occur in respectively 13 to 45% and 6 to 10% of cases (28,29). Bone marrow failure with neutropenia or pancytopenia as well as pure red cell aplasia have been reported (30,31).

##### 5) Myelodysplastic syndrome

Myelodysplastic syndrome (MDS) associated with chronic inflammatory syndrome, Sweet syndrome or relapsing polychondritis in a patient over 60 years old should lead to investigate *UBA1* mutation responsible for **VEXAS syndrome**.

Pediatric onset MDS with atypical CANDLE syndrome combining neutrophilic panniculitis with interstitial lung disease, basal ganglion calcification and B-cell lymphopenia can reveal **SAMD9L associated autoinflammatory disease (SAAD)**. *SAMD9L* mutations are usually

associated to familial and pediatric MDS and to ataxia pancytopenia syndrome (32,33). Rare variants producing a truncated-SAMD9L are responsible for a broadened syndrome including autoinflammation (15,34).

## **2-Hypogammaglobulinemia**

Serum protein electrophoresis is a simple and cost-effective test to guide the clinician. Some MSAID combine auto-inflammation and common variable immunodeficiency (CVID)-like with recurrent infections of respiratory tract and hypogammaglobulinemia (Table 2). They are distinguished by their type of auto-inflammatory presentation (Figure 3).

Aphthosis and Behçet-like vasculitis are suggestive of defect in the pathway of the transcription factor NF- $\kappa$ B which plays an important role in immune and inflammatory responses (Figure 2).

*NFKB1* heterozygous mutations are a frequent cause of CVID (35,36). Some mutations also induce autoinflammatory features (37). Phenotype differs from one patient to another depending on the causal mutation. Small vessel vasculitis with a variable association of arthritis, mucosal aphthous lesions, gut disease and fever flares are caused by p.H67R substitution whereas life-threatening postoperative hyperinflammatory reactions are associated with p.R157X variant. *NFKB1* encodes the protein p105 which is the precursor of the subunit p50 of NF- $\kappa$ B. LOF *NFKB1* mutations lead to p50 haploinsufficiency and subsequent NF- $\kappa$ B defect.

**A20 haploinsufficiency (HA20)** presents with early-onset Behçet-like disease characterized by recurrent fever and bipolar aphthosis in about 90% of cases, arthritis, folliculitis or axillary

abscess, ulcerative colitis and ocular inflammation. In rare cases, patients present recurrent infections due to hypogammaglobulinemia or even combined immunodeficiency (38,39). HA20 is caused by heterozygous LOF mutation of *TNFAIP3* which encodes the protein A20, a crucial inhibitor of the NF- $\kappa$ B pathway (Figure 2). Defective ubiquitinase and deubiquitinase activities of truncated A20 proteins leads to increased expression of NF- $\kappa$ B-mediated proinflammatory cytokines (40).

Bullous cutaneous lesions are suggestive of **APLAID syndrome** (auto-inflammation and PLC $\gamma$ 2-associated antibody deficiency and immune dysregulation) mutation described in a father and his daughter who developed in childhood an epidermolysis-bullosa-like eruption and recurrent blistering lesions which over time become sensitive to heat and sun exposure. They also presented non-specific interstitial pneumonitis with respiratory bronchiolitis, arthralgia, eye inflammation and enterocolitis. Biological inflammatory markers were increased (41). They both experienced recurrent sino-pulmonary infections associated with low serum levels of IgM and IgA immunoglobulins and low circulating switched memory B-cells. PLC $\gamma$ 2 is a phospholipase mainly expressed in hematopoietic cells and playing a key role in the regulation of immune response. Its activity is autoregulated by the SH2 domain inhibitor. APLAID syndrome is caused by heterozygous mutation in SH2 domain leading to enhanced PLC $\gamma$ 2 activity (41). Patients with PLAID syndrome (PLC $\gamma$ 2-associated antibody deficiency and immune dysregulation), caused by genomic large deletions in SH2 domain, have cold urticaria, infections, auto-immunity, allergies and hypogammaglobulinemia. Contrary to PLAID syndrome, patients with APLAID did not experience cold urticaria and were negative for auto-antibodies.

PAN (polyarteritis nodosa)-like presentation characterize **ADA2-deficient patients** which present a vasculitis of small- and medium-vessels with a peculiar early-onset, mostly before the age of ten. Cutaneous manifestations are the most frequent and consist in livedoid reticularis/racemosa rash and ulceration. About half of patients experience neurologic manifestations mainly haemorrhagic or ischaemic stroke (31). Digestive, liver, renal and coronary involvement are possible. Hypogammaglobulinemia occurs in 22% of cases and can be responsible of recurrent bacterial infections (28,29). Susceptibility to herpetic infections is also increased. Immunodeficiency due to B-cells deficiency is not so uncommon and can be in the foreground (42). As stipulate above, cytopenia(s) and lymphoproliferation are also common features of ADA2 deficiency (31). The exact pathogenesis of ADA2 is not fully established. It results from bi-allelic LOF *ADA2* mutations. Lack of ADA2 leads to chronic increased extracellular levels of adenosine. This promotes differentiation of monocytes toward proinflammatory M1 macrophages (43) and enhances NET (neutrophil extracellular traps) formation (44) leading to macrophage activation and secretion of anti-TNF $\alpha$ . In addition to its deaminase activity, ADA2 may have a growth factor activity especially in hematopoiesis which could explain hematological and immunological manifestations of ADA2-deficient patients (45).

A CANDLE-like (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature ) presentation resistant to JAK inhibitor can be associated with impairment of INF-signaling (15). The association to ectodermal dysplasia suggests a splice site variants of *IKBKG* causing **NEMO-Deleted exon 5 autoinflammatory syndrome (NEMO-NDAS)** (46) . The association to interstitial lung disease, hepatosplenomegaly with granulomatous hepatitis suggests **LRBA** (LPS-responsive beige-like anchor protein) **deficiency**. These both conditions are characterized by INF-signature. Patients present hypogammaglobulinemia due to



progressive B-cells lymphopenia without evidence of susceptibility infection and thrombocytopenia occurred in one third of patients (15).

Recurrent fever with skin rash, pulmonary alveolar proteinosis, inflammatory bowel disease, and susceptibility to viral respiratory infections evokes **OAI5 GOF heterozygous mutations** (47). Patients display hypogammaglobulinemia and low B-cells count during flares.

Chron-like colitis associated with skin rash and erosive arthritis is caused by **SYK mutation** (48). Most of the 6 patients display recurrent bacterial infections due to antibody deficiency but some also present low CD4+ T-cells. Susceptibility to B-cells lymphoma has also been reported in two patients (48). SYK is a tyrosine kinase involved in downstream signaling of immune - receptors like T- and B-cells receptors or Toll-like receptors. Heterozygous GOF mutation leads to constitutive activation of SYK and consequent enhanced response to immunoreceptor engagement. The SYK variants increased phosphorylation and enhanced downstream signaling.

The combination of immune deficiency due to hypogammaglobulinemia, sideroblastic anemia and developmental delay is suggestive of **SIFD** (8).

In **XLP-2**, hypogammaglobulinemia is associated with IBD and/or HLH.

Hypogammaglobulinemia can also occur in mutations of **HOIP, HOIL1** and **PSMB9** described in other sections.

### **3-Hypereosinophilia**

Hypereosinophilia is a marker of a particular recurrent fever due to **homozygous Serine-208 mutations in MEFV** (49). Oral ulcers, hepatosplenomegaly and lymphadenopathy with

eosinophils infiltrates as well as recurrent purpuric lesions due to leucocytoclastic vasculitis are associated. p.S208T mutation in exon 2 of *MEVF* is distinct of those responsible for FMF. It leads to constitutive pyrin inflammasome activation and increased levels of C-C-motif chemokine ligand 5 (*CCL5*) (49).

Hypereosinophilia can also be associated with other autoinflammatory diseases.

- Recurrent fever with urticaria are suggestive of cryopyrinopathy (CAPS). Hypereosinophilia occurs in **Muckle-Wells syndrome**, distinguished by hearing loss, and especially in **neonatal-onset multisystem inflammatory disease (CINCA/NOMID)**, characterized by supplemental neurological involvement and arthropathy (50,51). These are associated with heterozygous *NLRP3* GOF mutations.

- Juvenile sarcoidosis can evocate **Blau syndrome** which is characterized by polyarthritis with granuloma, uveitis and skin rashes beginning in the early childhood due to heterozygous *NOD2* mutation which impairs CARD15 binding causing a deregulated activity of caspase 1 with excessive IL-1 production (51).

#### **4-Lymphoproliferation**

Lymphoproliferation, consisting in lymphadenopathy and/or hepatosplenomegaly is a common feature of certain MSAID. The occurrence of recurrent fever and a neonatal onset make the clinician suspect auto-inflammatory disease.

Lymphadenopathies associated with recurrent fever beginning in the first year of life are evocative of **Mevalonate kinase Deficiency (MKD)** or **cleavage-resistant RIPK1-induced autoinflammatory (CRIA) syndrome**.

-In **MKD**, attacks begin in early childhood with recurrent fevers and predominant digestive features. Lymphoproliferation consist mainly in painful cervical lymphadenopathies with hepatosplenomegaly in some cases. During attacks, patients may also display aphthous, abdominal pain and diarrhea, arthralgia, skin rash or headaches. MKD is caused by homozygous LOF mutation in *MVK* encoding mevalonate kinase, a protein involved cholesterol production pathway. Its deficiency leads to mevalonic acid accumulation.

In **CRIA syndrome**, fever attacks usually last several days and occur every 2-4 week. Lymphoproliferation consist mainly in intermittent diffuse lymphadenopathy with splenomegaly or tonsilitis in some cases. During attacks, patients may also display abdominal pain but arthritis and cutaneous rash are absent. CRIA syndrome is also characterized by chronic increased levels of inflammatory markers. RIPK1 is a key determinant of cell response to TNF stimulation. Its ubiquitination status shifts the cell towards either a pro-survival inflammatory pathway via NF- $\kappa$ B activation, or cell death pathway via activation of caspase-8-dependent apoptosis or RIPK3/MLKL-dependent necroptosis (52). Heterozygous mutation of a key aspartate, described in 12 patients, residue prevents caspase-6/8 cleavage of RIPK1 and sensitizes cells to TNF-induced cell death (53). Of note, the phenotype is milder than RIPK1 deficiency described below as no vital organ are involved and tocilizumab provide markedly improvement.

Aseptic fistulizing adenitis and hepatosplenomegaly with systemic inflammation and intracranial calcifications have been described in three infant carrying a **GOF variant of *STAT2* gene** (54,55). STAT2 is a transcription factor belonging to IFN $\alpha/\beta$  pathway. This *STAT2*<sup>R148W</sup> variant was associated with elevated responses to IFN $\alpha/\beta$  and prolonged JAK-STAT signaling (54).

Some MSAID combine lymphoproliferative features to immunodeficiency.

Accepted Article

Recurrent fever with splenomegaly, infections and amylopectinosis characterize mutations of Linear ubiquitin chain assembly (LUBAC) complex composed of three proteins (Figure 2): HOIP (HOIL1 interacting protein), HOIL1 (Heme-Oxidized IRP2 Ubiquitin Ligase 1) and SHARPIN (SHANK interacting protein 1). LUBAC conjugates linear ubiquitin chains on NEMO to stabilize its recruitment to cytokine receptor (TNFR and IL1R). Consequences of LUBAC deficiency differed between cell types. It leads to impaired NF- $\kappa$ B dependent response to TNF $\alpha$  and IL-1 $\beta$  in fibroblast and B cells whereas in mononuclear leukocytes, it induces constitutive increased production of pro-inflammatory cytokines and enhance response to IL-1 $\beta$ .

Homozygous mutations of *RBCK1* encoding HOIL1 and of *RNF31* encoding HOIP have been described in respectively 3 patients (56) and 2 patients (57,58). In both situations, patients displayed recurrent fever attacks from the first year of life with persistent increase of biological inflammatory markers between flares.

**HOIL1 deficiency** is characterized by recurrent fever episodes with lymphadenopathies and hepatosplenomegaly with early onset and in some patients IBD with bloody and mucus stools, humoral deficiency with low switch memories B cells responsible of invasive and severe bacterial infections and symptomatic cardiomyopathy after the age of 4 years caused by muscle amylopectinosis deposits.

Patients with **HOIP deficiency** presented diarrhea, oral ulcers and persistent splenomegaly without lymphadenopathy. The first patient presented combined immunodeficiency with T cell lymphopenia, switch-memories B cells deficiency and hypogammaglobulinemia. The second patient displayed recurrent bacterial, viral and fungal infections without hypogammaglobulinemia nor lymphopenia but lacked response to pneumococcal antigens upon vaccination with polysaccharides non-conjugate pneumococcal vaccine. Systemic lymphangiectasia and subclinical amylopectinosis were associated.

Lymphoproliferative manifestations are also important features of **deficiency in ADA2** previously detailed. Patients may present splenomegaly (up to 30%) or lymphadenopathy (28). Autoimmune lymphoproliferative syndrome (ALPS)–like phenotype (59), T cell large granular lymphocytic (LGL) proliferation (60) and EBV-driven lymphoproliferation (61) have also been reported.

Lymphoproliferative manifestation including hepatosplenomegaly and lymphadenopathy in context of auto-immune features can be due to **SOCS1 haploinsufficiency** (16).

Lymphoproliferation with pancytopenia accompanying arthritis and inflammatory skin manifestations as pyoderma gangrenosum, pustular lesion or abscesses suggest **PAMI syndrome** described above (*PSTPIP1* mutations) (26).

Splenomegaly occurs frequently in conditions providing susceptibility to HLH. Associated symptoms of IBD are suggestive of **XIAP mutations** whereas recurrent fever and psoriatic lesions suggest **NOCARH syndrome**.

Of note, persistent splenomegaly with or without hepatomegaly in a patient of Mediterranean origin who present recurrent attack of fever and abdominal pain can revealed **Familial Mediterranean Fever** which is associated with *MEVF* exon 10 mutations. Splenomegaly occurs up to more than 50% of patients with FMF (62). It is more frequent in children and during attacks but can persist out of attacks especially in case of uncontrolled disease and even in absence of AA amyloidosis. <sup>p.S208T</sup> *MEVF* mutation are also associated hepatosplenomegaly as well as lymphadenopathies due to eosinophils infiltration (49).

## **6-Combined immunodeficiency**

Combined immunodeficiency (CID) is defined by impairment of humoral and cellular immunity, responsible of bacterial, viral, fungal, and opportunistic infections susceptibility. This syndrome covers a wide spectrum of genetic diseases including MSAID which may be suspected before digestive or dermatological inflammatory symptoms (Table 2).

Combined immune deficiency associated with neonatal-onset IBD is suggestive of **RIPK1 deficiency**. Some patients also present aphthous lesion and/or polyarthritis. RIPK1 is a key determinant of cell response to TNF stimulation (Figure 2). Its ubiquitination status shifts the cell towards either a pro-survival inflammatory pathway via NF- $\kappa$ B activation, or cell death pathway via activation of caspase-8-dependent apoptosis or RIPK3/MLKL-dependent necroptosis (52). RIPK1 deficiency, due to homozygous *RIPK1* LOF mutation, leads to reduced NF- $\kappa$ B activity, increased NLRP3 inflammasome activity and impaired T-cell and B-cell development. The prognosis is poor with high mortality rate.

Other even more rare defects of NF- $\kappa$ B pathway associated autoinflammation and combined immune deficiency: **mutations of HOIP**, characterized by recurrent fever with oral ulcers, diarrhea and splenomegaly (57), and GOF **mutation of *IKBKB*** characterized by ectodermal dysplasia and suppurative hidradenitis (63). This mutation of *IKBKB*, encoding IKK2, has been described in four patients from two kindreds. Its lead to enhanced NF- $\kappa$ B signaling as well as T and B cell functional defects (64).

Neutrophilic dermatosis and auto-immunity have been described in ***POMP-Related Autoinflammation and Immune Dysregulation (PRAID)*** (65). POMP deficiency is characterized by papulo-erythematous skin lesions on face, trunk and extremities and progressing to necrotizing lesion then scarring without lipodystrophy. Auto-immunity features consist in presence of anti-nuclear antibodies, anti-b2-glycoprotein and anti-thyroid.

Proteasome maturation protein (POMP) is a chaperone essential for the assembly of standard proteasome and immunoproteasome. The synthesis of a truncated protein due to heterozygous mutation of POMP has been reported in two unrelated patients. It results in impaired proteasome assembly, enhanced endoplasmic reticulum stress and increased expression of type-1-IFN-induced genes.

Fever, skin rash, myositis, and basal ganglia calcification is evocative of another particular proteasome-associated autoinflammatory syndrome (PRAAS) due to ***PSMB9* mutation** (66). Other manifestations include liver dysfunction and pulmonary arterial hypertension but not lipotrophy contrary to CANDLE syndrome caused by *PSMB8* mutation (66). This PRAAS with immune deficiency has been described in 2 newborns who displayed susceptibility to viral infection especially BK and JC virus. One presented hypogammaglobulinemia with B- and T-cells deficiency meanwhile the other presented T- and NK-cells deficiency. *PSMB9* encodes for  $\beta 1i$  subunit of immunoproteasome. Heterozygous mutation leads to 26S proteasome defect.

The combination of thrombopenia, lymphadenopathy, skin and digestive autoinflammatory manifestations and atopy associated to combined immunodeficiency occurs in **mutation of *ARPC1B*** describe above.

## **7-Other primary immunodeficiencies**

### 1) Interferon- $\gamma$ impairment

Interferon- $\gamma$  impairment results in susceptibility to mycobacterial infections.

Mycobacterial infection associated with calcification of cerebral basal ganglia during childhood and necrotic skin ulcers are characteristic of **Interferon-stimulated gene 15 (*ISG15*) deficiency** (67). *ISG15* encodes an INF inducible ubiquitine-like protein acting by its

conjugation to a target protein (ISGylation). ISG15 deficiency, caused by bi-allelic LOF mutations of *ISG15* gene, leads to impaired USP18 stabilization and subsequent loss of negative regulation of INF- $\alpha/\beta$  explaining auto-inflammatory manifestations. The lack of free extracellular ISG15 resulted in lower IFN- $\gamma$  production by lymphocyte conferring susceptibility to mycobacterial infection.

Mycobacterial infection associated with anhidrotic ectodermal dysplasia (EDA) and inflammatory liver damage mediated by neutrophils has been described in one patient carrying an **heterozygous *NFKB1A* missense GOF mutation** (68). This gene encodes I $\kappa$ B $\alpha$  which is one of the inhibitors of NF- $\kappa$ B (Figure 2). Mutations of *NFKB1A* are associated to EDA with immunodeficiency. L34P I $\kappa$ B $\alpha$  variant lead to impaired NF- $\kappa$ B activation in fibroblasts and macrophages but paradoxical hyperproduction of IL-1 $\beta$  (69).

## 2) Neutrophils impairment

Combination of recurrent fever and PID due to neutrophils impairment has been described in **PFIT syndrome**, described above, and in ***CEBPE* associated autoinflammation and immune impairment of neutrophils (CAIN) syndrome**.

In **PFIT syndrome**, fever attacks arise from the first week of life and last 3 to 7 days and neutrophils impairment results in recurrent severe bacterial infections (11). Other features include recurrent oral inflammation, recurrent perianal ulcerations and thrombopenia.

In **CAIN syndrome**, fever attacks arise in the puberty, last 4 to 5 days and are associated with abdominal pains. Neutrophils impairment results neutrophils hypossegmentation, recurrent nails, tongue, submandibular and gluteal abscesses, purulent wounds with delayed healing, paronychia complicated by lymphangitis and pulmonary infection. Other features include ulcers of buccal mucosal, intra-abdominal granuloma and pyoderma gangrenosum as well as moderate bleeding diathesis with epistaxis and a tendency toward hematomas without thrombocytopenia.



CAIN has been identified in a family whose 3 members carried homozygous germline mutations of *CEBPE* encoding the transcription factor CCAAT-enhancer-binding protein epsilon (C/EBPε)(70). C/EBPε is involved in terminal differentiation of neutrophils and expression of specific granule genes. The Arg219His mutation in the DNA-binding domain is responsible of decreased C/EBPε association with transcriptional repressor and increased chromatin binding leading to dysregulated transcription. It results in neutrophil dysfunction, alteration of interferon pathways and aberrant activation of noncanonical caspase-4/5 inflammasome. Heterozygous carriers present also widely dysregulated transcription, but homozygous mutations are required for clinical manifestations.

### 3) Type I interferon response impairment

Recurrent viral bronchitis in a context of recurrent fever, skin rash, inflammatory bowel disease, pulmonary alveolar proteinosis and hypogammaglobulinemia are caused by heterozygous ***OAS1* GOF mutation** (47). *OAS1* encodes oligoadenylate synthetase 1 which is a type 1 INF-inducible enzyme implicated in the antiviral immune response through the activation of ribonuclease L (RNase-L). GOF variants lead to inappropriate cellular RNA cleavage and therefore dysfunction and apoptosis of monocytes, macrophages and B cells.

## **Discussion**

Progress in genetic have allowed to expand the field of MSAID to cytopenias, lymphoproliferation and immune deficiency. Many MSAID have been identified through exome sequencing of patients suffering from PID with unknown genetic etiology. Most of them associate immune deficiency to cytopenias, especially thrombopenia, or to lymphoproliferation. Certain conditions offer a very florid picture of immuno-hematological feature like in ADA2

deficiency, one of the most common, which presents typically as vasculopathy but also with cytopenias, lymphoproliferation and/or humoral deficiency.

Genes and cellular mechanisms involved are various but two main pathophysiological pathways stand out: cytoskeletal abnormalities (*WDRI*, *ARPC1B* and *CDC42*), which all combine autoinflammation with cytopenia, and the defect of downstream TNFR1 pathway including RIPK1 and NF- $\kappa$ B pathway. Figure 4 summarizes main immuno-hematological features according to underlying mechanism. The type of mutation and its consequences for a same protein or the stage of the defect on a same pathway can result in different phenotypes. For example, homozygous *RIPK1* LOF mutation leads to immune deficiency whereas a peculiar heterozygous mutation leads to lymphoproliferation. *NFKB1A* GOF mutations have been associated with immunodeficiency and EDA, but the L34P I $\kappa$ B $\alpha$  variant provide additional autoinflammatory manifestations (68). Defect on pathway downstream TNFR1 provide various phenotype from exclusive autoinflammation in *OTULIN* deficiency to autoinflammation with susceptibility to infection in *RIPK1* deficiency, passing by a blended phenotype with autoinflammation, lymphoproliferation and immunodeficiency in LUBAC defect (71).

Suspect MSAID in front of hematological presentation or recurrent infections is challenging but some features may help. Recurrent fever and increased inflammatory markers without any infectious episode are the first sign that should arouse suspicion. The clinician can be guided by simple clinical signs as aphthosis or skin vasculitis which are atypical for a PID. The age and the family context are also essential aspects to considered. Most of MSAID we described are characterized by a very early-onset of inflammatory diseases like IBD, Behçet or vasculitis. Drawing family tree is here essential to identify the inheritance (recessive or dominant). In context of autoinflammation, blood count and hypogammaglobulinemia are basic features to orient the diagnosis.

This review is expected to evolve. Next generation sequencing (NGS) allowed to identified causative mutation of unexplained presentation in one family or even in one individual. Probably many other gene defects can be responsible for autoinflammation with immuno-hematological features and used wisely, whole-exome/genome sequencing will continue to help identify new MSAID. The comprehension of the pathophysiological pathways and the occurrence of hematological features set the stage for invasive therapeutic like HSCT whose effectiveness on auto-inflammatory manifestations has been reported (72,73). The purpose of this review was partly to make clinicians aware about the overlap between autoinflammation, immune deficiency, lymphoproliferation and to propose some keys for reasoning in daily clinical practice.

### **Conclusion**

Borders between autoinflammation and hematology are now blurred. Cytopenias, hypogammaglobulinemia, susceptibility to infections and lymphoproliferation are part of the spectrum of MSAID . The current review provides an update and propose a practical description of MSAID with immuno-hematological features. These disorders belong largely to the inborn errors of immunity.

### **Author contributions**

HV wrote the manuscript. HV and SGL collected the data. SGL contributed to the conceptualization of the study. SGL and CP revised the manuscript.

## References

1. Cox AJ, Zhao Y, Ferguson PJ. Chronic Recurrent Multifocal Osteomyelitis and Related Diseases—Update on Pathogenesis. *Curr Rheumatol Rep*. 2017 Mar 30;19(4):18.
2. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, Pelet A, et al. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *J Med Genet*. 2005 Jul 1;42(7):551–7.
3. Lordén G, Sanjuán-García I, de Pablo N, Meana C, Alvarez-Miguel I, Pérez-García MT, et al. Lipin-2 regulates NLRP3 inflammasome by affecting P2X7 receptor activation. *J Exp Med*. 2016 Dec 28;214(2):511–28.
4. Taft J, Markson M, Legarda D, Patel R, Chan M, Malle L, et al. Human TBK1 deficiency leads to autoinflammation driven by TNF-induced cell death. *Cell*. 2021 Aug 19;184(17):4447–4463.e20.
5. Oganessian A, Jachiet V, Chasset F, Hirsch P, Hage-Sleiman M, Fabiani B, et al. VEXAS syndrome: still expanding the clinical phenotype. *Rheumatol Oxf Engl*. 2021 Sep 1;60(9):e321–3.
6. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. *N Engl J Med*. 2020 Dec 31;383(27):2628–38.
7. Georjin-Lavialle S, Terrier B, Guedon AF, Heiblig M, Comont T, Lazaro E, et al. Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients. *Br J Dermatol*. 2021 Oct 10;
8. Wiseman DH, May A, Jolles S, Connor P, Powell C, Heeney MM, et al. A novel syndrome of congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD). *Blood*. 2013 Jul 4;122(1):112–23.
9. Giannelou A, Wang H, Zhou Q, Park YH, Abu-Asab MS, Ylaya K, et al. Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors. *Ann Rheum Dis*. 2018 Apr;77(4):612–9.
10. Höchsmann B, Murakami Y, Osato M, Knaus A, Kawamoto M, Inoue N, et al. Complement and inflammasome overactivation mediates paroxysmal nocturnal hemoglobinuria with autoinflammation. *J Clin Invest*. 2019 Dec 2;129(12):5123–36.
11. Kuhns DB, Fink DL, Choi U, Sweeney C, Lau K, Priel DL, et al. Cytoskeletal abnormalities and neutrophil dysfunction in WDR1 deficiency. *Blood*. 2016 Oct 27;128(17):2135–43.
12. Standing ASI, Malinova D, Hong Y, Record J, Moulding D, Blundell MP, et al. Autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia (PFIT) caused by mutation in actin-regulatory gene WDR1. *J Exp Med*. 2017 Jan;214(1):59–71.
13. Volpi S, Cicalese MP, Tuijnburg P, Tool ATJ, Cuadrado E, Abu-Halaweh M, et al. A combined immunodeficiency with severe infections, inflammation, and allergy caused by ARPC1B deficiency. *J Allergy Clin Immunol*. 2019 Jun;143(6):2296–9.
14. Kahr WHA, Pluthero FG, Elkadri A, Warner N, Drobac M, Chen CH, et al. Loss of the Arp2/3 complex component ARPC1B causes platelet abnormalities and predisposes to inflammatory disease. *Nat Commun*. 2017 Apr 3;8:14816.

- Accepted Article
15. Jesus AA de, Hou Y, Brooks S, Malle L, Biancotto A, Huang Y, et al. Distinct interferon signatures and cytokine patterns define additional systemic autoinflammatory diseases. *J Clin Invest*. 2020 Apr 1;130(4):1669–82.
  16. Hadjadj J, Castro CN, Tusseau M, Stolzenberg MC, Mazerolles F, Aladjidi N, et al. Early-onset autoimmunity associated with SOCS1 haploinsufficiency. *Nat Commun*. 2020 Oct 21;11(1):5341.
  17. Banka S, Newman WG. A clinical and molecular review of ubiquitous glucose-6-phosphatase deficiency caused by G6PC3 mutations. *Orphanet J Rare Dis*. 2013 Dec;8(1):1–17.
  18. Goenka A, Doherty JA, Al-Farsi T, Jagger C, Banka S, Cheesman E, et al. Neutrophil dysfunction triggers inflammatory bowel disease in G6PC3 deficiency. *J Leukoc Biol*. 2021 Jun;109(6):1147–54.
  19. Rodrigues F, Hentgen V, Bachmeyer C, Kone-Paut I, Belot A, Grateau G, et al. [NLRC4 associated autoinflammatory diseases: A systematic review of the current literature]. *Rev Med Interne*. 2018 Apr;39(4):279–86.
  20. Canna SW, de Jesus AA, Gouni S, Brooks SR, Marrero B, Liu Y, et al. An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. *Nat Genet*. 2014 Oct;46(10):1140–6.
  21. Latour S, Aguilar C. XIAP deficiency syndrome in humans. *Semin Cell Dev Biol*. 2015 Mar 1;39:115–23.
  22. Rigaud S, Fondanèche MC, Lambert N, Pasquier B, Mateo V, Soulas P, et al. XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. *Nature*. 2006 Nov 2;444(7115):110–4.
  23. Lam MT, Coppola S, Krumbach OHF, Prencipe G, Insalaco A, Cifaldi C, et al. A novel disorder involving dyshematopoiesis, inflammation, and HLH due to aberrant CDC42 function. *J Exp Med*. 2019 Dec 2;216(12):2778–99.
  24. Gernez Y, de Jesus AA, Alsaleem H, Macaubas C, Roy A, Lovell D, et al. Severe autoinflammation in 4 patients with C-terminal variants in cell division control protein 42 homolog (CDC42) successfully treated with IL-1 $\beta$  inhibition. *J Allergy Clin Immunol*. 2019 Oct;144(4):1122-1125.e6.
  25. A toxic palmitoylation of Cdc42 enhances NF- $\kappa$ B signaling and drives a severe autoinflammatory syndrome. *J Allergy Clin Immunol*. 2020 Nov 1;146(5):1201-1204.e8.
  26. Holzinger D, Fassl SK, de Jager W, Lohse P, Röhrig UF, Gattorno M, et al. Single amino acid charge switch defines clinically distinct proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1)-associated inflammatory diseases. *J Allergy Clin Immunol*. 2015 Nov;136(5):1337–45.
  27. Holzinger D, Roth J. Alarming consequences - autoinflammatory disease spectrum due to mutations in proline-serine-threonine phosphatase-interacting protein 1. *Curr Opin Rheumatol*. 2016 Sep;28(5):550–9.
  28. Meyts I, Aksentijevich I. Deficiency of Adenosine Deaminase 2 (DADA2): Updates on the Phenotype, Genetics, Pathogenesis, and Treatment. *J Clin Immunol*. 2018 Jul 1;38(5):569–78.
  29. Fayand A, Chasset F, Boutboul D, Queyrel V, Tieulié N, Guichard I, et al. DADA2 diagnosed in adulthood versus childhood: A comparative study on 306 patients including a systematic literature review and 12 French cases. *Semin Arthritis Rheum*. 2021 Sep 16;51(6):1170–9.

- Accepted Article
30. Ghurye RR, Sundaram K, Smith F, Clark B, Simpson MA, Fairbanks L, et al. Novel ADA2 mutation presenting with neutropenia, lymphopenia and bone marrow failure in patients with deficiency in adenosine deaminase 2 (DADA2). *Br J Haematol.* 2019;186(3):e60–4.
  31. Pinto B, Deo P, Sharma S, Syal A, Sharma A. Expanding spectrum of DADA2: a review of phenotypes, genetics, pathogenesis and treatment. *Clin Rheumatol* 40, 3883–3896 (2021)
  32. Nagata Y, Narumi S, Guan Y, Przychodzen BP, Hirsch CM, Makishima H, et al. Germline loss-of-function SAMD9 and SAMD9L alterations in adult myelodysplastic syndromes. *Blood.* 2018 Nov 22;132(21):2309–13.
  33. Chen DH, Below JE, Shimamura A, Keel SB, Matsushita M, Wolff J, et al. Ataxia-Pancytopenia Syndrome Is Caused by Missense Mutations in SAMD9L. *Am J Hum Genet.* 2016 Jun 2;98(6):1146–58.
  34. Russell AJ, Gray PE, Ziegler JB, Kim YJ, Smith S, Sewell WA, et al. SAMD9L autoinflammatory or ataxia pancytopenia disease mutations activate cell-autonomous translational repression. *Proc Natl Acad Sci U S A.* 2021 Aug 24;118(34):e2110190118.
  35. Fliegau M, Bryant VL, Frede N, Slade C, Woon ST, Lehnert K, et al. Haploinsufficiency of the NF- $\kappa$ B1 Subunit p50 in Common Variable Immunodeficiency. *Am J Hum Genet.* 2015 Sep 3;97(3):389–403.
  36. Schröder C, Sogkas G, Fliegau M, Dörk T, Liu D, Hanitsch LG, et al. Late-Onset Antibody Deficiency Due to Monoallelic Alterations in NFKB1. *Front Immunol.* 2019 Nov 14;10:2618.
  37. Kaustio M, Haapaniemi E, Göös H, Hautala T, Park G, Syrjänen J, et al. Damaging heterozygous mutations in NFKB1 lead to diverse immunologic phenotypes. *J Allergy Clin Immunol.* 2017 Sep 1;140(3):782–96.
  38. Aeschlimann FA, Batu ED, Canna SW, Go E, Gül A, Hoffmann P, et al. A20 haploinsufficiency (HA20): clinical phenotypes and disease course of patients with a newly recognised NF- $\kappa$ B-mediated autoinflammatory disease. *Ann Rheum Dis.* 2018 May;77(5):728–35.
  39. Gans MD, Wang H, Moura NS, Aksentjevich I, Rubinstein A. A20 Haploinsufficiency Presenting with a Combined Immunodeficiency. *J Clin Immunol.* 2020 Oct;40(7):1041–4.
  40. Zhou Q, Wang H, Schwartz DM, Stoffels M, Park YH, Zhang Y, et al. Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. *Nat Genet.* 2016 Jan;48(1):67–73.
  41. Zhou Q, Lee GS, Brady J, Datta S, Katan M, Sheikh A, et al. A Hypermorphic Missense Mutation in PLCG2, Encoding Phospholipase C $\gamma$ 2, Causes a Dominantly Inherited Autoinflammatory Disease with Immunodeficiency. *Am J Hum Genet.* 2012 Oct 5;91(4):713–20.
  42. Schepp J, Proietti M, Frede N, Buchta M, Hübscher K, Rojas Restrepo J, et al. Screening of 181 Patients With Antibody Deficiency for Deficiency of Adenosine Deaminase 2 Sheds New Light on the Disease in Adulthood. *Arthritis Rheumatol Hoboken NJ.* 2017 Aug;69(8):1689–700.
  43. Zavialov AV, Gracia E, Glaichenhaus N, Franco R, Zavialov AV, Lauvau G. Human adenosine deaminase 2 induces differentiation of monocytes into macrophages and stimulates proliferation of T helper cells and macrophages. *J Leukoc Biol.* 2010 Aug;88(2):279–90.
  44. Carmona-Rivera C, Khaznadar SS, Shwin KW, Irizarry-Caro JA, O’Neil LJ, Liu Y, et al. Deficiency of adenosine deaminase 2 triggers adenosine-mediated NETosis and TNF production in patients with DADA2. *Blood.* 2019 Jul 25;134(4):395–406.

- Accepted Article
45. Zavialov AV, Yu X, Spillmann D, Lauvau G, Zavialov AV. Structural basis for the growth factor activity of human adenosine deaminase ADA2. *J Biol Chem*. 2010 Apr 16;285(16):12367–77.
  46. Almeida de Jesus A, Lin B, Karlins E, Kahle D, Rastegar A, Mitchell J, Torreggiani S, Bhuyan F, Alehashemi S, Cetin Gedik K, Uss K, Lee C, Kuehn H, Rosenzweig S, Calvo K, Walkiewicz M, Lack J, Hanson E, Khojah A, Wu E, Scott C, Ronan Leahy T, MacDermott E, Kileen O, Arkachaisri T, Gucev Z, Cook K, Mammadova V, Nasrullayeva G, Canna S, Kuhns D, Dalgard C, Moran T, Oler A, Goldbach-Mansky R. Validation of Bioinformatics Pipeline to Detect NEMO-Deleted Exon 5 Autoinflammatory Syndrome (NEMO-NDAS) and Preliminary Clinical and Immunologic Characterization [abstract]. *Arthritis Rheumatol*. 2021; 73 (suppl 10).
  47. Magg T, Okano T, Koenig LM, Boehmer DFR, Schwartz SL, Inoue K, et al. Heterozygous OAS1 gain-of-function variants cause an autoinflammatory immunodeficiency. *Sci Immunol*. 2021 Jun 18;6(60):eabf9564.
  48. Wang L, Aschenbrenner D, Zeng Z, Cao X, Mayr D, Mehta M, et al. Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice. *Nat Genet*. 2021 Apr;53(4):500–10.
  49. Hong Y, Standing ASI, Nanthapaisal S, Sebire N, Jolles S, Omoyinmi E, et al. Autoinflammation due to homozygous S208 MEFV mutation. *Ann Rheum Dis*. 2019 Apr;78(4):571–3.
  50. Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, et al. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. *Arthritis Rheum*. 2002 Dec;46(12):3340–8.
  51. Navabi B, Upton JEM. Primary immunodeficiencies associated with eosinophilia. *Allergy Asthma Clin Immunol Off J Can Soc Allergy Clin Immunol*. 2016;12:27.
  52. Zhang J, Jin T, Aksentijevich I, Zhou Q. RIPK1-Associated Inborn Errors of Innate Immunity. *Front Immunol*. 2021;12:676946.
  53. Lalaoui N, Boyden SE, Oda H, Wood GM, Stone DL, Chau D, et al. Mutations that prevent caspase cleavage of RIPK1 cause autoinflammatory disease. *Nature*. 2020 Jan;577(7788):103–8.
  54. Duncan CJA, Thompson BJ, Chen R, Rice GI, Gothe F, Young DF, et al. Severe type I interferonopathy and unrestrained interferon signaling due to a homozygous germline mutation in STAT2. *Sci Immunol*. 2019 Dec 13;4(42):eaav7501.
  55. Gruber C, Martin-Fernandez M, Ailal F, Qiu X, Taft J, Altman J, et al. Homozygous STAT2 gain-of-function mutation by loss of USP18 activity in a patient with type I interferonopathy. *J Exp Med* [Internet]. 2020 Feb 24;217(5).
  56. Boisson B, Laplantine E, Prando C, Giliani S, Israelsson E, Xu Z, et al. Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. *Nat Immunol*. 2012 Dec;13(12):1178–86.
  57. Boisson B, Laplantine E, Dobbs K, Cobat A, Tarantino N, Hazen M, et al. Human HOIP and LUBAC deficiency underlies autoinflammation, immunodeficiency, amylopectinosis, and lymphangiectasia. *J Exp Med*. 2015 Jun 1;212(6):939–51.
  58. Oda H, Beck DB, Kuehn HS, Sampaio Moura N, Hoffmann P, Ibarra M, et al. Second Case of HOIP Deficiency Expands Clinical Features and Defines Inflammatory Transcriptome Regulated by LUBAC. *Front Immunol*. 2019;10:479.

- Accepted Article
59. Alsultan A, Basher E, Alqanatish J, Mohammed R, Alfadhel M. Deficiency of ADA2 mimicking autoimmune lymphoproliferative syndrome in the absence of livedo reticularis and vasculitis. *Pediatr Blood Cancer*. 2018 Apr;65(4).
  60. Trotta L, Martelius T, Siitonen T, Hautala T, Hämäläinen S, Juntti H, et al. ADA2 deficiency: Clonal lymphoproliferation in a subset of patients. *J Allergy Clin Immunol*. 2018 Apr;141(4):1534-1537.e8.
  61. Staples E, Simeoni I, Stephens JC, Allen HL, NIHR-BioResource, Wright P, et al. ADA2 deficiency complicated by EBV-driven lymphoproliferative disease. *Clin Immunol Orlando Fla*. 2020 Jun;215:108443.
  62. Gedalia A, Adar A, Gorodischer R. Familial Mediterranean fever in children. *J Rheumatol Suppl*. 1992 Oct;35:1–9.
  63. Cardinez C, Miraghazadeh B, Tanita K, da Silva E, Hoshino A, Okada S, et al. Gain-of-function IKBKB mutation causes human combined immune deficiency. *J Exp Med*. 2018 Nov 5;215(11):2715–24.
  64. Zilberman-Rudenko J, Shawver LM, Wessel AW, Luo Y, Pelletier M, Tsai WL, et al. Recruitment of A20 by the C-terminal domain of NEMO suppresses NF- $\kappa$ B activation and autoinflammatory disease. *Proc Natl Acad Sci U S A*. 2016 Feb 9;113(6):1612–7.
  65. Poli MC, Ebstein F, Nicholas SK, de Guzman MM, Forbes LR, Chinn IK, et al. Heterozygous Truncating Variants in POMP Escape Nonsense-Mediated Decay and Cause a Unique Immune Dysregulatory Syndrome. *Am J Hum Genet*. 2018 Jun 7;102(6):1126–42.
  66. Brehm A, Liu Y, Sheikh A, Marrero B, Omoyinmi E, Zhou Q, et al. Additive loss-of-function proteasome subunit mutations in CANDLE/PRAAS patients promote type I IFN production. *J Clin Invest*. 2015 Nov 2;125(11):4196–211.
  67. Zhang X, Bogunovic D, Payelle-Brogard B, Francois-Newton V, Speer SD, Yuan C, et al. Human intracellular ISG15 prevents interferon- $\alpha/\beta$  over-amplification and auto-inflammation. *Nature*. 2015 Jan 1;517(7532):89–93.
  68. Boisson B, Puel A, Picard C, Casanova JL. Human I $\kappa$ B $\alpha$  Gain of Function: a Severe and Syndromic Immunodeficiency. *J Clin Immunol*. 2017 Jul;37(5):397–412.
  69. Tan EEK, Hopkins RA, Lim CK, Jamuar SS, Ong C, Thoon KC, et al. Dominant-negative NFKBIA mutation promotes IL-1 $\beta$  production causing hepatic disease with severe immunodeficiency. *J Clin Invest*. 2020 Nov 2;130(11):5817–32.
  70. Göös H, Fogarty CL, Sahu B, Plagnol V, Rajamäki K, Nurmi K, et al. Gain-of-function CEBPE mutation causes noncanonical autoinflammatory inflammasomopathy. *J Allergy Clin Immunol*. 2019 Nov 1;144(5):1364–76.
  71. Boisson B, Casanova JL. LUBAC: A new function in immunity. *J Exp Med*. 2014 Jun 30;211(7):1272.
  72. Martinez CA, Ebstein F, Nicholas SK, De Guzman M, Forbes LR, Delmonte OM, et al. HSCT corrects primary immunodeficiency and immune dysregulation in patients with POMP-related auto-inflammatory disease. *Blood*. 2021 May 21;blood.2021011005.
  73. Hashem H, Kumar AR, Müller I, Babor F, Bredius R, Dalal J, et al. Hematopoietic stem cell transplantation rescues the hematological, immunological, and vascular phenotype in DADA2. *Blood*. 2017 Dec 14;130(24):2682–8.



## Figure's legend

### Figure 1. Orientation in front of anemia with autoinflammation.

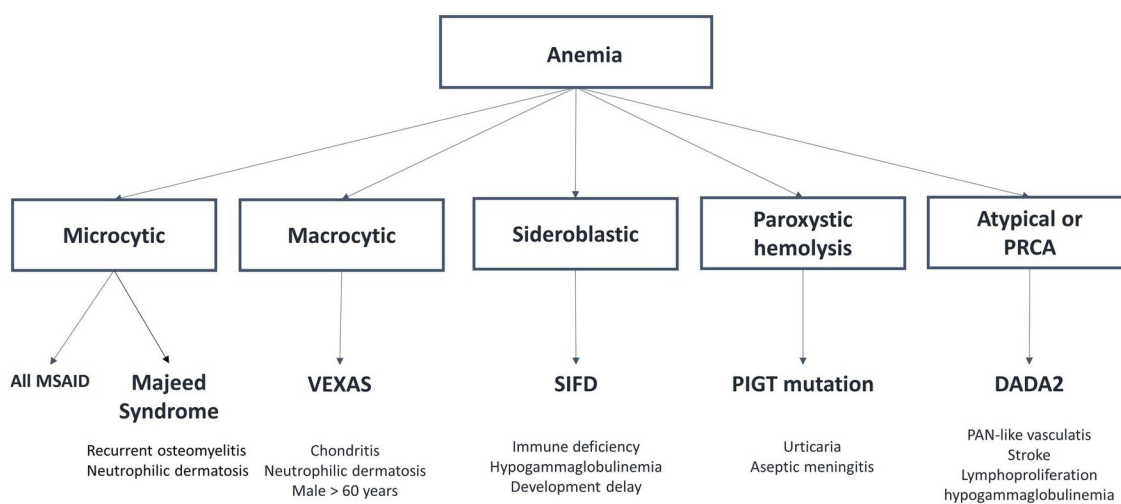
*Italicized notes precise main suggestive features*

### Figure 2. Pathway downstream TNFR1.

Pathways downstream TNFR include RIPK1 pathway and NF- $\kappa$ B pathway. RIPK1 (receptor-interacting serine/threonine kinase 1) mediates multimodal signaling downstream TNFR1. Modulation of intracellular signaling cascade can promote cell survival and inflammatory signaling through NF- $\kappa$ B nuclear translocation or induce caspase-8 mediated apoptosis or RIPK3-dependent necroptosis in the absence of caspase 8. NF- $\kappa$ B activation is regulated by a series of ubiquitination, deubiquitination and phosphorylation events triggered by various stimuli: cytokines including TNF $\alpha$  (shown on this figure) and interleukin-1, bacterial or viral proteins via Toll-like receptors and various stress signals. All these pathways converge to the activation of a complex composed of two catalytic subunits (IKK $\alpha$  and IKK $\beta$ ) and a regulatory subunit (NEMO also called IKK $\gamma$ ) resulting in phosphorylation and subsequent degradation of the inhibitor of NF- $\kappa$ B, I $\kappa$ B. This enables NF- $\kappa$ B to translocate into nucleus. The activation of NF- $\kappa$ B pathway by TNF receptor 1 (TNFR1) requires the formation of the signaling complex I composed of TRADD (TNFR1-associated death domain) and RIPK1. This permits the recruitment of diverse E3 ubiquitin ligase, including LUBAC (linear ubiquitin chain assembly complex). The linear ubiquitination of NEMO by LUBAC increase the phosphorylation and activation of IKK $\beta$ . OTULIN and A20 are negative regulators of linear ubiquitination-dependent NF- $\kappa$ B activation. TBK1 phosphorylates RIPK1 and inhibits the deubiquitinase CYDL, promoting TNFR1 engagement towards NF- $\kappa$ B pathway rather than RIPK induced cell-death.

### Figure 3. Orientation in front of hypogammaglobulinemia with auto-inflammation.

### Figure 4. Mains immuno-hematological features according to the main pathophysiological mechanism involved.



revised Figure 1.jpg

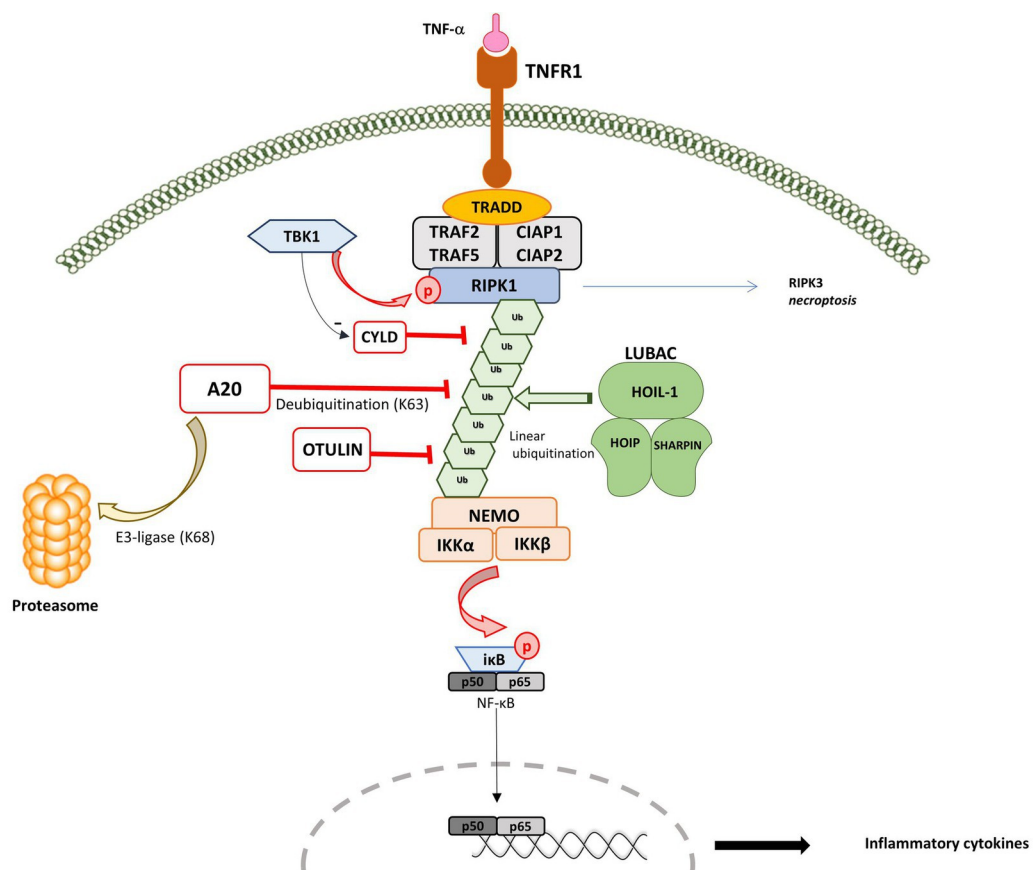


Figure 2.jpg

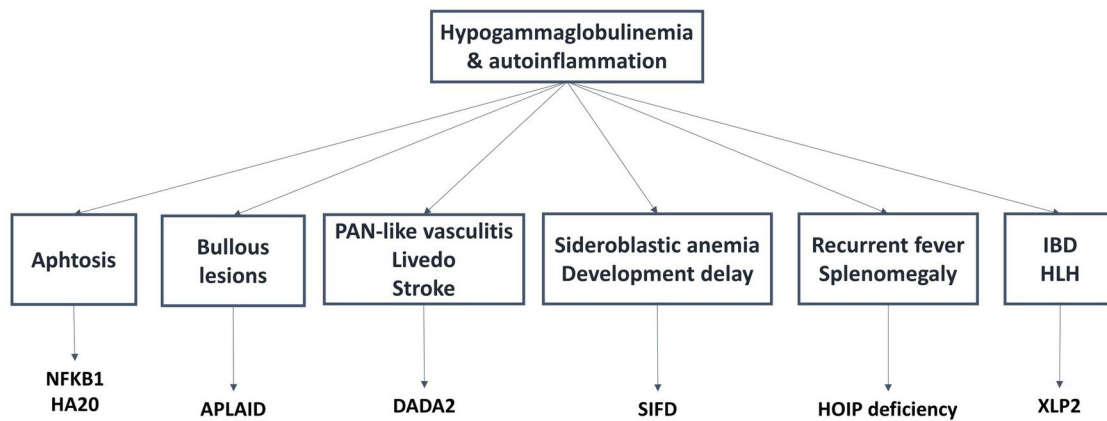


Figure 3.jpg

Main autoinflammatory disease mechanism	Inflammasomes activation	NF-KB pathway	ADA2 deficiency	Actine regulation pathway
Main immuno-hematological disorder	Chronic inflammatory anemia (+/- thrombosis)			
		Hypogammaglobulinemia		
		Macrocytic anemia ( <i>UBA1</i> )		Cytopenia (thrombocytopenia)
	Macrophagic activation syndrome ( <i>NLRCA</i> )		Various anemia/cytopenia	
	Rare hypereosinophilia ( <i>NLRP3</i> , <i>MEFv ex2</i> )			Immunodeficiency

Figure 4.jpg

Main autoinflammatory disease mechanism	Inflammasomes activation	NF-KB pathway	ADA2 deficiency	Actine regulation pathway
Main immuno-hematological disorder	Chronic inflammatory anemia (+/- thrombosis)			
		Hypogammaglobulinemia		
		Macrocytic anemia ( <i>UBA1</i> )		Cytopenia (thrombocytopenia)
	Macrophagic activation syndrome ( <i>NLRCA</i> )		Various anemia/cytopenia	
	Rare hypereosinophilia ( <i>NLRP3</i> , <i>MEFv ex2</i> )			Immunodeficiency

Figure\_4 (1).jpg

**Table 1. Genes involved according to the main immuno-hematological features**

Anemia	Thrombocytopenia	Neutropenia	Myelodysplasia	Hémophagocytosis	Hypogammaglobulinemia	Hypereosinophilia	Splenomegalia lymphadenopathies	Immune deficiency
<i>PIGT</i>	<i>ARPC1B</i>	<i>G6PC3</i> **	<i>SMAD9L</i>	<i>NLRC4</i>	<i>ADA2</i>	<i>NLRP3</i>	<i>CDC42</i>	<i>ARPC1B</i>
<i>PSTPIP1</i>	<i>IKBKG</i> del ex5	<i>PSTPIP1</i>	<i>UBA1</i>	<i>CDC42</i>	<i>IKBKG</i> del ex5	<i>MEVF</i> -ex2	<i>IKBKG</i> - del ex5	<i>CEBPE</i> **
<i>TBK1</i>	<i>LRBA</i>			<i>XIAP</i> *	<i>LRBA</i>	<i>NOD 2</i>	<i>LRBA</i>	<i>ISG15</i>
<i>TRNT1</i>	<i>PSTPIP1</i>				<i>NFKB1</i> **		<i>MEFV</i>	<i>NFKB1</i> **
<i>UBA1</i>	<i>SOCS1</i>				<i>OAS1</i> GOF		<i>MVK</i> *	<i>NFKBIA</i> GOF
<i>LPIN2</i>	<i>WDR1</i>				<i>PLGC2</i>		<i>PSTPIP1</i>	<i>PLGC2</i>
					<i>PSMB9</i>		<i>RIPK1</i> Htz	<i>POMP</i>
					<i>RNF31</i>		<i>SOCS1</i>	<i>PSMB9</i>
					<i>SYK</i> GOF		<i>STAT2</i>	<i>RIPK1</i> Hmz*
					<i>TRNT1</i>		<i>XIAP</i> *	<i>TRNT1</i>
					<i>XIAP</i> *			<i>WDR1</i>
	<i>ADA2</i> #				<i>TNFAIP3</i> ***			
<i>ADA2</i> #							<i>RBCK1</i> *	
							<i>RNF31</i>	
							<i>ADA2</i>	

*ADA2* = Adenosine Deaminase 2 ; *ARPC1B* = Actin Related Protein 2/3 Complex Subunit 1B ; *CDC42* = Cell Division Cycle 42; *CEBPE* = CCAAT Enhancer Binding Protein Epsilon ; ex = exon ; *G6PC3* = glucose-6-phosphatase catalytic subunit 3 ; *GOF* = gain of function ; *Hmz* = homozygous mutation ; *Htz* = heterozygous mutation ; *IKBKG* = Inhibitor Of Nuclear Factor Kappa B Kinase Regulatory Subunit Gamma ; *ISG15* = Interferon-stimulated gene 15 ; *LRBA* = LPS Responsive Beige-Like Anchor Protein ; *MVK* = mevalonate kinase ; *NFKB1* = nuclear-factor kappa B subunit 1 ; *NFKBIA* = NFKB Inhibitor Alpha ; *NLRC4* = NLR Family CARD Domain Containing 4 ; *OAS1* = 2'-5'-Oligoadenylate Synthetase 1; *PIGT* = Phosphatidylinositol Glycan T ; *PLGC2* = Phospholipase C Gamma 2; *POMP* = Proteasome Maturation Protein; *PSMB9* = proteasome subunit  $\beta$ -type 9 ; *PSTPIP1* = proline-serine-threonine phosphatase interacting protein 1; *RIPK1* = Receptor-interacting serine/threonine-protein kinase 1; *RNF31* = Ring Finger Protein 31; *SAMD9L* = Sterile Alpha Motif Domain Containing 9 Like ; *SOCS1* = suppressor of cytokine signaling protein 1; *STAT2* = Signal Transducer And Activator Of Transcription 2; *SYK* = Spleen Associated Tyrosine Kinase; *TBK1* = TANK binding kinase 1 ; *TNFAIP3* = TNF alpha induced protein 3; *TRNT1* = tRNA nucleotidyl transferase 1 ; *UBA1* = ubiquitin like modifier activating enzyme 1 ; *WDR1* = WD Repeat Domain 1; *XIAP* = X-linked inhibitor of apoptosis protein

#Features that are generally not in foreground and/or of rare occurrence but which could lead to the diagnosis

\*\* With apoptosis \* With Inflammatory bowel disease

**Table 2. MSAID associated with immunodeficiency**

<b>Mechanism</b>	<b>Gene</b>	<b>Condition</b>	<b>Infections</b>	<b>Auto-inflammatory features</b>	<b>Others features</b>	<b>Transmission</b>
<b>Humoral deficiency</b>	<i>PLCγ2**</i>	APLAID	Recurrent sino-pulmonary infections	EB-like eruption Arthralgia, Eye inflammation, Enterocolitis	RB-ILD	AD
	<i>ADA2*</i>	ADA2	Bacterial infections +/- HSV	PAN-like vasculitis ; stroke	Lymphoproliferation (ADP, SPM) cytopenia	AR
	<i>RBCK1*</i>	HOIL1 deficiency	Recurrent invasive pyogenic infections	Recurrent fever Early-onset IBD	Lymphoproliferation (ADP, HPSM) Systemic amylopectinosis	AR
	<i>NFKB1*</i>	NF-κB1 deficiency	Recurrent sino-pulmonary infections	Recurrent fever Behçet-like vasculitis: arthritis, aphthosis, diarrhea		AD
	<i>TRNT1*</i>	SIFD	Recurrent sino-pulmonary infections	Recurrent fever Vomiting/diarrhea, oral ulcers, skin cellulitis, arthritis	Sideroblastic anemia Developmental delay Seizure, cerebellar ataxia	AR
	<i>SYK*</i>	SYK constitutive activation	Recurrent invasive bacterial infection +/- HSV	Colitis Skin rash arthritis	Susceptibility to B-cells lymphoma	AD
<b>Combined immunodeficiency</b>	<i>ARPC1B*</i>	ARPC1B deficiency	Recurrent sino-pulmonary and skin bacterial infections; molluscum, warts	Skin vasculitis Hemorrhagic colitis arthritis	Eczema, allergies Thrombopenia Lymphoproliferation (ADP)	AR



	<i>RNF31</i> *	HOIP deficiency	Bacterial, viral, fungal infections Recurrent warts	Recurrent fever Diarrhea, oral ulcers	Lymphoprolifération (SPM) Subclinical amylopectinosis Lymphangectasia	AR
	<i>POMP</i> *	PRAID	Bacterial, viral and opportunistic infections	Neutrophilic dermatosis	Auto-immunity	AD
	<i>PSMB9</i>	PRAAS-ID	BK and JC viruses	Fever Skin rash Myositis	Pulmonary hypertension Basal ganglia calcification Liver dysfunction	AD
	<i>RIPK1</i> *	RIPK1 deficiency	Recurrent otitis media, pneumonia and invasive bacterial infections; Viral and fungal infections	Early-onset IBD Aphthosis Arthritis		AR
	<i>IKBKB</i> **	IKK2	Recurrent respiratory tract infections ; Mucocutaneous candidiasis	Suppurative hydradenitis	Ectodermal dysplasia Eczema Cataract	AD
<b>Neutrophils impairment</b>	<i>CEBPE</i> *	CAIN	Tongue and gluteal abscesses; paronychia; pulmonary infections	Recurrent fever and abdominal pains Oral ulcers PG and abdominal granuloma	Epistaxis, hematomas	AR
	<i>WDR1</i> *	PFIT	Severe bacterial infection	Recurrent fever Peri-anal ulceration	Thrombocytopenia	AR

<b>Interferon-<math>\gamma</math> impairment</b>	<i>NFKBIA</i> **	NFKBIA deficiency	Invasive bacterial and mycobacterial infections	Systemic inflammation Liver infiltration by neutrophils		AD
	<i>ISG15</i> *	ISG15 deficiency	Mycobacterial infections	Necrotic skin ulcers	Intra-cerebral calcification	AR
<b>Type 1 interferon impairment</b>	<i>OAS1</i>	OAS1 mutation **	Viral infections of respiratory tract	Recurrent fever Ulcerative skin rash IBD	Pulmonary alveolar proteinosis hypogammaglobulinemia	AD

*ADP = adenopathies ; APLAID = autoinflammation and PLCG 2-associated antibody deficiency and immune dysregulation ; CAIN = CEBPE associated Autoinflammation and immune impairment of neutrophils ; ; DADA2 = Deficiency in Adenosine Deaminase 2 ; EB = epidermolysis bullosa ; HEM-1 = Hematopoietic protein 1 ; HPSM = hepatosplenomegaly ; HLH = hemophagocytic lymphohistiocytosis ; HOIL-1 = heme-oxidized IRP2 ubiquitin ligase 1 ; HOIP = HOIL-1-interacting protein ; HSV = herpes simplex virus ; IBD = inflammatory bowel disease ; ISG15 = Interferon-stimulated gene 15 ; NF- $\kappa$ B = nuclear-factor kappa B ; NFKBIA = NFKB Inhibitor Alpha ; OAS1 = oligoadenylate synthetase 1 ; PAN = polyarteritis nodosa ; PFIT = Periodic Fever, Immunodeficiency, thrombocytopenia ; PG = Pyoderma gangrenosum ; PRAAS-ID = proteasome associated autoinflammatory syndrome with immune deficiency ; PRAID = POMP-related Autoinflammation and Immune Dysregulation ; RB-ILD = Respiratory bronchiolitis-associated interstitial lung disease ; SIFD = Sideroblastic anemia, Immune deficiency, periodic Fever, Developmental delay ; SPM = splenomegaly*

*\*loss of function mutation*

*\*\* gain of function mutation*