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AUTOIMMUNITY (TK TARRANT, SECTION EDITOR)

Update on the Genetics of Autoinflammatory Disorders

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Abstract
Purpose of the Review This review aims at presenting the most significant data obtained in the field of the genetics of autoinflammatory disorders (AID) over the last past 5 years.
Recent Findings More than 15 genes have been implicated in AID since 2014, unveiling new pathogenic pathways. Recent data have revealed atypical modes of transmission in several inherited AID, such as somatic mosaicism and digenism. First pieces of evidence showing an involvement of epigenetic modifications in the pathogenesis of AID have also been brought to light. Novel genetic data have been obtained on the molecular bases of genetically complex AID.
Summary The development of next-generation sequencing in routine clinical practice has led to an explosion in the identification of new AID genes. Advances in the knowledge of AID further blur the limits between monogenic and multifactorial forms of these syndromes, and between autoinflammatory and autoimmune conditions.

Keywords Autoinflammatory diseases · Genetics · Gene · Mosaicism · Digenism · Epigenetics

Introduction

The concept of autoinflammatory diseases (AID) was initially proposed, as opposed to autoimmune diseases, with the recognition of Mendelian disorders characterized by seemingly unprovoked inflammatory episodes without the high-titer autoantibodies or antigen-specific T cells seen in classic autoimmune diseases. AID are hyperinflammatory, immune-dysregulatory conditions that typically present during childhood with recurrent episodes of fever, rashes, and disease specific patterns of sterile organ inflammation.

At the beginning of the 2000s, the discovery of most AID genes benefited from the study of large familial forms and were the result of either positional cloning and/or candidate gene approaches. At that time, a huge load of studies revealed the first links bridging AID to a dysfunction of the innate immune system. One of the main discoveries was that of the inflammasome, a macromolecular pro-inflammatory complex, which is constitutively activated in some AID associated with marked interleukin (IL)-1β secretion. Many advances in the knowledge of disease mechanisms and treatments centered on IL-1β, leading some experts to propose a new definition of AID saying that they are IL-1-mediated diseases responding to anti-IL-1 therapies. More recently, the increasing use of next-generation sequencing (NGS) in routine clinical practice has led to an exponential increase in the number of genes implicated in AID. Atypical modes of inheritance and contribution of epigenetic factors, which will be presented in this review, have also been brought to light. Concomitantly, it has progressively become clear that autoinflammation can be due to a wide range of molecular defects affecting a variety of innate immune pathways, thereby paving the way to personalized medicine.

This article is part of the Topical Collection on *Autoimmunity*

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Expanding the Spectrum of Monogenic AID

The development of NGS has led to an explosion in the discovery of genes responsible for monogenic AID. This underlines the importance of genetic tests to reach a definitive

diagnosis, since AID are genetically diverse and display overlapping phenotypes. In this regard, Table 1 presents the chronology of the identification of genes responsible for Mendelian AID. The time required for in-depth functional and mechanistic analyses of variants found in novel genes is usually long, and it can take numerous years to fully understand the involvement of a gene in pathophysiological processes. Although knowledge of AID pathogenic mechanisms remains incomplete, it is now clear that, apart from IL-1β signaling, other cellular processes are implicated (Fig. 1). Several examples of new disease-causing genes, identified within the last past 5 years and classified according to the associated dysregulated pathway, are presented below.

Inflammasome and Interleukin-1 (IL-1) Mediated Diseases

IL-1β is a potent endogenous pyrogen, which amplifies the inflammatory response by recruiting several immune cell types and by activating the expression of numerous pro-inflammatory genes. Many AID are due to variants ultimately leading to increased IL-1β release. Among them, several disease-causing genes play a role in sensing danger-associated molecular pattern or pathogen-associated molecular pattern and trigger the formation of pro-inflammatory macromolecular complexes, such as inflammasomes.

As a first example, heterozygous gain-of-function variants in *NLRC4* have been shown to cause NLRC4-macrophage activation syndrome [34, 35]. Patients present infantile enterocolitis, recurrent febrile episodes, urticaria-like rash, and an increased risk of macrophage activation syndrome, which can be triggered by infections or physical stress. The *NLRC4* gene, which encodes a member of the Nod-like receptor (NLR) family, is an intracellular innate immune receptor that senses bacterial flagellin and induces the formation of an *NLRC4*-mediated inflammasome.

NLRP1 germline pathogenic variants are responsible for a wide spectrum of autosomal dominant disorders characterized by dyskeratosis, which may or not be associated with autoinflammatory and autoimmune features [44–46]. NLRP1 is a member of the Ced-4 family of apoptosis proteins and a member of the NLR family, which plays a major role in inflammatory and innate immune signaling pathways. These NLRP1-associated syndromes mainly result from the exacerbated activation of the NLRP1 inflammasome in keratinocytes.

Loss-of-function variants in *WDR1* are responsible for the autosomal recessive Periodic Fever, Immunodeficiency and Thrombocytopenia (PFIT) syndrome [49]. Patients experience recurrent infections, neutropenia, impaired wound healing, and severe stomatitis. *WDR1* encodes the actin-interacting protein 1 (AIP1), which regulates the actin cytosqueleton and, when mutated, activates the pyrin inflammasome.

Type-I IFN Mediated Diseases

Type-I interferons (IFNs) have potent immune-modulating functions. Similar to IL-1β, IFNs induce their own amplification loop and anti-IFN treatments are emerging as effective treatments in some patients with AID. Type-I interferonopathies are Mendelian diseases characterized by a specific signature given by the upregulated expression of genes induced by IFN. The number of type-I interferonopathies is growing rapidly, since IFN signatures are frequently recognized in patients with various types of autoinflammatory/autoimmune disorders. All type-I interferonopathies are not presented in this report, but other recent reviews are available [51]. The recent identification of gain-of-function variants in *TMEM173* causing SAVI (STING-associated vasculopathy with onset in infancy) constitutes a good example of an AID with a type-I IFN signature [33]. The SAVI syndrome is characterized by small vessel vasculitis in cold-sensitive areas, and progressive interstitial lung disease. *TMEM173* encodes a transmembrane protein, called STING (stimulator of interferon genes), which is a pattern recognition receptor that detects cytosolic double-strand DNA and transmits signals that activate type-I IFN responses.

Ubiquitination Disorders

Ubiquitination is a process that marks proteins post-translationally for degradation, leading to their clearance by the 20S proteasome. The immunoproteasome resembles the 20S-classical proteasome in structure, except that three β subunits of the catalytic 20S core are replaced by three different immunoproteasome βi subunits, all of which are inducible by IFN-γ stimulation or by oxidative stress.

Proteasome-associated autoinflammatory syndromes (PRASS) are caused by biallelic or digenic variants in the proteasome subunits PSMB8, PSMB9, PSMA3, and PSMB4 [40••]. A heterozygous variant has also been found in the proteasome assembly molecule POMP [40••]. Patients with PRAAS present with recurrent fever, cutaneous manifestations, lipodystrophy, arthralgia or arthritis, and myositis. Very recently, biallelic variants have also been identified in *PSMG2*, which encodes the proteasome assembly chaperone 2 [50].

Otulipenia is an autosomal recessive disorder due to variants in the *OTULIN* gene [47, 48]. The associated disease is characterized by recurrent fevers, panniculitis, lipodystrophy, diarrhea, and arthritis. *OTULIN* encodes a ubiquitin isopeptidase, which removes certain types of ubiquitin chains from proteins, thereby regulating the NF-κB signaling pathway.

Table 1 Chronology of the identification of genes responsible for Mendelian AID

Gene	Protein	Disorder	Mode of inheritance	Year of initial description	Initial references
MEFV	Pyrin/marenostrin	Familial Mediterranean fever (FMF)	AR	1997	[1, 2]
		Pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND)	AD	2016	[3••]
TNFRSF1A	TNFR1	Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	AD	1999	[4]
MVK	Mevalonate kinase	Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS)/mevalonate kinase deficiency (MKD)	AR	1999	[5,6]
			AD	2012	[7]
		Porokeratosis 3 (POROK3)/disseminated superficial actinic porokeratosis (DSAP)			
NLRP3	Cryopyrin/NLRP3	Cryopyrin-associated periodic syndrome (CAPS)	AD/de novo	2001	[8, 9]
NOD2	NOD2	Blau syndrome/early-onset sarcoidosis	AD	2001	[10]
SH3BP2	SH3BP2	Cherubism	AD	2001	[11]
PSTPIP1	PSTPIP1	Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA)	AD	2002	[12]
LPIN2	Lipin 2	Majeed syndrome	AR	2005	[13]
NLRP7	NLRP7	Hydatidiform mole	AR	2006	[14]
NLRP12	NLRP12	Familial cold autoinflammatory syndrome 2 (FACS2)/NLRP12-associated periodic syndrome (NAPS12)	AD	2008	[15]
IL1RN	IL-1 receptor antagonist	Deficiency of IL-1 receptor antagonist (DIRA)	AR	2009	[16, 17]
IL10RA, *IL10RB*	IL-10 receptors,	Very early-onset inflammatory bowel disease (VEOIBD)	AR	2009	[18]
IL10	IL-10	IL-10 deficiency (IL-10D)	AR	2010	[19]
SLC29A3	hENT3	Histiocytosis-lymphadenopathy plus syndrome	AR	2010	[20]
PSMB8	Immunoproteasome β5i subunit	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)/proteasome-associated autoinflammatory syndrome (PRASS)	AR	2010–11	[21, 22]
IL36RN	IL-36 receptor antagonist	Deficiency of IL-36 receptor antagonist (DITRA)	AR	2011	[23, 24]
CARD14	CARD14	CARD14 mediated psoriasis (CAMPS)/psoriasis susceptibility locus 2 (PSORS2)	AD	2012	[25, 26]
PLCG2	PLCγ2	Autoinflammatory PLCγ2-associated antibody deficiency and immune dysregulation (APLAID)	AD	2012	[27, 28]
RBCK1	HOIL-1	HOIL-1 deficiency	AR	2012	[29]
AP1S3	AP1S3	AP1S3-mediated psoriasis (AMPS)	AD	2014	[30]
ADA2	ADA2	Deficiency of adenosine deaminase 2 (DADA2)	AR	2014	[31, 32]
TMEM173	STING	STING-associated vasculopathy with onset in infancy (SAVI)	AD	2014	[33]
NLRC4	NLRC4	NLRC4-macrophage activation syndrome (NLRC4-MAS)	AD	2014	[34, 35]
TRNT1	TRNT1	Sideroblastic anemia with B cell immunodeficiency, fevers, and developmental delay (SIFD)	AR	2014	[36]
TNFRSF11A	TNFRSF11A	TNFRSF11A-associated periodic syndrome (TRAPS11)	AD	2014	[37]
RNF31	HOIP	HOIP deficiency	AR	2015	[38]
LACC1	LACC1/FAMIN	Monogenic form of systemic juvenile idiopathic arthritis (sJIA)	AR	2015	[39]
PSMA3 *PSMB4* *PSMB9*	Immunoproteasome subunits	PRASS	AR/s possible digenism	2015	[40••]
POMP	POMP	POMP-related autoinflammation and immune dysregulation disease (PRAID)	AD	2015	[40••]
TNFAIP3	A20	A20 haploinsufficiency (HA20)	AD	2016	[41, 42]
ADGRE2	ADGRE2	Vibratory urticaria	AD	2016	[43]

Table 1 (continued)

Gene	Protein	Disorder	Mode of inheritance	Year of initial description	Initial references
NLRP1	NLRP1	Multiple self-healing palmoplantar carcinoma (MSPC); familial keratosis lichenoides chronica (FKLC)/NLRP1-associated autoinflammation with arthritis and dyskeratosis (NAIAD)	AD	2013	[44–46]
OTULIN	OTULIN	Otulipenia/otulin-related autoinflammatory syndrome (ORAS)	AR	2016	[47, 48]
WDR1	WDR1	Periodic fever, immunodeficiency, and thrombocytopenia (PFIT)	AR	2017	[49]
PSMG2	PAC2	PRASS	AR	2019	[50]

Modes of inheritance: *AR* autosomal recessive; *AD* autosomal dominant. Proteins: *TNFR1* tumor necrosis factor receptor 1; *NLRP* nucleotide oligomerization domain (NOD)-like receptor family, leucine rich repeat, pyrin domain; *SH3BP2* SH3 binding protein 2; *PSTPIP* proline-serine-threonine phosphatase interacting protein; *hENT3* human equilibrative nucleoside transporter-3; *IL* interleukin; *CARD* caspase activation and recruitment domain; *PLCγ2* phospholipase Cγ2; *HOIL-1* heme-oxidized IRP2 ubiquitin ligase 1; *ADA2* adenosine deaminase 2; *STING* stimulator of interferon genes; *NLRC* nucleotide oligomerization domain (NOD)-like receptor family CARD domain-containing protein; *TRNT* tRNA nucleotidyltransferase; *TNFRSF11A* TNF receptor superfamily 11a; *HOIP* HOIL-1 interacting protein; *AP1S3* adaptor related protein complex 1 sigma 3; *FAMIN* fatty acid metabolic immune nexus; *POMP* proteasome maturation protein; *ADGRE2* adhesion G protein-coupled receptor E2; *WDR1* WD domain repeat containing protein 1; *PAC2* proteasome assembly chaperone 2

HOIL-1 and HOIP are both involved in two types of autosomal recessive AID characterized by multiorgan autoinflammation, immunodeficiency, and amylopectinosis. HOIL1 and HOIP are two major components of the linear ubiquitination chain assembly complex (LUBAC), and variants in the corresponding genes destabilize the whole complex.

Heterozygous loss-of-function variants in *TNFAIP3* cause A20 haploinsufficiency. Most variants identified in *TNFAIP3* leads to a Behçet-like autoinflammatory phenotype, when others have been implicated in an autoimmune lymphoproliferative syndrome [41, 42]. The protein encoded by this gene, A20, displays both ubiquitin ligase and deubiquitinase activities. Cells from patients exhibit persistent polyubiquitination of proteins such as TRAF6, RIP1, and NEMO, which are essential components of the NF-κB signaling pathway. Nevertheless, the precise molecular mechanism by which A20 interferes with NF-κB remains to be clarified.

AID Involving Inflammatory or Innate Immune Regulators of Various Types

Loss-of-function variants in *ADA2* cause the autosomal recessive DADA2 syndrome, which classically presents with recurrent fevers, early-onset strokes, vasculopathy, gastrointestinal manifestations, and various types of immunologic and hematologic signs [31, 32]. The ADA2 protein is one of two adenosine deaminases which regulate levels of adenosine. ADA2 acts as a growth factor for endothelial cells, explaining vascular fragility in patients. It also promotes the development of anti-inflammatory M2 macrophages. Measurement of ADA2 levels may be helpful in making the diagnosis.

Variants in *TNFRSF11A* have been implicated in TRAPS11, a disorder which present a number of similarities with one of the firstly reported AID, TRAPS [37]. The protein encoded by this gene is a member of the TNF-receptor superfamily. This receptor induces the activation of NF-κB and MAPK8/JNK signaling pathways. It is an important regulator of the interaction between T cells and dendritic cells, and this receptor is also an essential mediator for osteoclast and lymph node development. Variants in this gene have also been associated with familial expansile osteolysis, autosomal recessive osteopetrosis, and Paget disease of bone.

Loss-of-function variants in *ADGRE2* are responsible for a vibratory urticaria associating localized hives and systemic manifestations in response to dermal vibration, with coincident degranulation of mast cells and increased histamine levels in serum [43]. ADGRE2 is a seven-span transmembrane G protein coupled receptor, which promotes cell-cell adhesion, especially on mast cells. The variants identified in patients seem to sensitize mast cells to IgE-independent vibration-induced degranulation.

Loss-of-function variants in *TRNT1* cause an autosomal recessive multisystem AID with wide phenotypic heterogeneity called sideroblastic anemia with B cell immunodeficiency, periodic fever, and developmental delay syndrome (SIFD) [36]. TRNT1 is an essential enzyme, which catalyzes the addition of the CCA nucleotide triplet to the 3′ terminus of all tRNA molecules, a critical step in the maturation of both cytosolic and mitochondrial tRNA. TRNT1 also participates in the tRNA quality control process and in cellular stress response. The pathophysiological mechanisms involved in SIFD remain to be clarified.

Loss-of-function variants in *LACC1* have been shown to cause an autosomal recessive form of systemic juvenile idiopathic arthritis associating fever, cutaneous rashes, and chronic polyarthritis [39]. The fatty acid metabolic-immune nexus (FAMIN) protein encoded by this gene is an oxidoreductase that promotes fatty acid oxidation, with concomitant mitochondrial reactive oxygen species production and cytokine secretion.

AP1S3-mediated psoriasis (APMS) is an autosomal dominant disorder due to variants in *AP1S3* [30]. The disease is mainly characterized by generalized or palmoplantar pustular psoriasis with nail dystrophy. *AP1S3* encodes the σ1C adaptor protein complex 1 (AP-1) subunit involved in clathrin-mediated vesicular transport from the Golgi or endosomes. In *AP1S3*-deficient keratinocytes, autophagy is disrupted, causing abnormal accumulation of p62, a protein involved in NF-κB signaling. As a consequence, upregulation of IL-1 signaling and overexpression of IL-36α have been observed. The key role of IL-36 in psoriasis is also underlined by the previous identification of loss-of-function variants in *IL36RN*, in another form of psoriasis, called DITRA (deficiency of IL-36 receptor antagonist).

Novelty on the Inheritance Modes of AID

Although most AID are autosomal recessive or autosomal dominant, recent advances have shown atypical inheritance modes in several clinical entities. A global overview of the transmission mode associated with each AID is presented in Fig. 2.

Old Genes with New Inheritance Modes

Over the last past few years, some genes previously identified in a given monogenic AID have been shown to be responsible for another clinical entity with a different inheritance mode.

As a first example, *MEFV* is the gene responsible for the most frequent monogenic AID called familial Mediterranean fever (FMF), an autosomal recessive condition. Recently, this gene has been shown to be also responsible for a dominantly inherited chronic neutrophilic dermatosis named PAAND (pyrin-associated autoinflammation with neutrophilic dermatosis). On the one hand, FMF is characterized by short episodes of

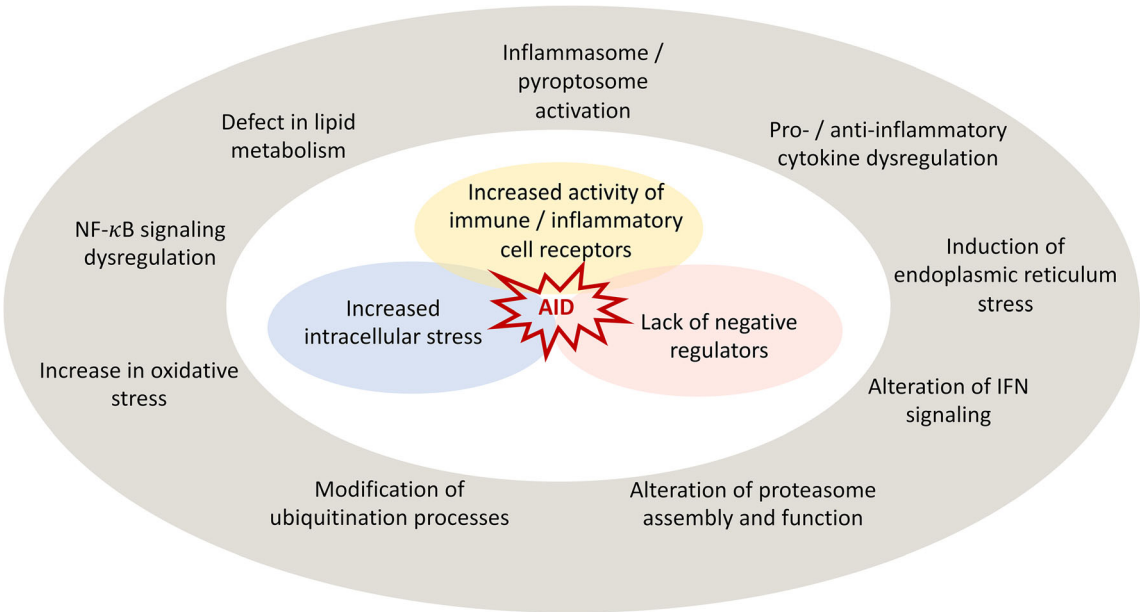

Fig. 1 Cellular processes involved in the pathogenesis of AID. Schematically, AID can be seen as disorders due to a defect in one of the three general cellular processes: increase in the activity of cell receptors triggering inflammatory/immune responses, increased intracellular stress, and lack of negative regulators of the inflammatory response. When considering pathophysiological pathways in more detail, each AID can combine several of the alterations depicted in the gray ring. All cellular dysfunctions underlying each form of AID are far from being elucidated. *AID* autoinflammatory disease, *IFN* interferon

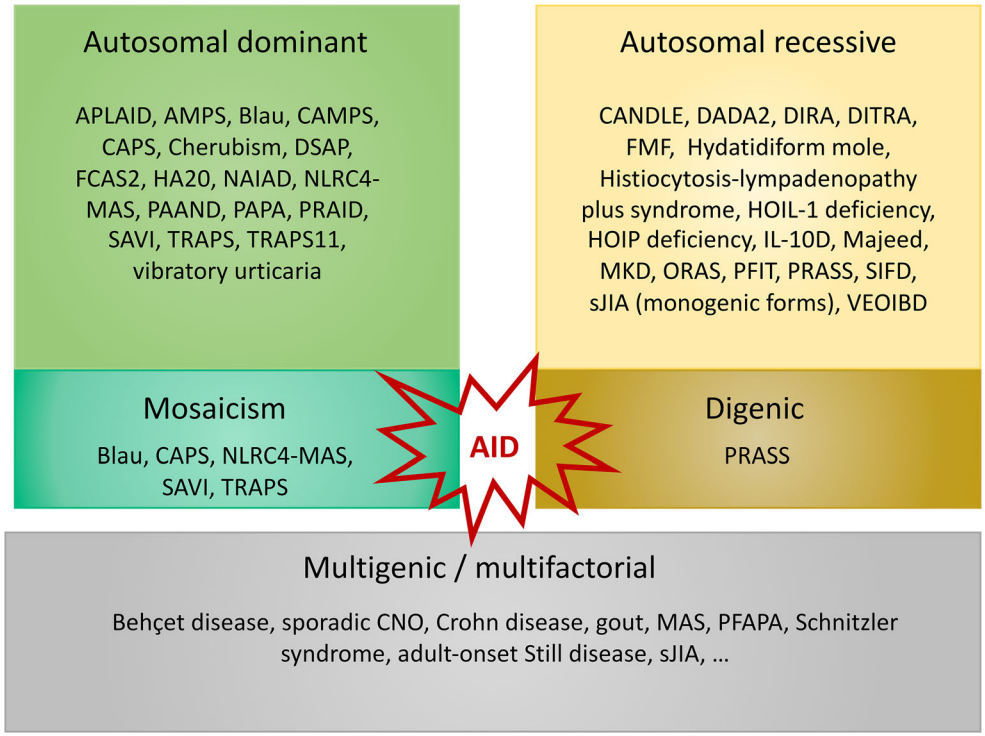

Fig. 2 Modes of inheritance in AID. The scheme presents the different modes of transmission observed in AID. Most AID have classical transmission modes: autosomal recessive or autosomal dominant. Recently, a few cases of mosaicism and digenism have been reported and the spectrum of multifactorial AID is expanding over time. Disorders: *APLAID* autoinflammatory PLCγ2-associated antibody deficiency and immune dysregulation; *AMPS* AP1S3-mediated psoriasis; *CAMPS* CARD-14 mediated psoriasis; *CANDLE* chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; *CAPS* cryopyrin-associated periodic syndrome; *CNO* chronic non-bacterial osteomyelitis; *DADA2* deficiency of adenosine deaminase 2; *DIRA* deficiency of IL-1 receptor antagonist; *DITRA* deficiency of IL-36 receptor antagonist; *DSAP* disseminated superficial actinic porokeratosis; *FACS2* familial cold autoinflammatory syndrome 2; *FMF* familial Mediterranean fever; *HA20* A20 haploinsufficiency; *IL-10D* IL-10 deficiency; *MAS* macrophage activation syndrome; *MKD* mevalonate kinase deficiency; *NAIAD* NLRP1-associated autoinflammation with arthritis and dyskeratosis; *NLRC4-MAS* NLRC4-macrophage activation syndrome; *ORAS* otulin-related autoinflammatory syndrome; *PAAND* pyrin-associated autoinflammation with neutrophilic dermatosis; *PAPA* pyogenic arthritis, pyoderma gangrenosum and acne; *PFAPA* periodic fever with aphtous stomatitis, pharyngitis, and cervical adenitis; *PFIT* periodic fever, immunodeficiency, and thrombocytopenia; *PRAID* POMP-related autoinflammation and immune dysregulation disease; *PRASS* proteasome-associated autoinflammatory syndromes; *SAVI* STING-associated vasculopathy with onset in infancy; *SIFD* sideroblastic anemia with B cell immunodeficiency, fevers, and developmental delay; *sJIA* monogenic form of systemic juvenile idiopathic arthritis; *TRAPS* TNFRSF1A-associated periodic syndrome; *TRAPS11* TNFRSF11A-associated periodic syndrome; *VEOIBD* very early-onset inflammatory bowel disease

high fever accompanied by severe abdominal and chest pain, pleurisy, arthralgia or arthritis, and myalgia, sometimes accompanied by erysipeloid erythema and renal amyloidosis. On the other hand, the PAAND syndrome associates long-lasting fever episodes, arthralgia, myalgia or myositis, and different types of neutrophilic dermatosis (severe acne, sterile skin abscesses, pyoderma gangrenosum, small vessel vasculitis). *MEFV* encodes the pyrin protein. Variants responsible for PAAND are located in a particular domain of pyrin, allowing pyrin binding with 14.3.3 regulatory partners. These PAAND-associated variants, which disrupt pyrin phosphorylation, induce 14.3.3 release and the subsequent activation of a pyrin-mediated inflammasome [3••, 52].

A similar observation was previously made with the *MVK* gene. This gene was involved in the autosomal recessive mevalonate kinase deficiency syndrome in 1999, and 13 years later in an autosomal dominant form of porokeratosis [5–7].

Digenism

In 2010, variants in *PSMB8*, which encodes the inducible immunoproteasome β5i subunit, have been shown to be responsible for an autosomal recessive immune-dysregulatory disease called CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), which is classified as a proteasome-associated autoinflammatory syndrome (PRAAS). More recently, the disease has been found to be digenic in several patients with double heterozygotes carrying one variant in an inducible proteasome component (PSMB8 or PSMB9) and one variant in a constitutive proteasome component (PSMB4 or PSMA3) [40••]. As mentioned

previously, these variants alter proteasome activity leading to increased type-I IFN production.

Mosaicism

Over the past few years, a growing number of studies demonstrated a role of somatic mosaicism in the pathogenesis of several monogenic AID. Mosaicism is defined by the presence of two or more populations of cells with different genetic contents in one individual [53]. This is the consequence of a mutational event that occurs post-zygotically, either during embryonic development or later, after birth. This post-zygotic mutation is a so-called de novo variant since it is absent in the patient's parents. Its body distribution directly depends on the precise time when the post-zygotic mutational event took place. When the mutational event is restricted to somatic cells, the phenomenon is called somatic mosaicism. When it is restricted to the gonadal tissue, it is named gonadal mosaicism. The term gonosomal mosaicism is used when a post-zygotic variant is present both in gonadal and extra-gonadal tissue. The variant can be missed when using Sanger sequencing, due to its low frequency in cells used for DNA extraction and its detection usually requires the use of NGS.

The first case of mosaicism in the field of AID was reported in 2005 in a patient with cryopyrin-associated periodic syndromes (CAPS) and carrying a pathogenic variant in the *NLRP3* gene [54••]. To date, most cases of somatic mosaicism are related to the *NLRP3* gene, with more than 10 independent reports [54••, 55–59]. Although the frequency of *NLRP3* mutant cells is usually similar in all analyzed tissues, several cases of somatic *NLRP3* mosaicism restricted to the myeloid lineage have recently been reported [60–62]. These patients present with a late-onset CAPS, as compared to patients with germline variants or patients with extended somatic *NLRP3* mosaicism, who usually develop symptoms during childhood. Also, in several cases of myeloid-restricted *NLRP3* mosaicism, the diagnosis was made in patients with a clinical diagnosis of Schnitzler syndrome, an AID characterized by a neutrophilic urticarial skin rash, monoclonal gammopathy, and positive response to anti-IL1 therapies [60].

Now, several dozen patients have been identified with somatic mosaicism in different genes implicated in monogenic AID. In 2014, Liu et al. have demonstrated somatic mosaicism for the *TMEM173* gene in the autosomal dominant stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) [33]. Another example has been found in a case of Blau syndrome, which is due to gain-of-function variants in *NOD2* [63]. In 2017, somatic mosaicism in *NLRC4*, the gene responsible for *NLRC4*-associated macrophage activation syndrome, has been reported in a patient initially referred for CAPS [64].

Gonosomal mosaicism has also been reported in several AID, including CAPS, TRAPS, Blau syndrome, and haploinsufficiency of A20 [65–68].

Complex AID

The study of genetically complex AID has benefited from the use of genome-wide association studies. One of the first complex AID to be well studied at the genetic level was Behçet disease. This disorder is mainly characterized by recurrent oral and genital ulcers, skin lesions, and uveitis. HLA-B*51 is the strongest genetic susceptibility factor in this entity, and an epistatic interaction with the endoplasmic reticulum-associated aminopeptidase 1 (ERAP1) determines its pathogenic role [69]. More recently, non-HLA susceptibility genes have been shown to contribute to the disease susceptibility by affecting the host sensitivity to microbial exposure and environmental triggers [70]. Genetic susceptibility factors involved in other AID have been identified over the last past 5 years. As an example, HLA-DRB1*11 and variants of the MHC class II locus have been shown to be strong risk factors for systemic juvenile idiopathic arthritis [71].

Epigenetics

Epigenetic modifications, which mainly involve DNA methylation and histone modification, play an important role in the regulation of gene expression [72]. Recent advances have shed light on the first pieces of evidence showing an involvement of epigenetic modifications in the pathogenesis of AID.

A recent study has analyzed DNA methylation levels of inflammasome-associated genes in patients with CAPS. Monocytes from untreated patients display more efficient DNA demethylation than those of healthy subjects. Interestingly, patients with CAPS treated with anti-IL-1 drugs display methylation levels similar to those of healthy controls, suggesting that the drug is effective in preventing the exacerbated demethylation of inflammasome genes [73]. The study of skin biopsies from patients with CAPS also reveals an altered expression of numerous genes encoding enzymes associated with histone modification [74]. Another study has revealed that expression of *MEFV* (the gene responsible for FMF) is decreased in FMF patients as compared to healthy controls, and this is associated with a slightly higher methylation level of *MEFV* exon 2 [75]. In mevalonate kinase deficiency (MKD), which is caused by loss-of-function variants in the *MVK* gene, monocytes of patients accumulate mevalonate, which induces histone modifications in inflammatory pathways. Consistently, statins, which block mevalonate generation, prevent this phenomenon [76].

Epigenetic dysregulation also plays a role in complex AID. Genome-wide DNA methylation analyses in monocytes and

CD4+ cells of patients with Behçet disease show different methylation levels, as compared to healthy controls. Notably, patients in remission after treatment show a partial restoration of the DNA methylation pattern [77]. Chronic non-bacterial osteomyelitis (CNO) is a chronic autoinflammatory syndrome that is characterized by multiple foci of painful swelling of bones. It has been proposed that the repression of IL-10 and IL-19, seen in this clinical entity, is due to an altered histone phosphorylation profile in their promoter region (altered histone H3 phosphorylation at serine residue 10—H3S10p), together with a differential DNA methylation in IL-10 intronic enhancer element [78]. Epigenetic alterations have also been reported in Crohn's disease (CD), one of the most frequent types of inflammatory bowel disease. The *DNMT3A* gene, encoding a DNA methyltransferase involved in de novo methylation, has been identified by a genome-wide association study as a susceptibility gene for CD [79]. The study of genome-wide methylation profiles in peripheral blood cells from CD patients has also revealed a specific methylation pattern with modifications in several genes playing a key role in host defense mechanisms [80].

Conclusions

What can we expect for the future? Despite all these advances in the discovery of new disease-causing genes, the rate of genetically unexplained forms of AID remains high. Within the coming years, we can expect that the spectrum of AID will continue to expand with the discovery of additional disease-causing genes, associated with undisclosed pathogenic mechanisms. Nevertheless, since most large familial forms have already been explored, new monogenic diseases will certainly correspond to very rare clinical entities due to private mutations. In this regard, the implication of new variants will require close collaborations between biologists and clinicians.

The use of NGS in routine clinical practice will certainly allow the identification of mosaicism in a growing number of clinical entities. This phenomenon expands the clinical spectrum associated with some AID towards milder phenotypes or late-onset forms of the disease. Characterization of diseases due to digenism in other entities than PRASS will represent an important challenge. At the present time, we have no clue to evaluate how frequent this mode of inheritance in AID is, and if it could explain a significant part of the genetically unexplained forms of AID.

The growing number of observations showing a role of epigenetic alterations in AID underlines that epigenetic mechanisms likely contribute to the pathophysiology of these disorders. Nevertheless, further studies are needed to fully understand the exact role of these epigenetic modifications in the disease process and response to treatment.

Over the last past 5 years, the discovery of numerous AID genes and associated pathways has improved our knowledge of the pathophysiology of AID and has further blurred the frontiers between autoinflammaory and autoimmune disorders. All these novelties should also allow more targeted therapies. As an example, the recent use of JAK inhibitors in interferonopathies has shown promising effects.

Compliance with Ethics Guidelines

Conflict of Interest Isabelle Jéru declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet. 1997;17(1):25–31.
2. The International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium. Cell. 1997;90(4):797–807.
3. •• Masters SL, Lagou V, Jeru I, Baker PJ, Van Eyck L, Parry DA, et al. Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation. Sci Transl Med. 2016;8(332):332ra45. **Comment: Involvement of *MEFV*, the gene responsible for the most frequent autosomal recessive AID, in a rare autosomal dominant disorder due to a particular pathogenic mechanism.**
4. McDermott MF, Aksentijevich I, Galon J, McDermott EM, Ogunkolade BW, Centola M, et al. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell. 1999;97(1):133–44.
5. Drenth JP, Cuisset L, Grateau G, Vasseur C, van de Velde-Visser SD, de Jong JG, et al. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. Nat Genet. 1999;22(2):178–81.
6. Houten SM, Kuis W, Duran M, de Koning TJ, van Royen-Kerkhof A, Romeijn GJ, et al. Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. Nat Genet. 1999;22(2):175–7.
7. Zhang SQ, Jiang T, Li M, Zhang X, Ren YQ, Wei SC, et al. Exome sequencing identifies MVK mutations in disseminated superficial actinic porokeratosis. Nat Genet. 2012;44(10):1156–60.
8. Feldmann J, Prieur AM, Quartier P, Berquin P, Certain S, Cortis E, et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet. 2002;71(1):198–203.

9. Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet. 2001;29(3):301–5.
10. Miceli-Richard C, Lesage S, Rybojad M, Prieur AM, Manouvrier-Hanu S, Hafner R, et al. CARD15 mutations in Blau syndrome. Nat Genet. 2001;29(1):19–20.
11. Ueki Y, Tiziani V, Santanna C, Fukai N, Maulik C, Garfinkle J, et al. Mutations in the gene encoding c-Abl-binding protein SH3BP2 cause cherubism. Nat Genet. 2001;28(2):125–6.
12. Wise CA, Gillum JD, Seidman CE, Lindor NM, Veile R, Bashiardes S, et al. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. Hum Mol Genet. 2002;11(8):961–9.
13. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, Pelet A, Munnich A, Lyonnet S, Majeed HA, El-Shanti H. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). J Med Genet. 2005;42(7):551–7.
14. Murdoch S, Djuric U, Mazhar B, Seoud M, Khan R, Kuick R, et al. Mutations in NALP7 cause recurrent hydatidiform moles and reproductive wastage in humans. Nat Genet. 2006;38(3):300–2.
15. Jeru I, Duquesnoy P, Fernandes-Alnemri T, Cochet E, Yu JW, Lackmy-Port-Lis M, et al. Mutations in NALP12 cause hereditary periodic fever syndromes. Proc Natl Acad Sci U S A. 2008;105(5):1614–9.
16. Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med. 2009;360(23):2426–37.
17. Reddy S, Jia S, Geoffrey R, Lorier R, Suchi M, Broeckel U, et al. An autoinflammatory disease due to homozygous deletion of the IL1RN locus. N Engl J Med. 2009;360(23):2438–44.
18. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schaffer AA, Noyan F, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med. 2009;361(21):2033–45.
19. Glocker EO, Kotlarz D, Klein C, Shah N, Grimbacher B. IL-10 and IL-10 receptor defects in humans. Ann N Y Acad Sci. 2011;1246:102–7.
20. Morgan NV, Morris MR, Cangul H, Gleeson D, Straatman-Iwanowska A, Davies N, et al. Mutations in SLC29A3, encoding an equilibrative nucleoside transporter ENT3, cause a familial histiocytosis syndrome (Faisalabad histiocytosis) and familial Rosai-Dorfman disease. PLoS Genet. 2010;6(2):e1000833.
21. Agarwal AK, Xing C, DeMartino GN, Mizrachi D, Hernandez MD, Sousa AB, et al. PSMB8 encoding the beta5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. Am J Hum Genet. 2010;87(6):866–72.
22. Arima K, Kinoshita A, Mishima H, Kanazawa N, Kaneko T, Mizushima T, et al. Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome. Proc Natl Acad Sci U S A. 2011;108(36):14914–9.
23. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med. 2011;365(7):620–8.
24. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet. 2011;89(3):432–7.
25. Fuchs-Telem D, Sarig O, van Steensel MA, Isakov O, Israeli S, Nousbeck J, et al. Familial pityriasis rubra pilaris is caused by mutations in CARD14. Am J Hum Genet. 2012;91(1):163–70.
26. Jordan CT, Cao L, Roberson ED, Pierson KC, Yang CF, Joyce CE, et al. PSORS2 is due to mutations in CARD14. Am J Hum Genet. 2012;90(5):784–95.
27. Ombrello MJ, Remmers EF, Sun G, Freeman AF, Datta S, Torabi-Parizi P, et al. Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. N Engl J Med. 2012;366(4):330–8.
28. Zhou Q, Lee GS, Brady J, Datta S, Katan M, Sheikh A, et al. A hypermorphic missense mutation in PLCG2, encoding phospholipase Cgamma2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. Am J Hum Genet. 2012;91(4):713–20.
29. 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;13(12):1178–86.
30. Setta-Kaffetzi N, Simpson MA, Navarini AA, Patel VM, Lu HC, Allen MH, et al. AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. Am J Hum Genet. 2014;94(5):790–7.
31. Navon Elkan P, Pierce SB, Segel R, Walsh T, Barash J, Padeh S, et al. Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. N Engl J Med. 2014;370(10):921–31.
32. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, et al. Early-onset stroke and vasculopathy associated with mutations in ADA2. N Engl J Med. 2014;370(10):911–20.
33. Liu Y, Jesus AA, Marrero B, Yang D, Ramsey SE, Sanchez GAM, et al. Activated STING in a vascular and pulmonary syndrome. N Engl J Med. 2014;371(6):507–18.
34. 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;46(10):1140–6.
35. Romberg N, Al Moussawi K, Nelson-Williams C, Stiegler AL, Loring E, Choi M, et al. Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. Nat Genet. 2014;46(10):1135–9.
36. Chakraborty PK, Schmitz-Abe K, Kennedy EK, Mamady H, Naas T, Durie D, et al. Mutations in TRNT1 cause congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD). Blood. 2014;124(18):2867–71.
37. Jeru I, Cochet E, Duquesnoy P, Hentgen V, Copin B, Mitjavila-GarciaMT, et al. Brief report: involvement of TNFRSF11A molecular defects in autoinflammatory disorders. Arthritis Rheum. 2014;66(9):2621–7.
38. 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;212(6):939–51.
39. Wakil SM, Monies DM, Abouelhoda M, Al-Tassan N, Al-Dusery H, Naim EA, et al. Association of a mutation in LACC1 with a monogenic form of systemic juvenile idiopathic arthritis. Arthritis Rheum. 2015;67(1):288–95.
40.•• 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;125(11):4196–211. **Comment: first example of digenism in AID.**
41. Takagi M, Ogata S, Ueno H, Yoshida K, Yeh T, Hoshino A, et al. Haploinsufficiency of TNFAIP3 (A20) by germline mutation is involved in autoimmune lymphoproliferative syndrome. J Allergy Clin Immunol. 2017;139(6):1914–22.
42. 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;48(1):67–73.

43. Boyden SE, Desai A, Cruse G, Young ML, Bolan HC, Scott LM, et al. Vibratory urticaria associated with a missense variant in ADGRE2. N Engl J Med. 2016;374(7):656–63.
44. Grandemange S, Sanchez E, Louis-Plence P, Tran Mau-Them F, Bessis D, Coubes C, et al. A new autoinflammatory and autoimmune syndrome associated with NLRP1 mutations: NAIAD (NLRP1-associated autoinflammation with arthritis and dyskeratosis). Ann Rheum Dis. 2017;76(7):1191–8.
45. Soler VJ, Tran-Viet KN, Galiacy SD, Limviphuvadh V, Klemm TP, St Germain E, et al. Whole exome sequencing identifies a mutation for a novel form of corneal intraepithelial dyskeratosis. J Med Genet. 2013;50(4):246–54.
46. Zhong FL, Mamai O, Sborgi L, Boussofara L, Hopkins R, Robinson K, et al. Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation. Cell. 2016;167(1):187–202 e17.
47. Damgaard RB, Walker JA, Marco-Casanova P, Morgan NV, Titheradge HL, Elliott PR, et al. The deubiquitinase OTULIN is an essential negative regulator of inflammation and autoimmunity. Cell. 2016;166(5):1215–30 e20.
48. Zhou Q, Yu X, Demirkaya E, Deuitch N, Stone D, Tsai WL, et al. Biallelic hypomorphic mutations in a linear deubiquitinase define otulipenia, an early-onset autoinflammatory disease. Proc Natl Acad Sci U S A. 2016;113(36):10127–32.
49. Standing AS, 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;214(1):59–71.
50. de Jesus AA, Brehm A, VanTries R, Pillet P, Parentelli AS, Montealegre Sanchez GA, et al. Novel proteasome assembly chaperone mutations in PSMG2/PAC2 cause the autoinflammatory interferonopathy CANDLE/PRAAS4. J Allergy Clin Immunol. 2019;143(5):1939–43 e8.
51. Davidson S, Steiner A, Harapas CR, Masters SL. An update on autoinflammatory diseases: interferonopathies. Curr Rheumatol Rep. 2018;20(7):38.
52. Jeru I, Papin S, L'Hoste S, Duquesnoy P, Cazeneuve C, Camonis J, et al. Interaction of pyrin with 14.3.3 in an isoform-specific and phosphorylation-dependent manner regulates its translocation to the nucleus. Arthritis Rheum. 2005;52(6):1848–57.
53. Biesecker LG, Spinner NB. A genomic view of mosaicism and human disease. Nat Rev Genet. 2013;14(5):307–20.
54.•• Saito M, Fujisawa A, Nishikomori R, Kambe N, Nakata-Hizume M, Yoshimoto M, et al. Somatic mosaicism of CIAS1 in a patient with chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheum. 2005;52(11):3579–85. **Comment: First example of somatic mosaicism in AID.**
55. Saito M, Nishikomori R, Kambe N, Fujisawa A, Tanizaki H, Takeichi K, et al. Disease-associated CIAS1 mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients. Blood. 2008;111(4):2132–41.
56. Arostegui JI, Lopez Saldana MD, Pascal M, Clemente D, Aymerich M, Balaguer F, et al. A somatic NLRP3 mutation as a cause of a sporadic case of chronic infantile neurologic, cutaneous, articular syndrome/neonatal-onset multisystem inflammatory disease: novel evidence of the role of low-level mosaicism as the pathophysiologic mechanism underlying Mendelian inherited diseases. Arthritis Rheum. 2010;62(4):1158–66.
57. Tanaka N, Izawa K, Saito MK, Sakuma M, Oshima K, Ohara O, et al. High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an International Multicenter Collaborative Study. Arthritis Rheum. 2011;63(11):3625–32.
58. Nakagawa K, Gonzalez-Roca E, Souto A, Kawai T, Umebayashi H, Campistol JM, et al. Somatic NLRP3 mosaicism in Muckle-Wells syndrome. A genetic mechanism shared by different phenotypes of cryopyrin-associated periodic syndromes. Ann Rheum Dis. 2015;74(3):603–10.
59. Rowczenio DM, Gomes SM, Arostegui JI, Mensa-Vilaro A, Omoyinmi E, Trojer H, et al. Late-onset cryopyrin-associated periodic syndromes caused by somatic NLRP3 mosaicism-UK single center experience. Front Immunol. 2017;8:1410.
60. de Koning HD, van Gijn ME, Stoffels M, Jongekrijg J, Zeeuwen PL, Elferink MG, et al. Myeloid lineage-restricted somatic mosaicism of NLRP3 mutations in patients with variant Schnitzler syndrome. J Allergy Clin Immunol. 2015;135(2):561–4.
61. Mensa-Vilaro A, Teresa Bosque M, Magri G, Honda Y, Martinez-Banaclocha H, Casorran-Berges M, et al. Brief report: late-onset cryopyrin-associated periodic syndrome due to myeloid-restricted somatic NLRP3 mosaicism. Arthritis Rheum. 2016;68(12):3035–41.
62. Zhou Q, Aksentijevich I, Wood GM, Walts AD, Hoffmann P, Remmers EF, et al. Brief report: cryopyrin-associated periodic syndrome caused by a myeloid-restricted somatic NLRP3 mutation. Arthritis Rheum. 2015;67(9):2482–6.
63. de Inocencio J, Mensa-Vilaro A, Tejada-Palacios P, Enriquez-Merayo E, Gonzalez-Roca E, Magri G, et al. Somatic NOD2 mosaicism in Blau syndrome. J Allergy Clin Immunol. 2015;136(2):484–7 e2.
64. Kawasaki Y, Oda H, Ito J, Niwa A, Tanaka T, Hijikata A, et al. Identification of a high-frequency somatic NLRC4 mutation as a cause of autoinflammation by pluripotent cell-based phenotype dissection. Arthritis Rheum. 2017;69(2):447–59.
65. Jimenez-Trevino S, Gonzalez-Roca E, Ruiz-Ortiz E, Yague J, Ramos E, Arostegui JI. First report of vertical transmission of a somatic NLRP3 mutation in cryopyrin-associated periodic syndromes. Ann Rheum Dis. 2013;72(6):1109–10.
66. Kadowaki T, Ohnishi H, Kawamoto N, Hori T, Nishimura K, Kobayashi C, et al. Haploinsufficiency of A20 causes autoinflammatory and autoimmune disorders. J Allergy Clin Immunol. 2018;141(4):1485–8 e11.
67. Mensa-Vilaro A, Cham WT, Tang SP, Lim SC, Gonzalez-Roca E, Ruiz-Ortiz E, et al. Brief report: first identification of intrafamilial recurrence of Blau syndrome due to gonosomal NOD2 mosaicism. Arthritis Rheum. 2016;68(4):1039–44.
68. Rowczenio DM, Trojer H, Omoyinmi E, Arostegui JI, Arakelov G, Mensa-Vilaro A, et al. Brief report: association of tumor necrosis factor receptor-associated periodic syndrome with gonosomal mosaicism of a novel 24-nucleotide TNFRSF1A deletion. Arthritis Rheum. 2016;68(8):2044–9.
69. Kirino Y, Bertsias G, Ishigatsubo Y, Mizuki N, Tugal-Tutkun I, Seyahi E, et al. Genome-wide association analysis identifies new susceptibility loci for Behcet's disease and epistasis between HLA-B*51 and ERAP1. Nat Genet. 2013;45(2):202–7.
70. Takeuchi M, Mizuki N, Meguro A, Ombrello MJ, Kirino Y, Satorius C, et al. Dense genotyping of immune-related loci implicates host responses to microbial exposure in Behcet's disease susceptibility. Nat Genet. 2017;49(3):438–43.
71. Ombrello MJ, Remmers EF, Tachmazidou I, Grom A, Foell D, Haas JP, et al. HLA-DRB1*11 and variants of the MHC class II locus are strong risk factors for systemic juvenile idiopathic arthritis. Proc Natl Acad Sci U S A. 2015;112(52):15970–5.
72. Bernstein BE, Meissner A, Lander ES. The mammalian epigenome. Cell. 2007;128(4):669–81.
73. Vento-Tormo R, Alvarez-Errico D, Garcia-Gomez A, Hernandez-Rodriguez J, Bujan S, Basagana M, et al. DNA demethylation of inflammasome-associated genes is enhanced in patients with cryopyrin-associated periodic syndromes. J Allergy Clin Immunol. 2017;139(1):202–11 e6.
74. Aubert P, Suarez-Farinas M, Mitsui H, Johnson-Huang LM, Harden JL, Pierson KC, et al. Homeostatic tissue responses in skin biopsies

from NOMID patients with constitutive overproduction of IL-1beta. PLoS One. 2012;7(11):e49408.
75. Kirectepe AK, Kasapcopur O, Arisoy N, Celikyapi Erdem G, Hatemi G, Ozdogan H, et al. Analysis of MEFV exon methylation and expression patterns in familial Mediterranean fever. BMC Med Genet. 2011;12:105.
76. Bekkering S, Arts RJW, Novakovic B, Kourtzelis I, van der Heijden C, Li Y, et al. Metabolic induction of trained immunity through the mevalonate pathway. Cell. 2018;172(1–2):135–46 e9.
77. Hughes T, Ture-Ozdemir F, Alibaz-Oner F, Coit P, Direskeneli H, Sawalha AH. Epigenome-wide scan identifies a treatment-responsive pattern of altered DNA methylation among cytoskeletal remodeling genes in monocytes and CD4+ T cells from patients with Behcet's disease. Arthritis Rheum. 2014;66(6):1648–58.
78. Hofmann SR, Kubasch AS, Ioannidis C, Rosen-Wolff A, Girschick HJ, Morbach H, et al. Altered expression of IL-10 family cytokines in monocytes from CRMO patients result in enhanced IL-1beta expression and release. Clin Immunol. 2015;161(2):300–7.
79. Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet. 2010;42(12):1118–25.
80. Nimmo ER, Prendergast JG, Aldhous MC, Kennedy NA, Henderson P, Drummond HE, et al. Genome-wide methylation profiling in Crohn's disease identifies altered epigenetic regulation of key host defense mechanisms including the Th17 pathway. Inflamm Bowel Dis. 2012;18(5):889–99.