

## Review Article

# The classification, genetic diagnosis and modelling of monogenic autoinflammatory disorders

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Monogenic autoinflammatory disorders are an increasingly heterogeneous group of conditions characterised by innate immune dysregulation. Improved genetic sequencing in recent years has led not only to the discovery of a plethora of conditions considered to be ‘autoinflammatory’, but also the broadening of the clinical and immunological phenotypic spectra seen in these disorders. This review outlines the classification strategies that have been employed for monogenic autoinflammatory disorders to date, including the primary innate immune pathway or the dominant cytokine implicated in disease pathogenesis, and highlights some of the advantages of these models. Furthermore, the use of the term ‘autoinflammatory’ is discussed in relation to disorders that cross the innate and adaptive immune divide. The utilisation of next-generation sequencing (NGS) in this population is examined, as are potential *in vivo* and *in vitro* methods of modelling to determine pathogenicity of novel genetic findings. Finally, areas where our understanding can be improved are highlighted, such as phenotypic variability and genotype–phenotype correlations, with the aim of identifying areas of future research.

## Introduction

The phrase ‘*autoinflammatory disease*’ was proposed as an alternative to ‘*autoimmune disease*’ by McDermott et al. [1] in the paper identifying the genetic cause of Tumour Necrosis Factor (TNF) Receptor Associated Periodic Syndrome (TRAPS). This was considered a suitably representative term at the time, as individuals with inherited periodic fever syndromes had innate immune dysregulation but lacked high titres of autoantibodies and self-reactive T cells [1]. Familial Mediterranean Fever (FMF) was the only genetically defined periodic fever syndrome prior to this publication and the clinical and biochemical features appeared to be well defined [2,3].

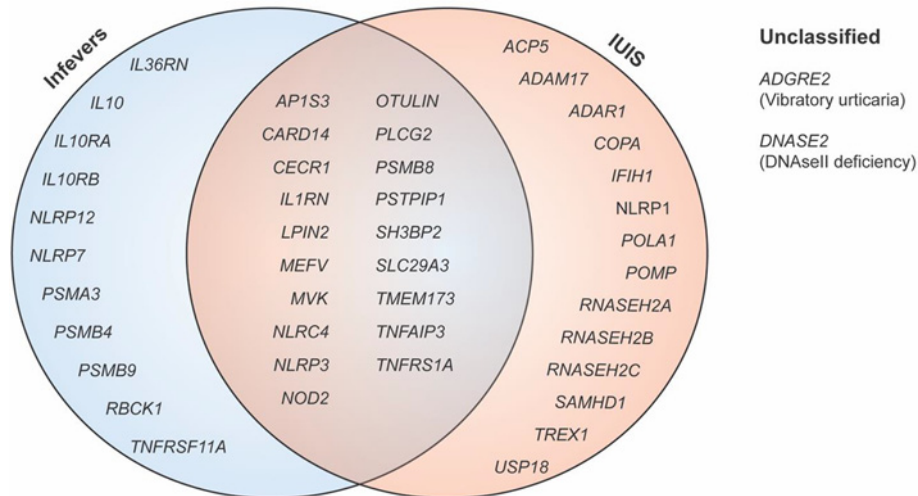
Since this time, over 30 conditions have been added to the list of monogenic autoinflammatory disorders. The significant broadening of clinical features, pathway perturbations and genes involved bring into question the utility of the original definition of these disorders, and whether an alternative is required that better encapsulates the spectrum of immune dysregulation seen. Highlighting the complexity of this task, the list of conditions considered ‘autoinflammatory’ by the International Union of Immunological Societies (IUIS) is incongruent with the *Infervers* database, a registry of mutations associated with autoinflammatory disorders maintained by the International Society for Systemic Autoinflammatory Diseases (ISSAID) (Figure 1) [4,5].

## Classification

The term inflammasomopathy was introduced in the first review of autoinflammatory disorders categorising conditions based on the pathway implicated in disease pathogenesis [6], including disorders affecting inflammasomes, the nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B) pathway, the complement system, protein folding, ‘cytokine signalling’ and those resulting in or from macrophage

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**Figure 1. Genes involved in monogenic autoinflammatory disorders**

Genes involved in monogenic autoinflammatory disorders according to ISSAID as listed in the Infervers database, compared with the IUIS.

activation. Since this time, a number of reviews have adopted a briefer version, with both inflammasome or interleukin (IL)-1 $\beta$  mediated disorders and NF- $\kappa$ B pathway-associated disorders universally included, but the other categories far less frequently [7]. The term ‘interferonopathies’ was first used to describe a group of monogenic disorders characterised by increased type I interferon (IFN) signalling in 2011 [8] but these disorders were only grouped with autoinflammatory disorders by the IUIS in 2017 [4]. No rationale for this change was provided, preventing a unified strategy of classification to be adopted those researching and managing these conditions.

## The pathway model

The pathway model has the advantage of highlighting possible targets for treatment downstream of an abnormal protein, as with Janus kinase (JAK) inhibitors for individuals with stimulator of IFN genes (STING)-associated vasculopathy with onset in infancy (SAVI), as well as possible candidate genes for autoinflammatory disorders, such as that encoding a member of the linear ubiquitin assembly complex (LUBAC), *SHARPIN*. There are, however, limitations to this classification. A clear example is the case of mutations in *TNFRSF1A* causing TRAPS. While TNF receptor 1 (TNFR1) is a key receptor in the NF- $\kappa$ B pathway, the disease is not necessarily caused by increased signalling through this pathway alone [1,9–13]. A number of pathogenic mechanisms have been explored, such as defective shedding of TNFR1 [1], retention of TNFR1 in cytoplasmic aggregates with reduced surface expression [11], and abnormal apoptosis and signalling [12].

This classification also neglects the complex interaction between signalling pathways that exist. NF- $\kappa$ B translocation to the nucleus is important for the expression of pro-IL-1 $\beta$  and NOD-like receptor (NLR) pyrin domain containing 3 (NLRP3), and the consequence of NF- $\kappa$ B dysfunction on inflammasome activation cannot be discounted. Key players in the regulation of NF- $\kappa$ B are also implicated in the regulation of NLRP3, as seen with A20 and the possible role of inflammasome activation in the inflammatory manifestations of haploinsufficiency of A20 (HA20) [14]. Furthermore, although not yet shown in human cells, transforming growth factor (TGF)- $\beta$  activated kinase-1 (TAK1) has been shown to regulate NLRP3, with spontaneous NLRP3 activation documented in TAK1-deficient murine macrophages [15]. The NF- $\kappa$ B and IFN pathways are also intimately linked, with a number of sensors leading to activation of both pathways. In the case of SAVI, literature to date suggests that the IFN pathway is dysregulated in this syndrome [16,17], but whether these two pathways are actually uncoupled in the case of an overactive STING *in vivo* is unclear. Breeding mutant STING mice to *Irf3*<sup>-/-</sup> mice did not rescue the inflammatory phenotype, raising questions, at least in the murine model, of the role of IFN regulatory transcription factor (IRF) 3 in the inflammation associated with SAVI [18]. Furthermore, the role of NF- $\kappa$ B as a member of the IFN- $\beta$  enhanceosome [19], a multicomponent complex that optimises transcriptional activation of IFN- $\beta$ , suggests that the pathways are closely connected.

## The cytokine model

An alternative classification strategy is based on the primary cytokine dysregulated, either increased or decreased, in individuals with autoinflammatory disorders [20]. This is of potential therapeutic benefit as the primary cytokine driving disease can be therapeutically targeted. An example of this is the treatment of individuals with cryopyrin-associated periodic syndrome (CAPS). In the original manuscript linking Neonatal Onset Multisystem Inflammatory Disease (NOMID) to mutations in *NLRP3*, cell lysates from unstimulated monocytes of a case had high pro-IL-1 $\beta$  expression as determined by Western blot, and increased *IL-1 $\beta$*  mRNA in unstimulated peripheral blood mononuclear cells (PBMCs) when compared with healthy controls [21]. The empiric treatment of two cases with recombinant IL-1 receptor antagonist and the rapid resolution of symptoms within hours, and inflammatory markers within days, highlighted the role of IL-1 $\beta$  in the disease pathogenesis [22]. Having said this, the detection of IL-1 $\beta$  in serum of cases is difficult, with both cases and healthy controls having levels below the detection limit of currently available assays. Most publications looking at the IL-1 $\beta$  levels and response to treatment in individuals with CAPS culture PBMCs and measure cytokine release over a 24-h period. The spontaneous secretion of IL-1 $\beta$  by CAPS PBMCs decreases with the initiation of IL-1 $\beta$ -targeted therapy [23]. From this it is clear that even without elevated serum levels, a therapeutic response to IL-1 $\beta$  neutralising therapy suggests that this cytokine is important [23,24]. The response of individuals with colchicine-resistant FMF [25], mevalonate kinase deficiency (MKD) [26], and TRAPS [27] to the neutralising anti-IL-1 $\beta$  antibody canakinumab, suggests that IL-1 $\beta$  is a key cytokine in all of these disorders. Supporting this is evidence of increased expression of *IL1B* and *IL1R1* as determined by microarray in individuals with TRAPS [28]. The gene expression profile of TRAPS moved towards the healthy control profile with canakinumab treatment [27]. More recently, the randomised, double-blind, placebo-controlled study of canakinumab in the above groups demonstrated efficacy in controlling and preventing disease flares [29]. An interesting addition to the literature was a retrospective analysis by Savic et al., of individuals with undifferentiated systemic autoinflammatory disorders who were treated with anakinra [30]. A total of 11 cases were identified over a 3-year period, and nine responded completely to treatment with anakinra within 4–6 weeks of commencement. Although individuals had undergone Sanger sequencing for *NLRP3*, *MEFV*, *TNFRSF1A* and *NOD2* with no pathogenic mutations detected, the marked response to treatment suggests that genes in the IL-1 $\beta$  pathway could be further interrogated for variants that may be causing disease. Conversely, subjects could undergo a broader approach with whole exome sequencing (WES) or whole genome sequencing (WGS) and novel genes involved in the IL-1 $\beta$  pathway may be revealed.

Evaluation of the major cytokine/s involved in monogenic autoinflammatory disorders may point to distinctions between conditions within the same pathway. The gain of function mutations in inflammasome forming proteins that lead to disease can be presumed to cause an increase in IL-1 $\beta$  processing and release. Mutations in *NLRC4* that result in an autoinflammatory phenotype are associated with markedly increased serum free IL-18 levels in cases when compared with healthy controls and individuals with CAPS [31,32,33].

There are also conditions that may involve pathways distinct from those used to categorise autoinflammatory disorders in the literature. Through the study of autosomal recessive generalised pustular psoriasis (GPP) in a number of multiplex families, Marrakchi et al. [34] identified homozygous missense mutations in *IL36RN*, which encodes the IL-36 receptor antagonist (IL-36Ra), causing deficiency in IL-36Ra (DITRA). IL-36 is a member of the IL-1 family of cytokines and, like IL-1 $\beta$ , acts via its receptor IL-36R and, in concert with IL-1 receptor accessory protein (IL1RAcP), signals to NF- $\kappa$ B through myeloid differentiation primary response 88 (MyD88). The binding of IL-36Ra to IL-36R prevents the association of IL1RAcP and downstream signalling. While there have been four case reports of the successful treatment of DITRA with anakinra therapy [35–38], therapeutic benefit has also resulted from TNF inhibition [39–41], IL-17 inhibition with secukinumab [42] and IL-12/IL-23 inhibition with ustekinumab [43–45]. This suggests that these agents may be targeting cytokines that are downstream of IL-36 [38]. The possibility of developing a therapeutic agent that is specific for IL-36 has been explored. Mbow et al. characterised a mouse anti-human antibody (MAB92) with high affinity to the IL-36 receptor that blocks signalling through this pathway [46]. Although highly specific for human IL-36R, the authors created MAB04, which cross-reacts with murine IL-36R for *in vivo* studies. Importantly, MAB04 inhibited imiquimod- and IL-36-induced skin inflammation in mice.

Deficiency in regulatory cytokines have also been described, and the clinical course of these individuals has been tumultuous. Homozygous mutations in *IL10*, *IL10RA* or *IL10RB*, leading to deficiencies in IL-10, IL-10R $\alpha$  or IL-10R $\beta$  respectively, have been reported to cause monogenic early onset inflammatory bowel disease (EOIBD) [47,48]. IL-10 has regulatory effects on the inflammatory response which are mediated through signal transducer and activator of transcription (STAT) 3, with IL-10-deficient mice developing chronic enterocolitis [49–51]. PBMCs from cases with loss of function of these proteins had higher proinflammatory cytokine responses to lipopolysaccharide (LPS) stimulation, including IL-6, TNF and IL-1 $\beta$ , when compared with healthy controls [48]. Although multiple agents have

been trialled in these cases including corticosteroids, azathioprine, methotrexate, cyclosporine A and anti-TNF therapy, only mild clinical benefit has resulted [52]. A number of cases have undergone allogeneic haemopoietic stem cell transplantation (HSCT) with marked improvement in their inflammatory bowel disease [52,53]. While recombinant human IL-10 replacement (rhuIL-10) in individuals with IL-10 deficiency would seem to be a therapeutic option, there have been issues with the response to and side effects from rhuIL-10 in trials of individuals with Crohn's disease [54]. Furthermore, this option would not be effective in individuals with mutations in *IL10RA* or *IL10RB*. At this point in time, HSCT is the only curative option.

A number of other conditions are presumed to result from dysregulation of a particular pathway because of their cytokine profile, but little is known about the steps that lead to this alteration. Proteasome-associated autoinflammatory syndrome (PRAAS) is an autosomal recessive autoinflammatory disorder that encompasses conditions previously considered distinct entities: Nakajo-Nishimura syndrome (NKJO), joint contractures, muscular atrophy, microcytic anaemia, and panniculitis-induced lipodystrophy syndrome (JMPS), as well as chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE). Three publications identified mutations in *PSMB8*, the  $\beta 5i$  catalytic component of the immunoproteasome, as the cause of disease [55–57]. Individuals with homozygous loss of function mutations in *PSMB8* experienced spontaneous febrile episodes with features of muscle weakness, lipodystrophy as well as neutrophilic and lymphocytic infiltrative skin nodules and evidence of cerebral calcification [55–57]. Homozygous mutations were associated with poor proteasome assembly as well as reduced chymotrypsin-like activity and accumulation of ubiquitinated proteins in either Epstein–Barr virus (EBV)-transformed B cells or immortalised lymphoblastoid cell lines from cases [55–57]. In these early papers, increased serum IL-6 was noted in all cases, but the role of IFN was only identified later [58]. Liu et al. noted an almost 80-fold increase in IFN- $\gamma$ -inducible protein 10 (IP-10) in cases compared with healthy controls and individuals with CAPS, prompting whole blood microarray analysis to determine the gene signature of these cases. The IFN pathway was the most differentially regulated pathway in individuals with PRAAS, further supported by stronger STAT1 phosphorylation in response to IFN- $\gamma$  stimulation of monocytes when compared with healthy controls. These authors also highlighted cases with the clinical phenotype of PRAAS without *PSMB8* mutations, later explored by Goldbach-Mansky et al. [59]. Digenic mutations involving *PSMA3* or *PSMB4* and *PSMB8* or *PSMB9*, encoding constitutive proteasome subunits  $\alpha 7$  and  $\beta 7$  or inducible subunits  $\beta 5i$  and  $\beta 1i$  respectively, were found in cases with the clinical diagnosis of PRAAS. One individual harboured a compound heterozygous mutation in *PSMB4*, and another a heterozygous mutation in *POMP*, encoding proteasome maturation protein. Similar to earlier reports, the mutant subunits were not efficiently assembled into the proteasome, resulting in reduced proteolytic activity. When compared with cases with homozygous *PSMB8* mutations, the chymotryptic proteolytic activity was less impaired, but deficiencies were noted in tryptic and caspase proteolytic activity. Similar to homozygous *PSMB8* mutations, there was inefficient clearing of ubiquitinated proteins and the presence of a type I IFN gene signature. Both siRNA models and proteasome inhibitors were used to recapitulate the IFN signature in PBMCs and fibroblasts. However, the mechanism/s by which proteasomal dysfunction leads to this response remains elusive. Classifying PRAAS by its IFN gene signature guides potential treatment considerations and also opens avenues for researchers to determine the role of the immunoproteasome in the IFN pathway.

Clarifying the dominant cytokine or pathway implicated in disease may lead to the development of targeted therapeutic strategies for autoinflammatory conditions, as reviewed in recent publications [60,61]. Recent work has looked at individuals with interferonopathies treated with JAK1/2 inhibitor baricitinib. Initial work was performed by Goldbach-Mansky et al. to determine a dosing regimen for paediatric cases with interferonopathies [62]. This work was then extended with treatment of a number of individuals with interferonopathies including PRAAS and SAVI and longitudinal assessment of response and adverse reactions [63]. Most patients were able to reduce their prednisolone requirements and five out of ten PRAAS cases achieved remission. Adverse events included upper respiratory infections, gastroenteritis and BK viremia. Given that only 18 patients were recruited over a span of 6 years, more work is needed to establish the clinical efficacy and adverse reaction profile in this selected population. The availability of this drug on compassionate grounds through NCT01724580 suggests that more information will become available in the future with ongoing recruitment and follow-up of these cases.

Similarly, elucidating elevated serum free IL-18 levels in an individual with autoinflammation with infantile enterocolitis, an NLRC4-associated autoinflammatory disease, lead to the successful therapeutic trial of a recombinant IL-18 binding protein (rhIL-18) [64]. Following from this, there is a Phase 3 randomised, double-blind, placebo-controlled trial of rhIL-18 in NLRC4-associated autoinflammatory diseases (NCT03113760) as well as an open-label extension (NCT03512314) underway. This not only highlights the importance of identifying driver or dominant cytokines for possible therapeutic manipulation, but also the potential differences between inflammasome effector and regulatory mechanisms as well as possible epigenetic factors, that results in one cytokine dominating over another.

## Autoinflammation, autoimmunity and immune deficiency

The boundaries of what is classified as an autoinflammatory disorder are also being blurred. The strict definition of innate immune dysregulation without self-reactive T cells or high titres of autoantibodies is increasingly in question, especially when one considers interferonopathies such as Aicardi–Goutières syndrome (AGS). AGS was originally described in the 1980s as a disorder of the central nervous system (CNS) associated with lymphocytosis on cerebrospinal fluid analysis and bilateral basal ganglia calcifications [65]. The genetic causes of AGS are numerous, and all involve the processing of nucleic acid, either self or foreign, in the cytoplasm. Loss of function mutations in genes encoding deoxyribonuclease three prime repair exonuclease 1 (TREX1) [66], deoxynucleoside triphosphate triphosphohydrolase SAM and HD domain containing protein 1 (SAMHD1) [67], ribonuclease components ribonuclease H2 (RNASEH2) A (RNASEH2A), RNASEH2B or RNASEH2C [68], or adenosine deaminase acting on RNA 1 (ADAR1) [69] have been identified in individuals with AGS. The link between AGS and autoimmunity was initially made when Aicardi and Goutières speculated that the phenotype of two individuals with infantile systemic lupus erythematosus overlapped AGS considerably. They hypothesised that the two may be either the same condition or linked by an increase in IFN- $\alpha$  [70]. The phenotypic link has subsequently been highlighted by a number of groups [71,72], although the number of subjects in a large cohort of 374 mutations confirmed that AGS with clinically diagnosed lupus was low [73]. An abnormal serum autoantibody profile was seen in a minority of individuals with AGS in one cohort study [74], however another detected persistent antinuclear antibodies (ANA) or autoantibodies against extractable nuclear antigens (ENA), dsDNA and cardiolipin in the majority of their cases with mutation confirmed AGS [72]. Subsequent work using multiplex autoantibody microarrays identified unique autoantibodies in cases with AGS [75]. Whether this condition, and indeed other interferonopathies, should be considered autoimmune or autoinflammatory is a matter of debate. AGS highlights that this distinction is not always clear.

Indeed, the spectrum of immune dysregulation and overlap between autoimmunity, autoinflammation and immune deficiencies has been seen in a number of recently described conditions. Homozygous loss of function mutations in *HOIL1* or *HOIP* have been described in cases with evidence of systemic inflammation, susceptibility to pyogenic infections, and amylopectinosis [76,77]. The original description by Boisson et al. highlighted the importance of haem-oxidised IRP2 ubiquitin ligase 1 (*HOIL1*) in maintaining the stability of the LUBAC, involved in the ubiquitination of components in the NF- $\kappa$ B pathway, as well as promoting the association of inhibitor of NF- $\kappa$ B kinase subunit  $\gamma$  (*IKK $\gamma$* ) with TNF or IL-1 receptor signalling complexes [76]. The authors noted cell-type specific defects associated with *HOIL1* deficiency. Fibroblasts and EBV-immortalised B cells from subjects displayed impaired canonical NF- $\kappa$ B pathway activation in response to TNF or IL-1 $\beta$  as well as partial impairment of the response to toll-like receptor (TLR) stimuli. The inflammatory phenotype was determined to originate from monocytes, with monocytes displaying hyper-responsiveness to IL-1 $\beta$  in terms of inflammatory cytokines produced compared with healthy control monocytes. The clinical and cellular phenotypes in the *HOIL1*-deficient cases overlap with those seen in an individual with homozygous loss of function mutations in *HOIP* [77]. The publication of a series of ten cases from eight families with polyglucosan storage myopathy harbouring either homozygous or compound heterozygous mutations in *HOIL1* [78] suggests that mutations in this gene, and potentially other components of LUBAC, may also present with a more limited clinical phenotype, and that much remains to be learnt about genotype–phenotype correlations in these disorders.

Classifying these as autoinflammatory diseases inherently fails to acknowledge the associated immunodeficiency, and *vice versa*. A similar problem concerns the conditions caused by mutations in *PLCG2* encoding phospholipase c  $\gamma$ -2 (*PLC $\gamma$ 2*), *PLC $\gamma$ 2*-associated antibody deficiency and immune dysregulation (*PLAID*) and autoinflammation and *PLAID* (*APLAID*) [79,80]. *PLC $\gamma$ 2* was linked to autoimmune and autoinflammatory diseases initially through an N-ethyl-N-nitrosourea (ENU) mutagenesis screen [81]. A heterozygous point mutation in *PLCG2* in mice led to spontaneous inflammation, arthritis and dermatitis with evidence of immune complex driven glomerulonephritis. Subsequently, by sequencing three families with dominantly inherited cold-induced urticaria, antibody deficiency and autoimmunity, in-frame deletions in *PLCG2* were identified and shown to segregate with disease [79]. These deletions affected the autoinhibitory C-terminal Src-homology 2 domain and resulted in constitutive phospholipase activity. Interestingly, and somewhat contradictory to the increased activity of *PLC $\gamma$ 2*, B cells and natural killer (NK) cells demonstrated reduced calcium flux and reduced phosphorylation of mitogen-activated protein kinase (MAPK) in response to stimulation with either IgM cross-linking or cross-linking of activating receptors respectively. This was determined to be temperature specific, however, with increasing MAPK pathway phosphorylation and cytosolic calcium in response to decreasing temperatures. This description was quickly followed by one of a family with a dominantly inherited autoinflammatory condition who had a missense mutation in *PLCG2*. Unlike the previous

report, the individuals had no evidence of autoimmunity, but did have hypogammaglobulinaemia and markedly reduced class switched memory B cells in addition to inflammatory manifestations in the form of skin inflammation and granulomata, enterocolitis, bronchiolitis and uveitis [80]. Of the two cases described, neither had cold-induced symptoms. Increased baseline PLC $\gamma$ 2 activity was noted in an overexpression COS-7 cell model. Chae et al. [82] progressed the understanding of the inflammatory manifestations of APLAID by showing that the increased activity of PLC $\gamma$ 2 and subsequent increase in inositol and release of Ca<sup>2+</sup> from ER stores, previously established by Kurosaki and Tsukada [83], resulted in increased NLRP3 activation and IL-1 $\beta$  release when assessing PBMCs from cases compared with healthy controls. It would be interesting to determine whether the same increase in NLRP3-driven IL-1 $\beta$  is seen when PBMCs from PLAID subjects are examined, as their inflammatory phenotype was not as profound, and was temperature dependent. Furthermore, the partial response to IL-1 $\beta$ -targeted therapy [80] suggests that there may be more than NLRP3 driving the inflammatory disease.

Clearly, more information is needed to tease out the different immunological consequences of mutations in *PLCG2*. This is, of course, not unique to this autoinflammatory disease. With the description of rare disorders and involvement of novel genes and mutations, one can expect the phenotypic spectrum to evolve as more cases are reported. In the case of deficiency of adenosine deaminase 2 (DADA2), homozygous loss of function mutations in *CECR1* were found in individuals with polyarteritis nodosa [84] as well as early onset stroke, vasculopathy and febrile episodes [85]. Although immunodeficiency and autoimmunity were not a major feature, IgM deficiency was noted in a number of cases [85]. Treatment of ten individuals with TNF targeting therapy by Levy-Lahad et al. led to significant clinical improvement, highlighting the role of this cytokine in disease pathogenesis [84]. The response to TNF directed therapy has since been reproduced [86,87]. In a subsequent study of 48 cases with polyarteritis nodosa associated with livedo reticularis and/or strokes, Gattorno et al. performed Sanger sequencing of *CECR1* and determined that 15 cases harboured homozygous or compound heterozygous mutations [88]. Since the time of the original description, there has been an expansion of the clinical phenotype of cases with DADA2, from cytopaenias and pure red cell aplasia [89], to lymphoproliferative disease [90–92], and combined immune deficiency, as well as common variable immune deficiency (CVID) [93]. Indeed, a cohort study of 181 cases with antibody deficiency diagnosed 11 individuals with mutation and enzyme activity confirmed DADA2 [94]. An interesting finding in this group was that anti-TNF therapy resulted in an improvement in IgM levels in one case, and there was an inverse correlation between c-reactive protein (CRP) and IgG in another. Further complicating the potential mechanisms of this disease, individuals with DADA2 have also been reported to have an IFN gene signature [95,96]. Researchers investigated individuals with features overlapping with AGS-5 (caused by mutations in *SAMHD1*). In each report, cases had enhanced IFN stimulated gene expression. These cases were treated with a range of immunosuppressive agents but had not been trialled on anti-TNF therapy. Given the reports of profound response in individuals with DADA2 to this therapy, it would be interesting to determine whether the IFN gene signature is abrogated with the use of anti-TNF therapy.

Furthermore, a number of conditions classified as disorders of predominantly antibody deficiency by the IUIS have marked autoinflammatory features. The syndrome of sideroblastic anemia with B-cell immunodeficiency, periodic fevers and developmental delay (SIFD) was first described by Wiseman et al. in 2013 [97], with 11 out of the 12 cases described experiencing periodic fevers. It was subsequently determined to be caused by homozygous or compound heterozygous mutations in *TRNT1* [98], encoding the CCA-adding enzyme tRNA nucleotidyltransferase [99]. Aksenitjevich et al. investigated the inflammatory phenotype of these cases, noting markedly elevated acute phase reactants and inflammatory cytokines in cases with active disease [100]. The authors documented reduced expression of mature cytosolic tRNA, as well as increased reactive oxygen species when corrected for live cells in fibroblasts after 72 h compared with healthy controls. Using an siRNA knockdown THP-1 cell model, *TRNT1*-knockdown cells demonstrated increased IL-1 $\beta$  production at baseline and in response to LPS which was reversed with the small molecule NLRP3 inhibitor MCC950, suggesting an NLRP3-dependent inflammatory phenotype.

## Autoinflammatory disease classification summary

From the above discussion, it is apparent that there are significant barriers to a simple definition or classification criteria for what are considered monogenic autoinflammatory disorders. As research progresses, the inflammatory component of disorders previously considered to be primarily of immune deficiency or autoimmunity will become more apparent. Provided in Figure 2 is a summary of conditions listed as autoinflammatory disorders in the latest IUIS Expert Committee for Primary Immunodeficiency (2017) as well as the *Infervers* database, documenting the spectrum of immunological manifestations recognised to date.

**Table 1 Monogenic autoinflammatory disorder summary table**

Condition	Gene/s	Protein	MOI	GOF/LOF	Pathway	Cytokine group	System involved	Human cell model	Potential murine model	Reference/s
ADAM17 deficiency	ADAM17	ADAM17	AR	LOF	Unknown	Unknown	Skin GIT	<b>PBMC:</b> ↓TNF-α response to LPS, PMA + anti-CD3/anti-CD28 antibodies	Nil	[148]
AGS1	TREX1	TREX1	AR or AD	LOF	IFN	T1FN	CNS	<b>Human neural stem cell-derived astrocytes, primary astrocytes, brain-derived endothelial cells:</b> shRNA knockdown → IFN gene signature + ↑ proinflammatory cytokines	<i>Trex1</i> <sup>-/-</sup> mice	[66,149–151]
AGS2	RNA5EH2B	RNA5EH2B	AR	LOF	IFN	T1FN	CNS		<i>Rna5eh2b</i> knockout first [KOF] mice	[68,74]
AGS3	RNA5EH2C	RNA5EH2C	AR	LOF	IFN	T1FN	CNS		<i>Rna5eh2c</i> <sup>-/-</sup> mice	[68,74,152,153,154]
AGS4	RNA5EH2A	RNA5EH2A	AR	LOF	IFN	T1FN	CNS		<i>Rna5eh2a</i> G37S/G37S	[68,74,149]
AGS5	SAMHD1	SAMHD1	AR	LOF	IFN	T1FN	CNS	<b>Hela cells:</b> transfection of mutant SAMHD1 showed abnormal localisation <b>Human neural stem cell-derived astrocytes primary astrocytes, brain-derived endothelial cells:</b> shRNA knockdown → IFN gene signature + ↑ proinflammatory cytokines	<i>Samhd1</i> <sup>-/-</sup> mice	[67,73,149,155–157]
AGS6	ADAR1	ADAR1	AR	LOF	IFN	T1FN	CNS	<b>HEK293T cells:</b> IFN reporter assay <b>Lymphoblastoid cell line:</b> ↓ ADAR1 expression of mutant c/w <b>Human neural stem cell-derived astrocytes, primary astrocytes, brain-derived endothelial cells:</b> shRNA knockdown minimal change in ISG/IFN cytokine profile	<i>Adar1</i> <sup>-/-</sup> SCL-Cre-ERT <sup>+</sup> mice	[149,158]
AGS7	IFIH1	MDA5	AD	GOF	IFN	T1FN	CNS		<i>Ifih1</i> <sup>9S4</sup> mice	[159–161]
AIADK	NLRP1	NLRP1	AD	GOF	Inflam	IL-18 ?IL-1β	Multiple		<i>Nlrp1a</i> Q593P mice*	[162,163]
AIPEC	NLRP4	NLRP4	AD	GOF	Inflam	IL-18	Multiple		mu-NLRP4 transgenic mice	[147,32,163–165]
ALLIK	COPA	COPA	AD	Dominant negative	?NF-κB ?IFN	Multiple incl lungs, kidney	Multiple	<b>Monocytes:</b> ↑IL-1β in response to PrgI priming + flagellin <b>Monocyte-derived macrophages:</b> ↑ cell death, ↑IL-1β, IL-18 with LPS	Nil	[166,167]
APLAID	PLCG2	PLCY2	AD	GOF	Unknown ?Inflam ?NF-κB	Unknown ?IL-1β	Multiple	<b>HEK293T cells:</b> ASC speck analysis and inflammasome reconstitution <b>iPSCs:</b> ↑IL-1β, IL-18 to LPS <b>CD4 T cells:</b> skewing to Th17 response <b>BLCL:</b> ↓ autophagy, ↑ transcription IL-1β, IL-6, IL-23 <b>HEK293T cells:</b> shRNA knockdown → ↑ ER stress	Multiple*	[80,82]
Biau syndrome	NOD2	NOD2	AD	GOF	NF-κB	Multiple TNF-α	Multiple	<b>PBMC:</b> response to NLRP3 activation <b>B cells:</b> ↓ ERK phosphorylation	<i>Nod2</i> 2939c mice	[168–170]
CAPS	NLRP3	NLRP3	AD	GOF	Inflam	IL-1β	Multiple	<b>HEK293T cells:</b> NF-κB luciferase assay, ↑ activity with transfection of mutants <b>PBMC:</b> single patient w novel variant ↓ NF-κB response <b>PBMC:</b> constitutively high IL-1β secretion, as well as IL-6 + TNF <b>THP1 cells:</b> ↑ IL-1β and IL-18 when transduced with mutant c/w WT <b>CD4 T cells:</b> α-CD3 + α-CD46 stimulation → ↑ IL-1β in patient cells c/w WT	<i>Nlrp3</i> <sup>A350V</sup> neoR/+ <i>Nlrp3</i> <sup>L351P</sup> neoR/+ mice <i>Nlrp3</i> <sup>R259W</sup> mice	[21,154,171–173]
Cherubism	SH3BP2	SH3BP2	AD	? GOF ? dominant negative	? NF-κB ? NFATc1	TNF-α	Bone		<i>Sh3bp2</i> P416R/+ mice	[174,175]
DADA2	CECR1	ADA2	AR	LOF	Unknown	?T1FN ?TNF-α	Multiple incl vascular bone	<b>PBMC:</b> ↑ B cell death when cultured without stimulation <b>Monocytes:</b> differentiate into M1→M2	Nil	[84,85,92,93]
DIRA	IL1RN	IL-1Ra	AR	LOF	IL-1β	Multiple	Multiple bone	<b>Mononuclear cells:</b> stimulation with IL-1β → ↑ IL-1α, MIP1α, TNF-α, IL-8, IL-6 c/w WT	<i>Il1rn</i> <sup>-/-</sup> mice*	[176,177,178,179,180,181,40–42]
DITRA	IL36RN	IL-36Ra	AR	LOF	Other	IL-36	Skin	<b>PBMC:</b> IL-36A stimulation → ↑ IL-1α, IL-6, IL-8, TNF-α c/w WT	<i>Il1f6</i> transgenic, <i>Il1f5</i> <sup>-/-</sup> mice	[182]

Continued over

**Table 1 Monogenic autoinflammatory disorder summary table (Continued)**

Condition	Gene/s	Protein	MOI	GOF/LOF	Pathway	Cytokine group	System involved	Human cell model	Potential murine model	Reference/s
EOIBD	<i>IL10</i> , <i>IL10RA</i> , <i>IL10RB</i>	IL10, IL10RA, IL10RB	AR	LOF	Other	IL-10	GIT	<p><b>PBMC:</b> Failure of IL-10 to J. LPS induced TNF-<math>\alpha</math> in patients with receptor mutations; More rapid TNF-<math>\alpha</math> response to LPS; Failure to phosphorylate STAT3 in response to IL10</p>	<i>IL10<sup>flac</sup>/flac</i> mice* <i>IL-10<sup>-/-</sup></i> Cx3cr1 <sup>fl</sup> /+ mice	[47,48,51,183]
FCAS2	<i>NLRP12</i>	NLRP12	AD	LOF	NF- $\kappa$ B ? Inflamm	TNF- $\alpha$ , IL-6, IL-1 $\beta$	Skin Multiple	<p><b>HEK293T cells:</b> NF-<math>\kappa</math>B luciferase assay</p> <p><b>PBMC:</b> <math>\uparrow</math> spontaneous TNF-<math>\alpha</math>, IL-6, IL-1<math>\beta</math> c/w WT</p>	<i>NLRP12<sup>-/-</sup></i> mice	[184–186]
FMF	<i>MEFV</i>	Pyrin	AR->AD	GOF	Inflamm	IL-1 $\beta$	Multiple	<p><b>PBMC:</b> no spontaneous IL-1<math>\beta</math> secretion when cultured. <math>\uparrow</math> IL-1<math>\beta</math> in response to LPS (inconsistent). Anti-CD3/CD28 stimulation <math>\rightarrow</math> <math>\uparrow</math> IL-17 and IL-22</p> <p><b>Neutrophils:</b> possible release of IL-1<math>\beta</math> through NETS</p>	<i>Me61M800/M830</i> mice <i>Me61M894V/M894V</i> mice <i>Me61V726AV/726A</i> mice	[178, 179, 187, 188]
H syndrome	<i>SLC29A3</i>	SLC29A3	AR	LOF	Unknown	Unknown	Multiple	<p><b>HEK293T cells:</b> NF-<math>\kappa</math>B luciferase assay</p>	<i>ENT3<sup>-/-</sup></i> mice	[189,190]
HA20	<i>TNFAIP3</i>	A20	AR	LOF	NF- $\kappa$ B Inflamm	Unknown	Multiple	<p><b>PBMC, fibroblasts:</b> <math>\uparrow</math> nuclear translocation p65 at rest + with TNF stimulation</p> <p><b>PBMC:</b> LPS <math>\rightarrow</math> <math>\uparrow</math> inflammatory cytokines; Polarisation to Th9, Th17 CD4 T cell lineage. LPS <math>\rightarrow</math> NLRP3 inflam activation</p>	<i>A20<sup>-/-</sup></i> mice*	[14]
HIDS	<i>MVK</i>	MVK	AR	LOF	Inflamm	IL-1 $\beta$	Multiple	<p><b>EBV-LCL:</b> accumulation unphosphorylated I<math>\kappa</math>B proteins (temperature dependent)</p>	<i>Mvk<sup>-/-</sup></i> mice	[191–195]
HOLL1 deficiency	<i>ABCK1</i>	HOLL1	AR	LOF	NF- $\kappa$ B	Multiple	Multiple	<p><b>Fibroblasts, B cells:</b> <math>\downarrow</math> NF-<math>\kappa</math>B activation, JNK phosphorylation normal. Impaired response to IL-1<math>\beta</math> &gt; TNF</p>	<i>Rock1<sup>-/-</sup></i> mice* (overtly normal)	[76]
HOIP deficiency	<i>AIM2</i>	HOIP	AR	LOF	NF- $\kappa$ B	Multiple	Multiple	<p><b>CD3+, CD19+, CD56+ cells:</b> No response to TNF or IL-1<math>\beta</math> stimulation</p> <p><b>Monocytes:</b> IL-1<math>\beta</math> stimulation <math>\rightarrow</math> <math>\uparrow</math> IL-6 and MIP-1<math>\alpha</math> c/w healthy control</p>	<i>Hcp1<sup>-/-</sup></i> mice (embryonically lethal). Various crosses	[77]
HYDM1	<i>NLRP7</i>	NLRP7	AR	Unknown	? Inflamm ? NF- $\kappa$ B	Unknown	Placenta	<p><b>B cells:</b> <math>\downarrow</math> CD80 up-regulation with CD40L + IL-21 or IL-4</p> <p><b>Monocytes:</b> IL-1<math>\beta</math> stimulation <math>\rightarrow</math> <math>\uparrow</math> IL-6 and IL-1<math>\beta</math> c/w healthy control</p>	Nil (no murine orthologue)	[180, 181, 196–199]
Majeed syndrome	<i>LIPIN2</i>	Lipin 2	AR	LOF	Inflamm	IL-1 $\beta$	Bone Skin Multiple	<p><b>HEK293T cells:</b> PAP activity assay.</p> <p>Hepati-6 cells: PPAR<math>\alpha</math> luciferase assay.</p>	<i>Lpin2<sup>-/-</sup></i> mice	[200–203]
MSPC	<i>NLRP1</i>	NLRP1	AD	GOF	Inflamm	IL-1 $\beta$	Skin	<p><b>HEK293T cells:</b> ASC speck assay, reconstitution of inflam <math>\uparrow</math> pro-IL-1<math>\beta</math> cleavage</p>	<i>Nlrp1<sup>G593P</sup></i> mice*	[153,204]
ORAS	<i>OTULIN</i>	Otlulin	AR	LOF	NF- $\kappa$ B	TNF	Multiple	<p><b>Primary keratinocytes:</b> spontaneous inflam activation</p> <p><b>PRMA differentiated THP1 cells:</b> Doxycycline induced <i>NLRP7</i> expression constructs. Mutants <math>\uparrow</math> IL-1<math>\beta</math> and cell death. ASC dependent</p>	CreERT2- <i>Otlulin<sup>flac</sup>/flac</i> mice	[205,206]
PAAND	<i>MEFV</i>	Pyrin	AD	GOF	Inflamm	?Multiple	Skin Multiple	<p><b>HEK293T cells:</b> transfection of mutant TNF-<math>\kappa</math>B pathway c/w WT; NF-<math>\kappa</math>B luciferase assay showed <math>\downarrow</math> inhibitory effect of mutant Otlulin c/w WT</p> <p><b>T cells:</b> Normal proliferation and NF-<math>\kappa</math>B response to TCR stimulation</p> <p><b>B cells:</b> Normal proliferation and NF-<math>\kappa</math>B response to BCR stimulation</p> <p><b>Fibroblasts:</b> Expression undetectable. <math>\uparrow</math>p-I<math>\kappa</math>B<math>\alpha</math>, p-I<math>\kappa</math>B<math>\beta</math>, p-P38 and p-JNK with TNF stimulation. <math>\downarrow</math> ability to deubiquitinate linear chains</p> <p><b>PBMC:</b> <math>\downarrow</math> ability to deubiquitinate linear chains</p> <p><b>Monocyte:</b> ASC speck formation, caspase-1 activity, c/w healthy control</p> <p><b>PBMC:</b> <math>\uparrow</math> IL-1<math>\beta</math> and IL-1Ra with LPS stimulation c/w healthy control</p> <p><b>HEK293T cells:</b> ASC speck assay. 1,4-3-3 binding in overexpression model</p>	Nil	[207,208]
PAPA syndrome	<i>PSTPIP1</i>	PSTPIP1	AD	Unknown	Inflamm	?IL-1 $\beta$	Skin, Joints Multiple	<p><b>THP1 cells:</b> Retroviral reconstitution and lentiviral reconstitution of <i>MEFV</i> KO cells. Mutants <math>\uparrow</math> cell death. <math>\uparrow</math>IL-1<math>\beta</math>, IL-18</p> <p><b>HeLa cells:</b> Transient cotransfection. Mutant PSTPIP1 hyperphosphorylated and <math>\uparrow</math> binding to pyrin</p> <p><b>CoS-7L cells:</b> inflammasome reconstitution assay. Mutant PSTPIP1 <math>\uparrow</math>IL-1<math>\beta</math> processing</p> <p><b>THP1 cells:</b> Immunoprecipitation to show interaction between PSTPIP1 and pyrin</p> <p><b>Macrophages:</b> <math>\downarrow</math> invasion and podosome formation</p> <p><b>T cells:</b> <math>\downarrow</math> numbers, <math>\downarrow</math> proliferation response to mitogen. Normal migration</p> <p><b>PBMC:</b> <math>\downarrow</math> IL-1Ra, <math>\uparrow</math>IL-1<math>\beta</math>, IL-6, TNF-<math>\alpha</math> and GM-CSF in response to multiple stimuli. siRNA knockdown of <i>NLRP3</i> <math>\downarrow</math>IL-1<math>\beta</math> in response to LPS</p>	Rosa- <i>PSTPIP1</i> A2301STOP <sup>del</sup> /+ mice	[209–213]

Continued over

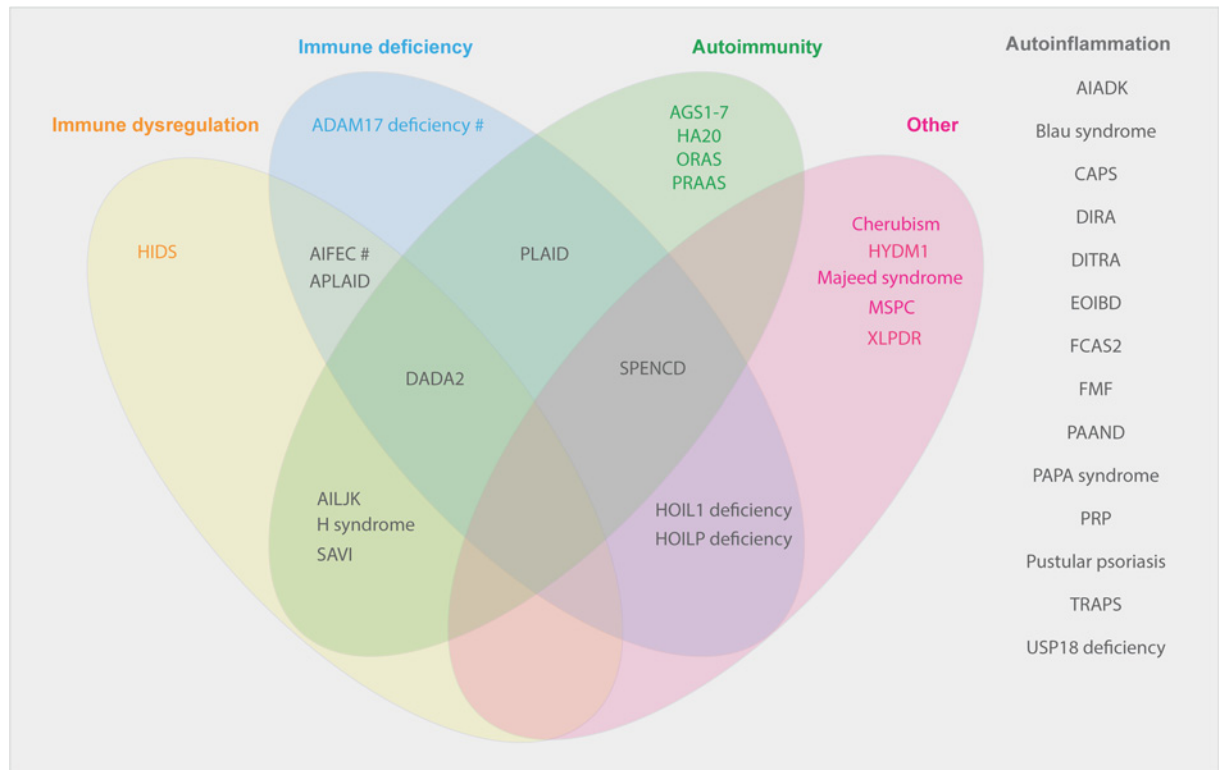


**Table 1 Monogenic autoinflammatory disorder summary table (Continued)**

Condition	Gene/s	Protein	MOI	GOF/LOF	Pathway	Cytokine group	System involved	Human cell model	Potential murine model	Reference/s
PLAID	<i>PLCG2</i>	PLCγ2	AD	GOF	Unknown	Unknown	Multiple	<b>COS7, A20 cells:</b> transfection model. Mutants- ↑phospholipase activity at subphysiological temperatures <b>LAD2 mast cells:</b> transfection of mutant → spontaneous degranulation at 20°C <b>B cells and NK cells:</b> ↓ERK phosphorylation in response to stimulation <b>T cells:</b> normal response to CD3 cross-linking	Multiple*	[79]
PRAAS	<i>PSMB8, PSMB9, PSMB4, PSMA3, POMP</i>	PSMB8, PSMB9, PSMB4, PSMA3, POMP	AR	LOF	?NF-κB ?IFN	T1IFN	Multiple	<b>HeLa cells:</b> Transfection studies show poor formation of proteasome with mutant c/w WT <b>Primary fibroblasts:</b> ↑ precursor complexes in patients. siRNA knockdown in control cells → IFN induction and proteasome dysfunction <b>Lymphoblastoid cell line:</b> ↑ precursor complexes, ↓ proteasome formation <b>EBV transformed B cells:</b> generally, ↓ chymotryptic like activity <b>Primary keratinocytes:</b> Ubiquitin aggregation	<i>Lmp7<sup>-/-</sup></i> mice	[59,214]
PRP	<i>CARD14</i>	CARD14	AD	GOF	NF-κB		Skin	<b>HEK293T cells:</b> NF-κB luciferase assay <b>Immortalised primary keratinocytes:</b> Expression + NF-κB activity	Nil	[215,216]
Pustular psoriasis	<i>AP1S3</i>	AP1S3	AR	LOF	?NF-κB	IL36 IL-1	Skin	<b>Primary keratinocytes and dermal fibroblasts:</b> abnormal autophagy, accumulation of p62. Abnormal TLR2/6 signalling	Nil	[217,218]
SAVI	<i>TMEM173</i>	STING	AD	GOF	IFN	T1IFN	Multiple incl lungs, vessels	<b>HEK293T cells:</b> <i>IFNB1</i> reporter assay. Immunoblot analysis of STING <b>CD4, CD8 T cells, CD19 B cells:</b> constitutive STAT1 phosphorylation <b>PBMC and dermal fibroblasts:</b> ↑ <i>IFNB1</i> transcription at rest. No change with cGAMP exposure. Transcription of <i>TNF</i> and <i>IL-6</i> ↑ at baseline and with cGAMP treatment	<i>Sting<sup>N153S/+</sup></i> mice	[16-18]
SPENCD	<i>ACP5</i>	ACP5	AR	LOF	IFN	T1IFN	Multiple	<b>Primary human macrophages:</b> colocalisation studies <b>Plasmacytoid dendritic cells:</b> co-localisation studies. TLR9 stimulation in shRNA <i>ACP5</i> knockdown studies → ↑ transcription ISGs <b>HEK293T cells:</b> cotransfection TRAP and osteopontin followed by immunoprecipitation <b>THP1 cells:</b> shRNA <i>ACP5</i> knockdown studies → ↑ phosphorylation of osteopontin	<i>Acp5<sup>-/-</sup></i> mice	[219-222]
TRAPS	<i>TNFRS1A</i>	TNFR1	AD	Unknown	NF-κB	?IL-1β	Multiple	<b>PBMC:</b> ↑surface expression TNFR1 + ↓shedding (conflicting data) <b>Monocytes:</b> ↑surface expression TNFR1 and ↓shedding; Abnormal autophagy → ↑IL-1β + NF-κB activation <b>Dermal fibroblasts:</b> Mutant TNFR1 ↓ receptor shedding <b>Neutrophils:</b> Mutant TNFR1 abnormal retention in cytoplasm <b>HEK293T cells:</b> minor differences in receptor shedding when TNFR1 WT or mutant overexpressed; Cytoplasmic retention and reduced surface expression of mutant	<i>Tnfrsf1a<sup>T50M/+</sup></i> mice (13) <i>Tnfrsf1a<sup>C33Y/+</sup></i> mice (232) <i>Tnfrsf1a<sup>p55deltINS</sup></i> mice (10)	[1,9-11,13,223-232]
USP18 deficiency	<i>USP18</i>	USP18	AR	LOF	IFN	T1IFN	CNS Liver	<b>Primary dermal fibroblasts:</b> ↑ transcription ISG after IFN stimulation. Persistent STAT2 phosphorylation. No sig difference in IL-6 response to IL-1β or poly(I:C) .↑ISGylation	<i>Usp18<sup>-/-</sup></i> mice*	[233]
XLPR	<i>POLA1</i>	POLA1	XLR	LOF	IFN > NF-κB	T1IFN	Multiple	<b>Primary dermal fibroblasts:</b> ↑IFN + NF-κB response to stimulation with poly(da:dt) or TNF; ↑IRF and NF-κB pathway activation; ↓RNA:DNA levels; Lentiviral transduction of WT rescued phenotype <b>Fibroblast and HeLa cell line:</b> siRNA <i>POLA1</i> knockdown → ↑ IFN + NF-κB response to stimulation with poly(da:dt) or TNF	Nil	[234]

Abbreviations: AD, autosomal dominant; AIADK, autoinflammation with arthritis and dyskeratosis; AID, autoinflammatory disorder; AIFEC, autoinflammation with infantile enterocolitis; AILJK, autoimmune interstitial lung, joint and kidney disease; AR, autosomal recessive; BLCL, EBV-transformed B-lymphoblastoid cell lines; c/w, compared with; CD, cluster of differentiation; COPA, coatomer subunit α; DIRA, deficiency of IL-1 receptor antagonist; ER, endoplasmic reticulum; FCAS2, familial cold autoinflammatory syndrome 2; GIT, gastrointestinal tract; GOF, gain of function; HIDS, hyper IgD syndrome, HYDM1, hydatidiform molar pregnancy; Inflam, inflammasome; ISG, IFN-stimulated gene; LOF, loss of function; MOI, mode of inheritance; MSPC, multiple self-healing palmoplantar carcinoma; NFATc1, nuclear factor of activated T cell, cytoplasmic 1; ORAS, otulin-related autoinflammatory syndrome; PAAND, pyrin-associated autoinflammation with neutrophilic dermatosis; POLA, DNA polymerase α catalytic subunit; PRP, pityriasis rubra pilaris; SMS, Singleton–Merten syndrome; SPENCD, spondyloenchondrodysplasia; T1IFN, type 1 IFN; XLPR, x-linked pigmentary disorder, reticulate, with systemic manifestations.

\*Murine model prior to the description of monogenic condition.



**Figure 2. Phenotypic spectrum of monogenic autoinflammatory disorders**

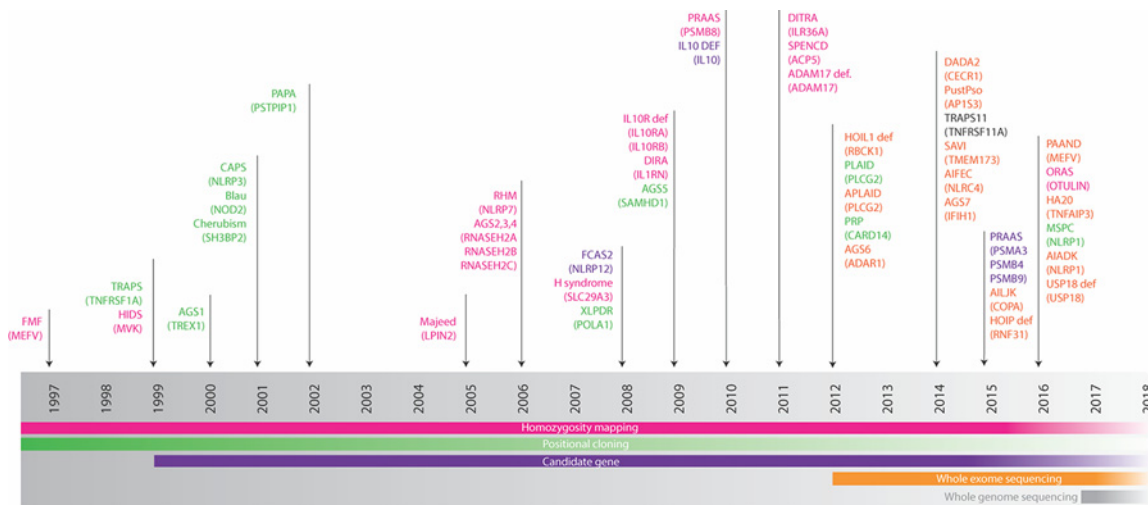
Abbreviations: AIADK, autoinflammation with arthritis and dyskeratosis; AID, autoinflammatory disorder; AIFEC, autoinflammation with infantile enterocolitis; AILJK, autoimmune interstitial lung, joint and kidney disease; DIRA, deficiency of IL-1 receptor antagonist; FCAS2, familial cold autoinflammatory syndrome 2; HIDS, hyper IgD syndrome; HYDM1, hydatidiform molar pregnancy; MSPC, multiple self-healing palmoplantar carcinoma; ORAS, otulin-related autoinflammatory syndrome; PAAND, pyrin-associated autoinflammation with neutrophilic dermatosis; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne; PRP, pityriasis rubra pilaris, SPENCD, spondyloenchondrodysplasia; XLPDR x-linked pigmentary disorder, reticulate, with systemic manifestations. #Susceptibility.

## Genetic sequencing of autoinflammatory disorders

The phenotypic heterogeneity of what is considered a monogenic autoinflammatory disorder, as well as the explosion in the number of newly described conditions, coincides with advances in genetic sequencing techniques. The gene mutated in FMF was determined to be *MEFV* using positional cloning methods in 1997, and since this time many more disease-causing genes have been recognised (Figure 3). Next-generation sequencing (NGS) technology has been used in the description of these conditions since 2012, starting with the identification of *RBCK1* as the gene implicated in HOIL1 deficiency [76].

### NGS

The now widely adopted NGS, also known as massive parallel or deep sequencing, is a broad term encompassing a number of different technologies that share the ability to generate and analyse millions of sequences per run. There are a large number of platforms on which NGS can be performed, and the specifics of the sequencing method varies depending on the instrument used [102]. In general, the sequencing process involves the preparation of a library of short DNA fragments through either enzymatic or sonication techniques. These short strands of DNA are then ligated to generic adapters *in vitro*. PCR amplification follows, performed using either emulsion PCR in oil–water emulsion micelles, or bridge PCR on a solid surface coated with complementary primers. Subsequent sequencing of the amplicon is performed by either pyrosequencing, sequencing by ligation or sequencing by synthesis. The large number of short reads generated from this process must then be aligned against a reference sequence. A plethora of software have been developed not only to align the reads, but to also determine where deviations from a reference sequence exist. Furthermore, considering that WES or WGS of an individual identifies 20000 or 4000000 variants



**Figure 3. Timeline of monogenic autoinflammatory disorder discovery and genetic sequencing technique used**

Abbreviations: AIADK, autoinflammation with arthritis and dyskeratosis; AIFEC, autoinflammation with infantile enterocolitis; AILJK, autoimmune interstitial lung, joint and kidney disease; DIRA, deficiency of IL-1 receptor antagonist; Dysreg, dysregulation (including lymphoproliferation); FCAS2, familial cold autoinflammatory syndrome 2; HIDS, hyper IgD syndrome; HYDM1, hydatidiform molar pregnancy; MSPC, multiple self-healing palmoplantar carcinoma; ORAS, otulin-related autoinflammatory syndrome; PAAND, pyrin-associated autoinflammation with neutrophilic dermatosis; PAPA pyogenic arthritis, pyoderma gangrenosum and acne; RAAS, proteasome associated autoinflammatory syndrome; PRP, pityriasis rubra pilaris; SPENCD, spondyloenchondrodysplasia; XLPDR, x-linked pigmentary disorder, reticulate, with systemic manifestations. Adapted and updated from [101] with permission granted by Springer Nature, licence number: 4371831027106.

respectively, an appropriate filtering strategy must be employed to determine which of these variants are potentially pathogenic [103,104].

NGS has been employed in the diagnostic evaluation of individuals with autoinflammatory disorders. Ceccherini et al. compared the performance of three NGS platforms in a pilot study interrogating 10 genes (*MEFV*, *MVK*, *TNFRSF1A*, *NLRP3*, *NLRP12*, *NOD2*, *PSTPIP1*, *IL1RN*, *LPIN2* and *PSMB8*) from 50 cases with genetically confirmed autoinflammatory disorders [105]. The expected mutations were correctly called in most cases, although there was a failure to detect p.Val377Ile *MVK* in a number of cases due to low coverage. Additional variants were also noted, a number of which were false positives and detected on only one of the three platforms used. Importantly, true positive incidental variants did not alter the clinical diagnosis or management of the individual. Taking a different approach, Nakayama et al. [106] prospectively recruited individuals with a clinical diagnosis of an autoinflammatory disorder prior to any genetic testing. Using an MiSeq platform developed in house, they sequenced 9 genes (*IL1RN*, *MEFV*, *MVK*, *NLRP12*, *NLRP3*, *NOD2*, *PSMB8*, *PSTPIP1* and *TNFRSF1A*) in 108 cases. A total of 27 missense mutations were identified and confirmed with Sanger sequencing. Unfortunately, the authors did not outline any genotype–phenotype correlation, nor did they include positive controls to ensure that all pathogenic mutations were detected. A further addition to the literature was by Omoyinmi et al. [107] with their development of a vasculitis and inflammation panel targeting up to 166 genes. Initially, 16 samples with known pathogenic mutations were analysed and the best performing pipeline carried over to the assessment of individuals with unknown diagnosis. Pathogenic mutations were detected in 12% of cases, and likely pathogenic variants in 22%. Furthermore, the depth of coverage was sufficient to be able to detect a 3% somatic mosaicism in *NLRP3*.

## Somatic mosaicism

Somatic mosaicism in *NLRP3* causing disease was first described in 2005 in an individual with a p.Tyr507Cys variant occurring at a frequency of 16.7% detected using Sanger sequencing [108]. Somatic mosaicism in *NLRP3* has since been reported by multiple groups with a mutation frequency as low as 2.7% noted [109–116]. Importantly, a recent study highlighted that NGS was able to detect somatic *NLRP3* mutations in eight individuals symptomatic of CAPS who had previously tested negative for mutations in *NLRP3* sequencing using Sanger techniques [116]. Retrospective review of the Sanger chromatogram identified small peaks in only three of the eight cases, each with an allele frequency

of greater than 10%, suggesting that Sanger sequencing is not a sensitive technique for detecting low frequency somatic mosaicism.

## Autoinflammatory genetics summary

While the use of NGS panels for the diagnosis of autoinflammatory disorders in the clinical setting is increasing, the key limitation from a research perspective is the inability to discover new disease-causing genes. In using WES or WGS, novel variants in genes known to cause disease, and also variants in novel genes, may be uncovered. The rationale for the use of WES is based on the finding that the majority of pathogenic variants causing Mendelian diseases that have been identified to date are located in protein-coding regions [117–119]. While WGS has the benefit of capturing introns and intergenic regions, and detecting copy number variants [104], a large volume of data must be interrogated, and the bioinformatics analysis is complex. Both strategies raise the possibility of detecting an incidental finding that has implications for the health of the individual and their family. Furthermore, neither method negates the requirement for the validation of pathogenicity of a novel variant.

## Modelling monogenic autoinflammatory disorders

Modelling genetic findings experimentally is of great importance in determining the clinical significance of a novel variant. In recent years, many groups have taken advantage of clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 gene editing techniques. CRISPR/Cas9 gene editing utilises features of an adaptive immune response seen in bacteria and archaea.

## CRISPR approaches for functional validation

CRISPR/Cas9 techniques have improved the ability to create models of diseases caused by point mutations. Previously, creating point mutations in mice would require homologous recombination in embryonic stem cells, a lengthy and expensive process to generate a homozygous mouse strain [120]. *In vivo* editing with CRISPR/Cas9 has allowed for genome editing of fertilised mouse eggs [121,122]. Briefly, plasmids with DNA encoding the editing tools, including the guide RNA and Cas9, are injected into the cytoplasm of a one-cell embryo, generating a target-specific double-strand break (DSB). The subsequent repair of this break is mediated by non-homologous end joining (NHEJ) or homology directed repair (HDR). The former often results in frameshift mutations and loss of function. HDR, on the other hand, can result in substitutions, insertions or deletions if the one-cell embryo is co-injected with a single-strand oligonucleotide (ssOligo) that acts as a template. Soon after this technique was first published, the efficiency of gene disruption by frameshift mutations through NHEJ using this method was reported to be approximately 80–90% whereas introducing a point mutation through HDR is approximately 50–80% [122,123].

Introduction of point mutations in human cells using CRISPR/Cas9 techniques has also been described. Early reports of CRISPR/Cas9 editing in HEK293T cells demonstrated NHEJ efficiency of up to 33% [124–127], but HDR efficiency of only 3–8% [126]. Improved efficacy was noted through cell synchronisation techniques that control the timing of delivery of single guide RNA (sgRNA) and ssOligo to HEK293T cells, with HDR in up to 38% of cells [128]. Various strategies have also been employed in an attempt to improve efficiency in cells that are difficult to nucleofect, a process by which components of the editing system are delivered to the nucleus of the target cell, including the use of a ssDNA template provided by recombinant adeno-associated virus (rAAV) [129,130]. The process, however, remains less efficient than NHEJ and its widespread application in research is still limited.

A significant recent addition to the literature has been the description ‘base editors’, able to create point mutations in human cell lines without generating a DSB. In the initial descriptions, a catalytically dead Cas9 was fused to a cytidine deaminase enzyme, with the unit guided to a locus of interest with an sgRNA [131,132]. This complex allowed for a targeted C•G to T•A substitution in human and murine cell lines in up to 40% of total sequencing reads, with a maximum base editing yield possible of 50%. Subsequent base editors have included the adaptation of tRNA adenosine deaminase to edit DNA, allowing for A•T to G•C conversion [133]. The significance of this development in the potential for disease modelling and future gene editing was highlighted by the correction of the *c.845G>A HFE* mutation implicated in hereditary haemochromatosis in an immortalised-lymphoblastoid cell line [133]. Despite the difficulty with which these cells are transfected, an efficiency rate of 28% was noted, with no off-target effects. Similar to the process of CRISPR/Cas9 with HDR, this technique is not yet used widely. However, significant advances in a short period of time suggests that either may become a routine method for modelling diseases caused by point mutations.

## Autoinflammatory disease models using mice

*In vivo* murine models have provided great insight into disease pathology given genetic homologies between humans and mice and the ability to create transgenic, knockout and knockin mice. For example, the initial murine model of CAPS published in 2009 by Hoffman et al. recapitulated the IL-1 $\beta$ -mediated inflammation [134]. Furthermore, a number of teams have used murine models to explore the skeletal consequences of CAPS [135,136]. More recently, the generation of *Nlrp3* mutant mice on *Il1b/Il18*, *casp-1/casp-11* or *Tnf*-deficient backgrounds raised the possible role of TNF in CAPS disease pathology [137]. There are, however, shortcomings here. The recent attempt to model LPS-responsive and beige-like anchor protein (LRBA) deficiency using *Lrba*<sup>-/-</sup> mice, which in humans cause a range of manifestations including autoimmunity, hypogammaglobulinaemia, organomegaly and chronic diarrhoea [138], failed to recapitulate the clinical or immunological phenotype [139,140]. Furthermore, differences between murine and human pyrin led to many years of work predicated on pyrin as anti-inflammatory, rather than an inflammasome forming protein. Modelling of disorders that act through the pyrin pathway, such as Pyogenic Arthritis, Pyoderma gangrenosum and Acne (PAPA) syndrome caused by mutations in *PSTPIP1* may thus be similarly problematic. Additionally, humanised mouse models, using immunodeficient mice engrafted with human haematopoietic cells, are useful in the study of haematopoiesis, but have been limited in the investigation of the innate immune system due to quantitative and functional deficiencies of a number of cells including monocytes and macrophages [141].

## Autoinflammatory subject derived induced pluripotent stem cells

An alternative method of modelling autoinflammatory disorders is the use of subject-derived induced pluripotent stem cells (iPSCs). This method of reprogramming somatic cells to pluripotency [142] allows for indefinite propagation as well as differentiation to a variety of human cell types that would previously have been unobtainable [143–145]. Saito et al. utilised this method in the investigation of autoinflammatory disorders involving NLRP3 [146] and NLRC4 [147]. Two individuals with somatic mutations in *NLRP3* had both wild-type (WT) and mutant NLRP3 iPSC lines generated [146]. The WT iPSC lines served as a comparator, with the authors able to determine that only macrophages differentiated from mutant NLRP3 iPSC lines showed abnormal IL-1 $\beta$  secretion. A subsequent publication generated iPSC lines from an individual suspected of CAPS but without pathogenic mutations in *NLRP3* [147]. Heterogeneous responses to LPS stimulation in the iPSC clones prompted WES, with clones having a robust response to LPS possessing a mutation in *NLRC4*. Subsequent deletion of *NLRC4* using CRISPR/Cas9 techniques in the mutant clones abrogated the enhanced response to stimulation, indicating that the mutation was likely pathogenic. As the frequency of the mutation was later determined to be approximately 63%, WES would most likely have identified this as a candidate variant of interest. Furthermore, despite its promise, the generation of a cell line from case samples demands expertise, as well as specific ethical considerations. It also requires access to case samples which may be difficult in the case of critically ill individuals who succumb to disease prior to genetic evaluation.

Having said this, the use of these cells has the potential to overcome a significant limitation in the modelling of autoinflammatory disorders to date. Using either the genetic manipulation of healthy iPSCs or subject-derived iPSCs, it is possible to explore the effect of a genetic mutation on a variety of cell types. For example, in our recent paper exploring a novel *NLRC4* variant, THP-1 monocyte like cells were used to model and the variant was determined to be pathogenic [31]. iPSCs would have permitted exploration of the effect of this variant on NK cells and T cells, allowing for addressing questions that remain unanswered including the pathogenesis of macrophage activation syndrome in this population. Likewise, the use of iPSCs differentiated to keratinocytes would allow interrogation of mechanisms of the dermatological manifestations in specific autoinflammatory disorders. As summarised in Table 1, most monogenic autoinflammatory disorders described to date have not had immunological assessment of multiple cell types.

## Future directions and questions

Questions remain in the field about the phenotype–genotype correlation as well as phenotypic variability of individuals with a specific genetic variant. This includes disorders of ‘variable penetrance’. There are alternative explanations for differing phenotypes among cases with the same genetic variant. One consideration is the presence of another genetic variant that affects disease presentation. A true digenic disorder requires the inheritance of a distinct heterozygous mutation in two genes that, when inherited separately, do not cause a phenotype [235,236]. The broader term of epistasis refers to possible interactions between genes [237]. Determining genetic epistasis is complex and requires an appropriate pedigree, which includes more than one gene mutated in a single pedigree, a range of genetic permutations and at least one member with WT alleles in both genes [238,239].

Another possible explanation for the phenotypic heterogeneity among cases is epigenetic differences. Epigenetic processes such as DNA methylation, histone modifications, chromatin remodelling and non-coding RNAs can alter the activity of a gene without changing the DNA sequence. For example, a transcriptionally active gene has minimal DNA methylation and an open chromatic structure. Monozygotic and dizygotic twin studies of concordance have been used for some time to determine the contribution of a particular genotype to phenotype [240]. More recently, this has been combined with methods of quantifying epigenetic changes. In a study of monozygotic twins discordant for the clinical diagnosis of CVID, a DNA methylation array performed on CD19+ B cells revealed that both switched and unswitched memory B cells of the twin with CVID had higher DNA methylation in genes relevant to B-cell function [241]. This finding highlights that epigenetic factors could account for phenotypic variations. There have been two publications assessing DNA methylation in individuals with monogenic autoinflammatory disorders, but in each case the diseased population was compared with a healthy control [242,243]. Vento-Tormo et al. [243] assessed the DNA methylation status of genes encoding various components of the inflammasome in monocytes of cases with CAPS and compared this with healthy controls. They noted that genes such as *IL1B*, *IL1RN* and *ASC* were demethylated more efficiently in CAPS monocytes when compared with healthy controls, a feature that normalised when individuals were treated with anti-IL1 therapy. Determining the epigenetic factors contributing to the phenotypic variability of a particular genotype is not simple. With a small number of cases, one possible approach is to compare the methylation status of genes potentially involved in the phenotype observed. An alternative approach is genome-wide DNA methylation profiling [244]. However, drawing conclusions from only a few individuals with different genetic backgrounds may not be feasible.

Exploring factors that can account for this phenotypic variability may provide insight into the pathways involved in disease. Furthermore, the comprehensive genetic evaluation and investigation of various immune and non-immune cells of individuals with these conditions will likely enlighten the field to the intimate link between the innate and adaptive immune system as well as the role of ‘innate immune’ proteins in non-immune cells.

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## Author contribution

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## Competing interests

The authors declare that there are no competing interests associated with the manuscript.

## Abbreviations

AGS, Aicardi–Goutieres syndrome; APLAID, autoinflammation and PLC $\gamma$ 2-associated antibody deficiency and immune dysregulation; CAPS, cryopyrin-associated periodic syndrome; CARD, caspase activation and recruitment domain; CRISPR, clustered regularly interspaced short palindromic repeat; CVID, common variable immune deficiency; DADA2, deficiency of adenosine deaminase 2; DITRA, deficiency in IL-36Ra; DSB, double-strand break; EBV, Epstein–Barr virus; FMF, familial mediterranean fever; HDR, homology directed repair; HHMI, Howard Hughes Medical Institute; HOIL1, haem-oxidised IRP2 ubiquitin ligase 1; HSCT, haemopoietic stem cell transplantation; IFN, interferon; IL, interleukin; IL-36Ra, IL-36 receptor antagonist; IL1RAcP, IL-1 receptor accessory protein; iPSC, induced pluripotent stem cell; IUIS, International Union of Immunological Societies; JAK, Janus kinase; LPS, lipopolysaccharide; LUBAC, linear ubiquitin assembly complex; MAPK, mitogen-activated protein kinase; NF- $\kappa$ B, nuclear factor  $\kappa$ -light-chain-enhancer of activated B cell; NGS, next-generation sequencing; NHEJ, non-homologous end joining; NHMRC, National Health and Medical Research Council; NK, natural killer; NLR, NOD-like receptor; NOD, nucleotide-binding oligomerization domain; PBMC, peripheral blood mononuclear cell; PLAID, PLC $\gamma$ 2-associated antibody deficiency and immune dysregulation; PLC $\gamma$ 2, phospholipase c  $\gamma$ -2; PRAAS, proteasome-associated autoinflammatory syndrome; rAAV, recombinant adeno-associated virus; rhuIL-10, recombinant human IL-10; RNASEH2, ribonuclease H2; SAMHD1, SAM and HD domain containing protein 1; SAVI, STING-associated vasculopathy with onset in infancy; sgRNA, single guide RNA; ssOligo, single-strand oligonucleotide; STAT, signal transducer and activator of transcription; STING, stimulator of IFN gene; TAK1, transforming growth factor- $\beta$  activated kinase-1; TNF, tumour necrosis factor; TNFR1, TNF receptor 1; TRAPS, TNF receptor associated periodic syndrome; WES, whole exome sequencing; WGS, whole genome sequencing; WT, wild-type.

## References

- 1 McDermott, M.F., Aksentjevich, I., Galon, J., McDermott, E.M., Ogunkolade, B.W., Centola, M. et al. (1999) Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. *Cell* **97**, 133–144, [https://doi.org/10.1016/S0092-8674\(00\)80721-7](https://doi.org/10.1016/S0092-8674(00)80721-7)
- 2 FF Consortium (1997) A candidate gene for familial Mediterranean fever. *Nat. Genet.* **17**, 25–31, <https://doi.org/10.1038/ng0997-25>
- 3 TIF Consortium (1997) Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. The International FMF Consortium. *Cell* **90**, 797–807, [https://doi.org/10.1016/S0092-8674\(00\)80539-5](https://doi.org/10.1016/S0092-8674(00)80539-5)
- 4 Bousfiha, A., Jeddane, L., Picard, C., Ailal, F., Bobby Gaspar, H., Al-Herz, W. et al. (2018) The 2017 IUIS phenotypic classification for primary immunodeficiencies. *J. Clin. Immunol.* **38**, 129–143, <https://doi.org/10.1007/s10875-017-0465-8>
- 5 Milhavel, F., Cuisset, L., Hoffman, H.M., Slim, R., El-Shanti, H., Aksentjevich, I. et al. (2008) The infEVERS autoinflammatory mutation online registry: update with new genes and functions. *Hum. Mutat.* **29**, 803–808, <https://doi.org/10.1002/humu.20720>
- 6 Masters, S.L., Simon, A., Aksentjevich, I. and Kastner, D.L. (2009) Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease (\*). *Annu. Rev. Immunol.* **27**, 621–668, <https://doi.org/10.1146/annurev.immunol.25.022106.141627>
- 7 Manthiram, K., Zhou, Q., Aksentjevich, I. and Kastner, D.L. (2017) The monogenic autoinflammatory diseases define new pathways in human innate immunity and inflammation. *Nat. Immunol.* **18**, 832–842
- 8 Crow, Y.J. (2011) Type I interferonopathies: a novel set of inborn errors of immunity. *Ann. N.Y. Acad. Sci.* **1238**, 91–98, <https://doi.org/10.1111/j.1749-6632.2011.06220.x>
- 9 Huggins, M.L., Radford, P.M., McIntosh, R.S., Bainbridge, S.E., Dickinson, P., Draper-Morgan, K.A. et al. (2004) Shedding of mutant tumor necrosis factor receptor superfamily 1A associated with tumor necrosis factor receptor-associated periodic syndrome: differences between cell types. *Arthritis Rheum.* **50**, 2651–2659, <https://doi.org/10.1002/art.20380>
- 10 Xanthoulea, S., Pasparakis, M., Kousteni, S., Brakebusch, C., Wallach, D., Bauer, J. et al. (2004) Tumor necrosis factor (TNF) receptor shedding controls thresholds of innate immune activation that balance opposing TNF functions in infectious and inflammatory diseases. *J. Exp. Med.* **200**, 367–376, <https://doi.org/10.1084/jem.20040435>
- 11 Todd, I., Radford, P.M., Draper-Morgan, K.A., McIntosh, R., Bainbridge, S., Dickinson, P. et al. (2004) Mutant forms of tumour necrosis factor receptor I that occur in TNF-receptor-associated periodic syndrome retain signalling functions but show abnormal behaviour. *Immunology* **113**, 65–79, <https://doi.org/10.1111/j.1365-2567.2004.01942.x>
- 12 Siebert, S., Amos, N., Fielding, C.A., Wang, E.C., Aksentjevich, I., Williams, B.D. et al. (2005) Reduced tumor necrosis factor signaling in primary human fibroblasts containing a tumor necrosis factor receptor superfamily 1A mutant. *Arthritis Rheum.* **52**, 1287–1292, <https://doi.org/10.1002/art.20955>
- 13 Simon, A., Park, H., Maddipati, R., Lobito, A.A., Bulua, A.C., Jackson, A.J. et al. (2010) Concerted action of wild-type and mutant TNF receptors enhances inflammation in TNF receptor 1-associated periodic fever syndrome. *Proc. Natl. Acad. Sci. U.S.A.* **107**, 9801–9806, <https://doi.org/10.1073/pnas.091418107>
- 14 Zhou, Q., Wang, H., Schwartz, D.M., Stoffels, M., Park, Y.H., Zhang, Y. et al. (2016) Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease. *Nat. Genet.* **48**, 67–73, <https://doi.org/10.1038/ng.3459>
- 15 Malireddi, R.K.S., Gurung, P., Mavuluri, J., Dasari, T.K., Klco, J.M., Chi, H. et al. (2018) TAK1 restricts spontaneous NLRP3 activation and cell death to control myeloid proliferation. *J. Exp. Med.*, <https://doi.org/10.1084/jem.20171922>
- 16 Liu, Y., Jesus, A.A., Marrero, B., Yang, D., Ramsey, S.E., Montealegre Sanchez, G.A. et al. (2014) Activated STING in a vascular and pulmonary syndrome. *N. Engl. J. Med.* **371**, 507–518, <https://doi.org/10.1056/NEJMoa1312625>
- 17 Melki, I., Rose, Y., Ugenti, C., Van Eyck, L., Fremont, M.L., Kitabayashi, N. et al. (2017) Disease-associated mutations identify a novel region in human STING necessary for the control of type I interferon signaling. *J. Allergy Clin. Immunol.* **140**, 543.e5–552.e5, <https://doi.org/10.1016/j.jaci.2016.10.031>
- 18 Warner, J.D., Irizarry-Caro, R.A., Bennion, B.G., Ai, T.L., Smith, A.M., Miner, C.A. et al. (2017) STING-associated vasculopathy develops independently of IRF3 in mice. *J. Exp. Med.* **214**, 3279–3292
- 19 Yoneyama, M., Kikuchi, M., Natsukawa, T., Shinobu, N., Imaizumi, T., Miyagishi, M. et al. (2004) The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat. Immunol.* **5**, 730–737, <https://doi.org/10.1038/ni1087>
- 20 Moghaddas, F. and Masters, S.L. (2015) Monogenic autoinflammatory diseases: cytokinopathies. *Cytokine* **74**, 237–246, <https://doi.org/10.1016/j.cyto.2015.02.012>
- 21 Aksentjevich, I., Nowak, M., Mallah, M., Chae, J.J., Watford, W.T., Hofmann, S.R. et al. (2002) 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.* **46**, 3340–3348, <https://doi.org/10.1002/art.10688>
- 22 Hawkins, P.N., Lachmann, H.J. and McDermott, M.F. (2003) Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. *N. Engl. J. Med.* **348**, 2583–2584, <https://doi.org/10.1056/NEJM200306193482523>
- 23 Goldbach-Mansky, R., Dailey, N.J., Canna, S.W., Gelabert, A., Jones, J., Rubin, B.I. et al. (2006) Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. *N. Engl. J. Med.* **355**, 581–592, <https://doi.org/10.1056/NEJMoa055137>
- 24 Lachmann, H.J., Kone-Paut, I., Kuemmerle-Deschner, J.B., Leslie, K.S., Hachulla, E., Quartier, P. et al. (2009) Use of canakinumab in the cryopyrin-associated periodic syndrome. *N. Engl. J. Med.* **360**, 2416–2425, <https://doi.org/10.1056/NEJMoa0810787>
- 25 Laskari, K., Boura, P., Dalekos, G.N., Garyfallos, A., Karokis, D., Pikazis, D. et al. (2017) Longterm beneficial effect of canakinumab in colchicine-resistant Familial Mediterranean fever. *J. Rheumatol.* **44**, 102–109, <https://doi.org/10.3899/jrheum.160518>

- 26 Arostegui, J.I., Anton, J., Calvo, I., Robles, A., Iglesias, E., Lopez-Montesinos, B. et al. (2017) Open-label, Phase II study to assess the efficacy and safety of canakinumab treatment in active hyperimmunoglobulinemia D with periodic fever syndrome. *Arthritis Rheumatol.* **69**, 1679–1688, <https://doi.org/10.1002/art.40146>
- 27 Gattorno, M., Obici, L., Cattalini, M., Tormey, V., Abrams, K., Davis, N. et al. (2017) Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. *Ann. Rheum. Dis.* **76**, 173–178, <https://doi.org/10.1136/annrheumdis-2015-209031>
- 28 Borghini, S., Ferrera, D., Prigione, I., Fiore, M., Ferraris, C., Mirisola, V. et al. (2016) Gene expression profile in TNF receptor-associated periodic syndrome reveals constitutively enhanced pathways and new players in the underlying inflammation. *Clin. Exp. Rheumatol.* **34**, S121–S128
- 29 De Benedetti, F., Gattorno, M., Anton, J., Ben-Chetrit, E., Frenkel, J., Hoffman, H.M. et al. (2018) Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. *N. Engl. J. Med.* **378**, 1908–1919, <https://doi.org/10.1056/NEJMoa1706314>
- 30 Harrison, S.R., McGonagle, D., Nizam, S., Jarrett, S., van der Hilst, J., McDermott, M.F. et al. (2016) Anakinra as a diagnostic challenge and treatment option for systemic autoinflammatory disorders of undefined etiology. *JCI Insight* **1**, e86336, <https://doi.org/10.1172/jci.insight.86336>
- 31 Moghaddas, F., Zeng, P., Zhang, Y., Schutze, H., Brenner, S., Hofmann, S.R. et al. (2018) Autoinflammatory mutation in NLRC4 reveals an LRR-LRR oligomerization interface. *J. Allergy Clin. Immunol.*, <https://doi.org/10.1016/j.jaci.2018.04.033>
- 32 Romberg, N., Al Moussawi, K., Nelson-Williams, C., Stiegler, A.L., Loring, E., Choi, M., Overton, J., Meffre, E., Khokha, M.K., Huttner, A.J., West, B., Podolitsv, N.A., Boggon, T.J., Kazmierczak, B.I., Lifton, R.P. et al. (2014) Mutation of NLRC4 causes a syndrome of enterocolitis and autoinflammation. *Nat. Genet.* **46**, 1135–1139, <https://doi.org/10.1038/ng.3066>
- 33 Canna, S.W., de Jesus, A.A., Gouni, S., Brooks, S.R., Marrero, B., Liu, Y., DiMattia, M.A., Zaal, K.J., Sanchez, G.A., Kim, H., Chapelle, D., Plass, N., Huang, Y., Villarino, A.V., Biancotto, A., Fleisher, T.A., Duncan, J.A., O’Shea, J.J., Benselev, S., Grom, A., Deng, Z., Laxer, R.M. and Goldbach-Mansky, R. (2014) An activating NLRC4 inflammasome mutation causes autoinflammation with recurrent macrophage activation syndrome. *Nat. Genet.* **46**, 1140–6, <https://doi.org/10.1038/ng.3089>
- 34 Marrakchi, S., Guigue, P., Renshaw, B.R., Puel, A., Pei, X.Y., Fraitag, S. et al. (2011) Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N. Engl. J. Med.* **365**, 620–628, <https://doi.org/10.1056/NEJMoa1013068>
- 35 Huffmeier, U., Watzold, M., Mohr, J., Schon, M.P. and Mossner, R. (2014) Successful therapy with anakinra in a patient with generalized pustular psoriasis carrying IL36RN mutations. *Br. J. Dermatol.* **170**, 202–204, <https://doi.org/10.1111/bjd.12548>
- 36 Podlipnik, S., Morgado-Carrasco, D., Fusta-Novell, X., Mensa-Vilaro, A., Arostegui, J.I., Alsina-Gibert, M. et al. (2017) Dynamics of plasma cytokines in a patient with deficiency of interleukin-36 receptor antagonist successfully treated with anakinra. *Br. J. Dermatol.*, <https://doi.org/10.1111/bjd.16063>
- 37 Rossi-Semerano, L., Piram, M., Chiaverini, C., De Ricaud, D., Smahi, A. and Kone-Paut, I. (2013) First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra. *Pediatrics* **132**, e1043–7, <https://doi.org/10.1542/peds.2012-3935>
- 38 Tauber, M., Viguier, M., Le Gall, C., Smahi, A. and Bachelez, H. (2014) Is it relevant to use an interleukin-1-inhibiting strategy for the treatment of patients with deficiency of interleukin-36 receptor antagonist? *Br. J. Dermatol.* **170**, 1198–1199, <https://doi.org/10.1111/bjd.12805>
- 39 Fialova, J., Vojackova, N., Vanousova, D. and Hercogova, J. (2014) Juvenile generalized pustular psoriasis treated with etanercept. *Dermatol. Ther.* **27**, 105–108, <https://doi.org/10.1111/dth.12065>
- 40 Matsumoto, A., Komine, M., Karakawa, M., Kishimoto, M. and Ohtsuki, M. (2017) Adalimumab administration after infliximab therapy is a successful treatment strategy for generalized pustular psoriasis. *J. Dermatol.* **44**, 202–204, <https://doi.org/10.1111/1346-8138.13632>
- 41 Zangrilli, A., Papoutsaki, M., Talamonti, M. and Chimenti, S. (2008) Long-term efficacy of adalimumab in generalized pustular psoriasis. *J. Dermatolog. Treat.* **19**, 185–187, <https://doi.org/10.1080/09546630701759587>
- 42 Kostner, K., Prelog, M., Almanzar, G., Fesq, H., Haas, J.P. and Hugle, B. (2018) Successful use of secukinumab in a 4-year-old patient with deficiency of interleukin-36 antagonist. *Rheumatology (Oxford)*, <https://doi.org/10.1093/rheumatology/kex510>
- 43 Arakawa, A., Ruzicka, T. and Prinz, J.C. (2016) Therapeutic efficacy of interleukin 12/interleukin 23 blockade in generalized pustular psoriasis regardless of IL36RN mutation status. *JAMA Dermatol.* **152**, 825–828, <https://doi.org/10.1001/jamadermatol.2016.0751>
- 44 Bonekamp, N., Caorsi, R., Viglizzo, G.M., Graaf, M., Minoia, F., Grossi, A. et al. (2017) High-dose ustekinumab for severe childhood deficiency of interleukin-36 receptor antagonist (DITRA). *Ann. Rheum. Dis.*, <https://doi.org/10.1136/annrheumdis-2017-211805>
- 45 Cherqaoui, J.B., Rossi-Semerano, L., Piram, M. and Kone-Paut, I. (2017) Standard dose of Ustekinumab for childhood-onset deficiency of interleukin-36 receptor antagonist. *Ann. Rheum. Dis.*, <https://doi.org/10.1136/annrheumdis-2017-212793>
- 46 Ganesan, R., Raymond, E.L., Mennerich, D., Woska, J.R., Caviness, G., Grimaldi, C. et al. (2017) Generation and functional characterization of anti-human and anti-mouse IL-36R antagonist monoclonal antibodies. *MAbs* **9**, 1143–1154, <https://doi.org/10.1080/19420862.2017.1353853>
- 47 Glocker, E.O., Frede, N., Perro, M., Sebire, N., Elawad, M., Shah, N. et al. (2010) Infant colitis—it’s in the genes. *Lancet* **376**, 1272, [https://doi.org/10.1016/S0140-6736\(10\)61008-2](https://doi.org/10.1016/S0140-6736(10)61008-2)
- 48 Glocker, E.O., Kotlarz, D., Boztug, K., Gertz, E.M., Schaffer, A.A., Noyan, F. et al. (2009) Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N. Engl. J. Med.* **361**, 2033–2045, <https://doi.org/10.1056/NEJMoa0907206>
- 49 Williams, L., Bradley, L., Smith, A. and Foxwell, B. (2004) Signal transducer and activator of transcription 3 is the dominant mediator of the anti-inflammatory effects of IL-10 in human macrophages. *J. Immunol.* **172**, 567–576, <https://doi.org/10.4049/jimmunol.172.1.567>
- 50 Berg, D.J., Kuhn, R., Rajewsky, K., Muller, W., Menon, S., Davidson, N. et al. (1995) Interleukin-10 is a central regulator of the response to LPS in murine models of endotoxic shock and the Shwartzman reaction but not endotoxin tolerance. *J. Clin. Invest.* **96**, 2339–2347, <https://doi.org/10.1172/JCI118290>
- 51 Kuhn, R., Lohler, J., Rennick, D., Rajewsky, K. and Muller, W. (1993) Interleukin-10-deficient mice develop chronic enterocolitis. *Cell* **75**, 263–274, [https://doi.org/10.1016/0092-8674\(93\)80068-P](https://doi.org/10.1016/0092-8674(93)80068-P)



- 52 Engelhardt, K.R., Shah, N., Faizura-Yeop, I., Kocacik Uygun, D.F., Frede, N., Muise, A.M. et al. (2013) Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. *J. Allergy Clin. Immunol.* **131**, 825–830, <https://doi.org/10.1016/j.jaci.2012.09.025>
- 53 Kotlarz, D., Beier, R., Murugan, D., Diestelhorst, J., Jensen, O., Boztug, K. et al. (2012) Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. *Gastroenterology* **143**, 347–355, <https://doi.org/10.1053/j.gastro.2012.04.045>
- 54 Buruiana, F.E., Sola, I. and Alonso-Coello, P. (2010) Recombinant human interleukin 10 for induction of remission in Crohn's disease. *Cochrane Database Syst. Rev.* CD005109, <https://doi.org/10.1002/14651858.CD005109.pub3>
- 55 Kitamura, A., Maekawa, Y., Uehara, H., Izumi, K., Kawachi, I., Nishizawa, M. et al. (2011) A mutation in the immunoproteasome subunit PSMB8 causes autoinflammation and lipodystrophy in humans. *J. Clin. Invest.* **121**, 4150–4160, <https://doi.org/10.1172/JCI58414>
- 56 Arima, K., Kinoshita, A., Mishima, H., Kanazawa, N., Kaneko, T., Mizushima, T. et al. (2011) 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.* **108**, 14914–14919, <https://doi.org/10.1073/pnas.1106015108>
- 57 Agarwal, A.K., Xing, C., DeMartino, G.N., Mizrachi, D., Hernandez, M.D., Sousa, A.B. et al. (2010) PSMB8 encoding the beta5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. *Am. J. Hum. Genet.* **87**, 866–872, <https://doi.org/10.1016/j.ajhg.2010.10.031>
- 58 Liu, Y., Ramot, Y., Torreló, A., Paller, A.S., Si, N., Babay, S. et al. (2012) Mutations in proteasome subunit beta type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum.* **64**, 895–907, <https://doi.org/10.1002/art.33368>
- 59 Brehm, A., Liu, Y., Sheikh, A., Marrero, B., Omoyinmi, E., Zhou, Q. et al. (2015) Additive loss-of-function proteasome subunit mutations in CANDLER/PRAAS patients promote type I IFN production. *J. Clin. Invest.* **125**, 4196–4211, <https://doi.org/10.1172/JCI81260>
- 60 Awad, F., Assrawi, E., Louvrier, C., Jumeau, C., Georgin-Lavalie, S., Grateau, G. et al. (2018) Inflammasome biology, molecular pathology and therapeutic implications. *Pharmacol. Ther.* **187**, 133–149, <https://doi.org/10.1016/j.pharmthera.2018.02.011>
- 61 Lachmann, H.J. (2017) Periodic fever syndromes. *Best Pract. Res. Clin. Rheumatol.* **31**, 596–609, <https://doi.org/10.1016/j.berh.2017.12.001>
- 62 Kim, H., Brooks, K.M., Tang, C.C., Wakim, P., Blake, M., Brooks, S.R. et al. (2017) Pharmacokinetics, pharmacodynamics, and proposed dosing of the oral JAK1 and JAK2 inhibitor baricitinib in pediatric and young adult CANDLER and SAVI patients. *Clin. Pharmacol. Ther.*, <https://doi.org/10.1002/cpt.936>
- 63 Sanchez, G.A.M., Reinhardt, A., Ramsey, S., Wittkowski, H., Hashkes, P.J., Berkun, Y. et al. (2018) JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. *J. Clin. Invest.*, <https://doi.org/10.1172/JCI98814>
- 64 Novick, D. and Dinarello, C.A. (2017) IL-18 binding protein reverses the life-threatening hyperinflammation of a baby with the NLRC4 mutation. *J. Allergy Clin. Immunol.* **140**, 316, <https://doi.org/10.1016/j.jaci.2017.02.037>
- 65 Aicardi, J. and Goutieres, F. (1984) A progressive familial encephalopathy in infancy with calcifications of the basal ganglia and chronic cerebrospinal fluid lymphocytosis. *Ann. Neurol.* **15**, 49–54, <https://doi.org/10.1002/ana.410150109>
- 66 Crow, Y.J., Hayward, B.E., Parmar, R., Robins, P., Leitch, A., Ali, M. et al. (2006) Mutations in the gene encoding the 3'-5' DNA exonuclease TREX1 cause Aicardi-Goutieres syndrome at the AGS1 locus. *Nat. Genet.* **38**, 917–920, <https://doi.org/10.1038/ng1845>
- 67 Rice, G.I., Bond, J., Asipu, A., Brunette, R.L., Manfield, I.W., Carr, I.M. et al. (2009) Mutations involved in Aicardi-Goutieres syndrome implicate SAMHD1 as regulator of the innate immune response. *Nat. Genet.* **41**, 829–832, <https://doi.org/10.1038/ng.373>
- 68 Crow, Y.J., Leitch, A., Hayward, B.E., Garner, A., Parmar, R., Griffith, E. et al. (2006) Mutations in genes encoding ribonuclease H2 subunits cause Aicardi-Goutieres syndrome and mimic congenital viral brain infection. *Nat. Genet.* **38**, 910–916, <https://doi.org/10.1038/ng1842>
- 69 Rice, G.I., Kasher, P.R., Forte, G.M., Mannion, N.M., Greenwood, S.M., Szykiewicz, M. et al. (2012) Mutations in ADAR1 cause Aicardi-Goutieres syndrome associated with a type I interferon signature. *Nat. Genet.* **44**, 1243–1248, <https://doi.org/10.1038/ng.2414>
- 70 Aicardi, J. and Goutieres, F. (2000) Systemic lupus erythematosus or Aicardi-Goutieres syndrome? *Neuropediatrics* **31**, 113, <https://doi.org/10.1055/s-2000-7533>
- 71 De Laet, C., Goyens, P., Christophe, C., Ferster, A., Mascart, F. and Dan, B. (2005) Phenotypic overlap between infantile systemic lupus erythematosus and Aicardi-Goutieres syndrome. *Neuropediatrics* **36**, 399–402, <https://doi.org/10.1055/s-2005-873058>
- 72 Ramantani, G., Kohlhase, J., Hertzberg, C., Innes, A.M., Engel, K., Hunger, S. et al. (2010) Expanding the phenotypic spectrum of lupus erythematosus in Aicardi-Goutieres syndrome. *Arthritis Rheum.* **62**, 1469–1477, <https://doi.org/10.1002/art.27367>
- 73 Crow, Y.J., Chase, D.S., Lowenstein Schmidt, J., Szykiewicz, M., Forte, G.M., Gornall, H.L. et al. (2015) Characterization of human disease phenotypes associated with mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1. *Am. J. Med. Genet. Part A* **167a**, 296–312, <https://doi.org/10.1002/ajmg.a.36887>
- 74 Rice, G., Patrick, T., Parmar, R., Taylor, C.F., Aeby, A., Aicardi, J. et al. (2007) Clinical and molecular phenotype of Aicardi-Goutieres syndrome. *Am. J. Hum. Genet.* **81**, 713–725, <https://doi.org/10.1086/521373>
- 75 Cuadrado, E., Vanderver, A., Brown, K.J., Sandza, A., Takanohashi, A., Jansen, M.H. et al. (2015) Aicardi-Goutieres syndrome harbours abundant systemic and brain-reactive autoantibodies. *Ann. Rheum. Dis.* **74**, 1931–1939, <https://doi.org/10.1136/annrheumdis-2014-205396>
- 76 Boisson, B., Laplantine, E., Prando, C., Giliiani, S., Israelsson, E., Xu, Z. et al. (2012) Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. *Nat. Immunol.* **13**, 1178–1186, <https://doi.org/10.1038/ni.2457>
- 77 Boisson, B., Laplantine, E., Dobbs, K., Cobat, A., Tarantino, N., Hazen, M. et al. (2015) Human HOIP and LUBAC deficiency underlies autoinflammation, immunodeficiency, amylopectinosis, and lymphangiectasia. *J. Exp. Med.* **212**, 939–951, <https://doi.org/10.1084/jem.20141130>
- 78 Nilsson, J., Schoser, B., Laforet, P., Kalev, O., Lindberg, C., Romero, N.B. et al. (2013) Polyglucosan body myopathy caused by defective ubiquitin ligase RBBK1. *Ann. Neurol.* **74**, 914–919, <https://doi.org/10.1002/ana.23963>

- 79 Ombrello, M.J., Remmers, E.F., Sun, G., Freeman, A.F., Datta, S., Torabi-Parizi, P. et al. (2012) Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. *N. Engl. J. Med.* **366**, 330–338, <https://doi.org/10.1056/NEJMoa1102140>
- 80 Zhou, Q., Lee, G.S., Brady, J., Datta, S., Katan, M., Sheikh, A. et al. (2012) A hypermorphic missense mutation in PLCG2, encoding phospholipase Cgamma2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. *Am. J. Hum. Genet.* **91**, 713–720, <https://doi.org/10.1016/j.ajhg.2012.08.006>
- 81 Yu, P., Constien, R., Dear, N., Katan, M., Hanke, P., Bunney, T.D. et al. (2005) Autoimmunity and inflammation due to a gain-of-function mutation in phospholipase C gamma 2 that specifically increases external Ca<sup>2+</sup> entry. *Immunity* **22**, 451–465, <https://doi.org/10.1016/j.immuni.2005.01.018>
- 82 Chae, J.J., Park, Y.H., Park, C., Hwang, I.Y., Hoffmann, P., Kehrl, J.H. et al. (2015) Connecting two pathways through Ca<sup>2+</sup> signaling: NLRP3 inflammasome activation induced by a hypermorphic PLCG2 mutation. *Arthritis Rheumatol.* **67**, 563–567, <https://doi.org/10.1002/art.38961>
- 83 Kurosaki, T. and Tsukada, S. (2000) BLNK: connecting Syk and Btk to calcium signals. *Immunity* **12**, 1–5, [https://doi.org/10.1016/S1074-7613\(00\)80153-3](https://doi.org/10.1016/S1074-7613(00)80153-3)
- 84 Navon Elkan, P., Pierce, S.B., Segel, R., Walsh, T., Barash, J., Padeh, S. et al. (2014) Mutant adenosine deaminase 2 in a polyarteritis nodosa vasculopathy. *N. Engl. J. Med.* **370**, 921–931, <https://doi.org/10.1056/NEJMoa1307362>
- 85 Zhou, Q., Yang, D., Ombrello, A.K., Zavalov, A.V., Toro, C., Zavalov, A.V. et al. (2014) Early-onset stroke and vasculopathy associated with mutations in ADA2. *N. Engl. J. Med.* **370**, 911–920, <https://doi.org/10.1056/NEJMoa1307361>
- 86 Ombrello, A., Stone, D., Hoffmann, P., Jones, A., Barham, B., Barron, K. et al. (2015) The deficiency of adenosine deaminase type 2—results of therapeutic intervention. *Pediatr. Rheumatol.* **13**, 040, <https://doi.org/10.1186/1546-0096-13-S1-040>
- 87 Sahin, S., Adrovic, A., Barut, K., Ugurlu, S., Turanli, E.T., Ozdogan, H. et al. (2018) Clinical, imaging and genotypical features of three deceased and five surviving cases with ADA2 deficiency. *Rheumatol. Int.* **38**, 129–136, <https://doi.org/10.1007/s00296-017-3740-3>
- 88 Caorsi, R., Penco, F., Grossi, A., Insalaco, A., Omenetti, A., Alessio, M. et al. (2017) ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study. *Ann. Rheum. Dis.* **76**, 1648–1656, <https://doi.org/10.1136/annrheumdis-2016-210802>
- 89 Ben-Ami, T., Revel-Vilk, S., Brooks, R., Shaag, A., Hershfield, M.S., Kelly, S.J. et al. (2016) Extending the clinical phenotype of adenosine deaminase 2 deficiency. *J. Pediatr.* **177**, 316–320, <https://doi.org/10.1016/j.jpeds.2016.06.058>
- 90 Van Eyck, L., Liston, A. and Wouters, C. (2014) Mutant ADA2 in vasculopathies. *N. Engl. J. Med.* **371**, 480
- 91 Van Eyck, Jr, L., Hershfield, M.S., Pombal, D., Kelly, S.J., Ganson, N.J., Moens, L. et al. (2015) Hematopoietic stem cell transplantation rescues the immunologic phenotype and prevents vasculopathy in patients with adenosine deaminase 2 deficiency. *J. Allergy Clin. Immunol.* **135**, 2835–287.e5, <https://doi.org/10.1016/j.jaci.2014.10.010>
- 92 Alsultan, A., Basher, E., Alqanatish, J., Mohammed, R. and Alfadhel, M. (2017) Deficiency of ADA2 mimicking autoimmune lymphoproliferative syndrome in the absence of livedo reticularis and vasculitis. *Pediatr. Blood Cancer*, <https://doi.org/10.1002/pbc.26912>
- 93 Schepp, J., Bulashevska, A., Mannhardt-Laakmann, W., Cao, H., Yang, F., Seidl, M. et al. (2016) Deficiency of adenosine deaminase 2 causes antibody deficiency. *J. Clin. Immunol.* **36**, 179–186, <https://doi.org/10.1007/s10875-016-0245-x>
- 94 Schepp, J., Proietti, M., Frede, N., Buchta, M., Hubscher, K., Rojas Restrepo, J. et al. (2017) Screening of 181 patients with antibody deficiency for deficiency of adenosine deaminase 2 sheds new light on the disease in adulthood. *Arthritis Rheumatol.* **69**, 1689–1700, <https://doi.org/10.1002/art.40147>
- 95 Belot, A., Wassmer, E., Twilt, M., Lega, J.C., Zeef, L.A., Oojageer, A. et al. (2014) Mutations in CECR1 associated with a neutrophil signature in peripheral blood. *Pediatr. Rheumatol. Online J.* **12**, 44, <https://doi.org/10.1186/1546-0096-12-44>
- 96 Skrabl-Baumgartner, A., Plecko, B., Schmidt, W.M., Konig, N., Hershfield, M., Gruber-Sedlmayr, U. et al. (2017) Autoimmune phenotype with type I interferon signature in two brothers with ADA2 deficiency carrying a novel CECR1 mutation. *Pediatr. Rheumatol. Online J.* **15**, 67, <https://doi.org/10.1186/s12969-017-0193-x>
- 97 Wiseman, D.H., May, A., Jolles, S., Connor, P., Powell, C., Heeney, M.M. et al. (2013) A novel syndrome of congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD). *Blood* **122**, 112–123, <https://doi.org/10.1182/blood-2012-08-439083>
- 98 Chakraborty, P.K., Schmitz-Abe, K., Kennedy, E.K., Mamady, H., Naas, T., Durie, D. et al. (2014) Mutations in TRNT1 cause congenital sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD). *Blood* **124**, 2867–2871, <https://doi.org/10.1182/blood-2014-08-591370>
- 99 Lizano, E., Schuster, J., Muller, M., Kelso, J. and Morl, M. (2007) A splice variant of the human CCA-adding enzyme with modified activity. *J. Mol. Biol.* **366**, 1258–1265, <https://doi.org/10.1016/j.jmb.2006.12.016>
- 100 Giannelou, A., Wang, H., Zhou, Q., Park, Y.H., Abu-Asab, M.S., Ylaja, K. et al. (2018) Aberrant tRNA processing causes an autoinflammatory syndrome responsive to TNF inhibitors. *Ann. Rheum. Dis.* **77**, 612–619, <https://doi.org/10.1136/annrheumdis-2017-212401>
- 101 Sarrabay, G., Barat-Houari, M., Annakib, S. and Toutou, I. (2015) The autoinflammatory diseases: a fashion with blurred boundaries. *Semin. Immunopathol.* **37**, 359–362, <https://doi.org/10.1007/s00281-015-0495-3>
- 102 Goodwin, S., McPherson, J.D. and McCombie, W.R. (2016) Coming of age: ten years of next-generation sequencing technologies. *Nat. Rev. Genet.* **17**, 333–351, <https://doi.org/10.1038/nrg.2016.49>
- 103 Chou, J., Ohsumi, T.K. and Geha, R.S. (2012) Use of whole exome and genome sequencing in the identification of genetic causes of primary immunodeficiencies. *Curr. Opin. Allergy Clin. Immunol.* **12**, 623–628, <https://doi.org/10.1097/ACI.0b013e3283588ca6>
- 104 Belkadi, A., Bolze, A., Itan, Y., Cobat, A., Vincent, Q.B., Antipenko, A. et al. (2015) Whole-genome sequencing is more powerful than whole-exome sequencing for detecting exome variants. *Proc. Natl. Acad. Sci. U.S.A.* **112**, 5473–5478, <https://doi.org/10.1073/pnas.1418631112>
- 105 Rusmini, M., Federici, S., Caroli, F., Grossi, A., Baldi, M., Obici, L. et al. (2016) Next-generation sequencing and its initial applications for molecular diagnosis of systemic auto-inflammatory diseases. *Ann. Rheum. Dis.* **75**, 1550–1557, <https://doi.org/10.1136/annrheumdis-2015-207701>
- 106 Nakayama, M., Oda, H., Nakagawa, K., Yasumi, T., Kawai, T., Izawa, K. et al. (2017) Accurate clinical genetic testing for autoinflammatory diseases using the next-generation sequencing platform MiSeq. *Biochem. Biophys. Rep.* **9**, 146–152, <https://doi.org/10.1016/j.bbrep.2016.12.002>

- 107 Omoyinmi, E., Standing, A., Keylock, A., Price-Kuehne, F., Melo Gomes, S., Rowczenio, D. et al. (2017) Clinical impact of a targeted next-generation sequencing gene panel for autoinflammation and vasculitis. *PLoS ONE* **12**, e0181874, <https://doi.org/10.1371/journal.pone.0181874>
- 108 Saito, M., Fujisawa, A., Nishikomori, R., Kambe, N., Nakata-Hizume, M., Yoshimoto, M. et al. (2005) Somatic mosaicism of CIAS1 in a patient with chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum.* **52**, 3579–3585, <https://doi.org/10.1002/art.21404>
- 109 Arostegui, J.I., Lopez Saldana, M.D., Pascal, M., Clemente, D., Aymerich, M., Balaguer, F. et al. (2010) 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.* **62**, 1158–1166, <https://doi.org/10.1002/art.27342>
- 110 Tanaka, N., Izawa, K., Saito, M.K., Sakuma, M., Oshima, K., Ohara, O. et al. (2011) High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an International Multicenter Collaborative Study. *Arthritis Rheum.* **63**, 3625–3632, <https://doi.org/10.1002/art.30512>
- 111 Jimenez-Trevino, S., Gonzalez-Roca, E., Ruiz-Ortiz, E., Yague, J., Ramos, E. and Arostegui, J.I. (2013) First report of vertical transmission of a somatic NLRP3 mutation in cryopyrin-associated periodic syndromes. *Ann. Rheum. Dis.* **72**, 1109–1110, <https://doi.org/10.1136/annrheumdis-2012-202913>
- 112 Nakagawa, K., Gonzalez-Roca, E., Souto, A., Kawai, T., Umehayashi, H., Campistol, J.M. et al. (2015) Somatic NLRP3 mosaicism in Muckle-Wells syndrome. A genetic mechanism shared by different phenotypes of cryopyrin-associated periodic syndromes. *Ann. Rheum. Dis.* **74**, 603–610, <https://doi.org/10.1136/annrheumdis-2013-204361>
- 113 Zhou, Q., Aksentijevich, I., Wood, G.M., Walts, A.D., Hoffmann, P., Remmers, E.F. et al. (2015) Brief report: cryopyrin-associated periodic syndrome caused by a myeloid-restricted somatic NLRP3 mutation. *Arthritis Rheumatol.* **67**, 2482–2486, <https://doi.org/10.1002/art.39190>
- 114 Mensa-Vilaro, A., Teresa Bosque, M., Magri, G., Honda, Y., Martinez-Banaclocha, H., Casorran-Berges, M. et al. (2016) Brief report: late-onset cryopyrin-associated periodic syndrome due to myeloid-restricted somatic NLRP3 mosaicism. *Arthritis Rheumatol.* **68**, 3035–3041, <https://doi.org/10.1002/art.39770>
- 115 Lasiglie, D., Mensa-Vilaro, A., Ferrera, D., Caorsi, R., Penco, F., Santamaria, G. et al. (2017) Cryopyrin-associated periodic syndromes in Italian patients: evaluation of the rate of somatic NLRP3 mosaicism and phenotypic characterization. *J. Rheumatol.* **44**, 1667–1673, <https://doi.org/10.3899/jrheum.170041>
- 116 Rowczenio, D.M., Gomes, S.M., Arostegui, J.I., Mensa-Vilaro, A., Omoyinmi, E., Trojer, H. et al. (2017) Late-onset cryopyrin-associated periodic syndromes caused by somatic NLRP3 mosaicism-UK single center experience. *Front. Immunol.* **8**, 1410, <https://doi.org/10.3389/fimmu.2017.01410>
- 117 Botstein, D. and Risch, N. (2003) Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. *Nat. Genet.* **33**, 228–237, <https://doi.org/10.1038/ng1090>
- 118 Majewski, J., Schwartzentruber, J., Lalonde, E., Montpetit, A. and Jabado, N. (2011) What can exome sequencing do for you? *J. Med. Genet.* **48**, 580–589, <https://doi.org/10.1136/jmedgenet-2011-100223>
- 119 Cooper, D.N., Chen, J.M., Ball, E.V., Howells, K., Mort, M., Phillips, A.D. et al. (2010) Genes, mutations, and human inherited disease at the dawn of the age of personalized genomics. *Hum. Mutat.* **31**, 631–655, <https://doi.org/10.1002/humu.21260>
- 120 Hochheiser, K., Kueh, A.J., Gebhardt, T. and Herold, M.J. (2018) CRISPR/Cas9: a tool for immunological research. *Eur. J. Immunol.*, <https://doi.org/10.1002/eji.201747131>
- 121 Shen, B., Zhang, J., Wu, H., Wang, J., Ma, K., Li, Z. et al. (2013) Generation of gene-modified mice via Cas9/RNA-mediated gene targeting. *Cell Res.* **23**, 720–723, <https://doi.org/10.1038/cr.2013.46>
- 122 Li, D., Qiu, Z., Shao, Y., Chen, Y., Guan, Y., Liu, M. et al. (2013) Heritable gene targeting in the mouse and rat using a CRISPR-Cas system. *Nat. Biotechnol.* **31**, 681–683, <https://doi.org/10.1038/nbt.2661>
- 123 Yang, H., Wang, H. and Jaenisch, R. (2014) Generating genetically modified mice using CRISPR/Cas-mediated genome engineering. *Nat. Protoc.* **9**, 1956–1968, <https://doi.org/10.1038/nprot.2014.134>
- 124 Pattanayak, V., Lin, S., Guilinger, J.P., Ma, E., Doudna, J.A. and Liu, D.R. (2013) High-throughput profiling of off-target DNA cleavage reveals RNA-programmed Cas9 nuclease specificity. *Nat. Biotechnol.* **31**, 839–843, <https://doi.org/10.1038/nbt.2673>
- 125 Mali, P., Yang, L., Esvelt, K.M., Aach, J., Guell, M., DiCarlo, J.E. et al. (2013) RNA-guided human genome engineering via Cas9. *Science* **339**, 823–826, <https://doi.org/10.1126/science.1232033>
- 126 Cong, L., Ran, F.A., Cox, D., Lin, S., Barretto, R., Habib, N. et al. (2013) Multiplex genome engineering using CRISPR/Cas systems. *Science* **339**, 819–823, <https://doi.org/10.1126/science.1231143>
- 127 Cho, S.W., Kim, S., Kim, J.M. and Kim, J.S. (2013) Targeted genome engineering in human cells with the Cas9 RNA-guided endonuclease. *Nat. Biotechnol.* **31**, 230–232, <https://doi.org/10.1038/nbt.2507>
- 128 Lin, S., Staahl, B.T., Alla, R.K. and Doudna, J.A. (2014) Enhanced homology-directed human genome engineering by controlled timing. *Elife* **3**, e04766
- 129 Vasileva, A. and Jessberger, R. (2005) Precise hit: adeno-associated virus in gene targeting. *Nat. Rev. Microbiol.* **3**, 837–847, <https://doi.org/10.1038/nrmicro1266>
- 130 Kaulich, M. and Dowdy, S.F. (2015) Combining CRISPR/Cas9 and rAAV templates for efficient gene editing. *Nucleic Acid Ther.* **25**, 287–296, <https://doi.org/10.1089/nat.2015.0545>
- 131 Nishida, K., Arazoe, T., Yachie, N., Banno, S., Kakimoto, M., Tabata, M. et al. (2016) Targeted nucleotide editing using hybrid prokaryotic and vertebrate adaptive immune systems. *Science* **353**, <https://doi.org/10.1126/science.aaf8729>
- 132 Komor, A.C., Kim, Y.B., Packer, M.S., Zuris, J.A. and Liu, D.R. (2016) Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. *Nature* **533**, 420–424, <https://doi.org/10.1038/nature17946>
- 133 Gaudelli, N.M., Komor, A.C., Rees, H.A., Packer, M.S., Badran, A.H., Bryson, D.I. et al. (2017) Programmable base editing of A•T to G•C in genomic DNA without DNA cleavage. *Nature* **551**, 464–471, <https://doi.org/10.1038/nature24644>

- 134 Brydges, S.D., Mueller, J.L., McGeough, M.D., Pena, C.A., Misaghi, A., Gandhi, C. et al. (2009) Inflammasome-mediated disease animal models reveal roles for innate but not adaptive immunity. *Immunity* **30**, 875–887, <https://doi.org/10.1016/j.immuni.2009.05.005>
- 135 Bonar, S.L., Brydges, S.D., Mueller, J.L., McGeough, M.D., Pena, C., Chen, D. et al. (2012) Constitutively activated NLRP3 inflammasome causes inflammation and abnormal skeletal development in mice. *PLoS ONE* **7**, e35979, <https://doi.org/10.1371/journal.pone.0035979>
- 136 Snouwaert, J.N., Nguyen, M., Repenning, P.W., Dye, R., Livingston, E.W., Kovarova, M. et al. (2016) An NLRP3 mutation causes arthropathy and osteoporosis in humanized mice. *Cell Rep.* **17**, 3077–3088, <https://doi.org/10.1016/j.celrep.2016.11.052>
- 137 McGeough, M.D., Wree, A., Inzaugarat, M.E., Haimovich, A., Johnson, C.D., Pena, C.A. et al. (2017) TNF regulates transcription of NLRP3 inflammasome components and inflammatory molecules in cryopyrinopathies. *J. Clin. Invest.*, <https://doi.org/10.1172/JCI90699>
- 138 Alkhairy, O.K., Abolhassani, H., Rezaei, N., Fang, M., Andersen, K.K., Chavoshzadeh, Z. et al. (2016) Spectrum of phenotypes associated with mutations in LRBA. *J. Clin. Immunol.* **36**, 33–45, <https://doi.org/10.1007/s10875-015-0224-7>
- 139 Gamez-Diaz, L., Neumann, J., Jager, F., Proietti, M., Felber, F., Soulas-Sprauel, P. et al. (2017) Immunological phenotype of the murine Lrba knockout. *Immunol. Cell Biol.* **95**, 789–802, <https://doi.org/10.1038/icb.2017.52>
- 140 Burnett, D.L., Parish, I.A., Masle-Farquhar, E., Brink, R. and Goodnow, C.C. (2017) Murine LRBA deficiency causes CTLA-4 deficiency in Tregs without progression to immune dysregulation. *Immunol. Cell Biol.* **95**, 775–788, <https://doi.org/10.1038/icb.2017.50>
- 141 Rongvaux, A., Willinger, T., Martinek, J., Strowig, T., Gearty, S.V., Teichmann, L.L. et al. (2014) Development and function of human innate immune cells in a humanized mouse model. *Nat. Biotechnol.* **32**, 364–372, <https://doi.org/10.1038/nbt.2858>
- 142 Takahashi, K. and Yamanaka, S. (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* **126**, 663–676, <https://doi.org/10.1016/j.cell.2006.07.024>
- 143 Avior, Y., Sagi, I. and Benvenisty, N. (2016) Pluripotent stem cells in disease modelling and drug discovery. *Nat. Rev. Mol. Cell Biol.* **17**, 170–182, <https://doi.org/10.1038/nrm.2015.27>
- 144 Anderson, R.H. and Francis, K.R. (2018) Modeling rare diseases with induced pluripotent stem cell technology. *Mol. Cell Probes*, <https://doi.org/10.1016/j.mcp.2018.01.001>
- 145 Grskovic, M., Javaherian, A., Strulovici, B. and Daley, G.Q. (2011) Induced pluripotent stem cells—opportunities for disease modelling and drug discovery. *Nat. Rev. Drug Discov.* **10**, 915–929
- 146 Tanaka, T., Takahashi, K., Yamane, M., Tomida, S., Nakamura, S., Oshima, K. et al. (2012) Induced pluripotent stem cells from CINCA syndrome patients as a model for dissecting somatic mosaicism and drug discovery. *Blood* **120**, 1299–1308, <https://doi.org/10.1182/blood-2012-03-417881>
- 147 Kawasaki, Y., Oda, H., Ito, J., Niwa, A., Tanaka, T., Hijikata, A. et al. (2017) Identification of a High-Frequency somatic NLR4 mutation as a cause of autoinflammation by pluripotent cell-based phenotype dissection. *Arthritis Rheumatol.* **69**, 447–459, <https://doi.org/10.1002/art.39960>
- 148 Blaydon, D.C., Biancheri, P., Di, W.L., Plagnol, V., Cabral, R.M., Brooke, M.A. et al. (2011) Inflammatory skin and bowel disease linked to ADAM17 deletion. *N. Engl. J. Med.* **365**, 1502–1508, <https://doi.org/10.1056/NEJMoa1100721>
- 149 Cuadrado, E., Michailidou, I., van Bodegraven, E.J., Jansen, M.H., Sluijs, J.A., Geerts, D. et al. (2015) Phenotypic variation in Aicardi-Goutieres syndrome explained by cell-specific IFN-stimulated gene response and cytokine release. *J. Immunol.* **194**, 3623–3633, <https://doi.org/10.4049/jimmunol.1401334>
- 150 Thomas, C.A., Tejwani, L., Trujillo, C.A., Negraes, P.D., Herai, R.H., Mesci, P. et al. (2017) Modeling of TREX1-dependent autoimmune disease using human stem cells highlights L1 accumulation as a source of neuroinflammation. *Cell Stem Cell* **21**, 319–331.e8, <https://doi.org/10.1016/j.stem.2017.07.009>
- 151 Stetson, D.B., Ko, J.S., Heidmann, T. and Medzhitov, R. (2008) Trex1 prevents cell-intrinsic initiation of autoimmunity. *Cell* **134**, 587–598, <https://doi.org/10.1016/j.cell.2008.06.032>
- 152 Hiller, B., Achleitner, M., Glage, S., Naumann, R., Behrendt, R. and Roers, A. (2012) Mammalian RNase H2 removes ribonucleotides from DNA to maintain genome integrity. *J. Exp. Med.* **209**, 1419–1426, <https://doi.org/10.1084/jem.20120876>
- 153 Masters, S.L., Gerlic, M., Metcalf, D., Preston, S., Pellegrini, M., O'Donnell, J.A. et al. (2012) NLRP1 inflammasome activation induces pyroptosis of hematopoietic progenitor cells. *Immunity* **37**, 1009–1023, <https://doi.org/10.1016/j.immuni.2012.08.027>
- 154 Haverkamp, M.H., van de Vosse, E., Goldbach-Mansky, R. and Holland, S.M. (2014) Impaired cytokine responses in patients with cryopyrin-associated periodic syndrome (CAPS). *Clin. Exp. Immunol.* **177**, 720–731, <https://doi.org/10.1111/cei.12361>
- 155 Dale, R.C., Gornall, H., Singh-Grewal, D., Alcausin, M., Rice, G.I. and Crow, Y.J. (2010) Familial Aicardi-Goutieres syndrome due to SAMHD1 mutations is associated with chronic arthropathy and contractures. *Am. J. Med. Genet. Part A* **152a**, 938–942, <https://doi.org/10.1002/ajmg.a.33359>
- 156 Berger, A., Sommer, A.F., Zwarg, J., Hamdorf, M., Welzel, K., Eslly, N. et al. (2011) SAMHD1-deficient CD14+ cells from individuals with Aicardi-Goutieres syndrome are highly susceptible to HIV-1 infection. *PLoS Pathog.* **7**, e1002425, <https://doi.org/10.1371/journal.ppat.1002425>
- 157 Goncalves, A., Karayel, E., Rice, G.I., Bennett, K.L., Crow, Y.J., Superti-Furga, G. et al. (2012) SAMHD1 is a nucleic-acid binding protein that is mislocalized due to aicardi-goutieres syndrome-associated mutations. *Hum. Mutat.* **33**, 1116–1122, <https://doi.org/10.1002/humu.22087>
- 158 Hartner, J.C., Walkley, C.R., Lu, J. and Orkin, S.H. (2009) ADAR1 is essential for maintenance of hematopoiesis and suppression of interferon signaling. *Nat. Immunol.* **10**, 109–115, <https://doi.org/10.1038/ni.1680>
- 159 Oda, H., Nakagawa, K., Abe, J., Awaya, T., Funabiki, M., Hijikata, A. et al. (2014) Aicardi-Goutieres syndrome is caused by IFIH1 mutations. *Am. J. Hum. Genet.* **95**, 121–125, <https://doi.org/10.1016/j.ajhg.2014.06.007>
- 160 Rice, G.I., del Toro Duany, Y., Jenkinson, E.M., Forte, G.M., Anderson, B.H., Ariaudo, G. et al. (2014) Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling. *Nat. Genet.* **46**, 503–509, <https://doi.org/10.1038/ng.2933>
- 161 Funabiki, M., Kato, H., Miyachi, Y., Toki, H., Motegi, H., Inoue, M. et al. (2014) Autoimmune disorders associated with gain of function of the intracellular sensor MDA5. *Immunity* **40**, 199–212, <https://doi.org/10.1016/j.immuni.2013.12.014>

- 162 Grandemange, S., Sanchez, E., Louis-Pence, P., Tran Mau-Them, F., Bessis, D., Coubes, C. et al. (2017) A new autoinflammatory and autoimmune syndrome associated with NLRP1 mutations: NAIAD (NLRP1-associated autoinflammation with arthritis and dyskeratosis). *Ann. Rheum. Dis.* **76**, 1191–1198, <https://doi.org/10.1136/annrheumdis-2016-210021>
- 163 Canna, S.W., Girard, C., Malle, L., de Jesus, A., Romberg, N., Kelsen, J. et al. (2017) Life-threatening NLRC4-associated hyperinflammation successfully treated with IL-18 inhibition. *J. Allergy Clin. Immunol.* **139**, 1698–1701, <https://doi.org/10.1016/j.jaci.2016.10.022>
- 164 Kitamura, A., Sasaki, Y., Abe, T., Kano, H. and Yasutomo, K. (2014) An inherited mutation in NLRC4 causes autoinflammation in human and mice. *J. Exp. Med.* **211**, 2385–2396, <https://doi.org/10.1084/jem.20141091>
- 165 Volker-Touw, C.M., de Koning, H.D., Giltay, J.C., de Kovel, C.G., van Kempen, T.S., Oberndorff, K.M. et al. (2017) Erythematous nodes, urticarial rash and arthralgias in a large pedigree with NLRC4-related autoinflammatory disease, expansion of the phenotype. *Br. J. Dermatol.* **176**, 244–248, <https://doi.org/10.1111/bjd.14757>
- 166 Watkin, L.B., Jessen, B., Wiszniewski, W., Vece, T.J., Jan, M., Sha, Y. et al. (2015) COPA mutations impair ER-Golgi transport and cause hereditary autoimmune-mediated lung disease and arthritis. *Nat. Genet.* **47**, 654–660, <https://doi.org/10.1038/ng.3279>
- 167 Volpi, S., Tsui, J., Mariani, M., Pastorino, C., Caorsi, R., Sacco, O. et al. (2018) Type I interferon pathway activation in COPA syndrome. *Clin. Immunol.* **187**, 33–36, <https://doi.org/10.1016/j.clim.2017.10.001>
- 168 Kanazawa, N., Okafuji, I., Kambe, N., Nishikomori, R., Nakata-Hizume, M., Nagai, S. et al. (2005) Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome. *Blood* **105**, 1195–1197, <https://doi.org/10.1182/blood-2004-07-2972>
- 169 Ong, L.T., Nachbur, U., Rowczenio, D., Ziegler, J.B., Fischer, E. and Lin, M.W. (2017) A novel nucleotide oligomerisation domain 2 mutation in a family with Blau syndrome: phenotype and function. *Innate Immun.* **23**, 578–583, <https://doi.org/10.1177/1753425917727063>
- 170 Maeda, S., Hsu, L.C., Liu, H., Bankston, L.A., Iimura, M., Kagnoff, M.F. et al. (2005) Nod2 mutation in Crohn's disease potentiates NF-kappaB activity and IL-1beta processing. *Science* **307**, 734–738, <https://doi.org/10.1126/science.1103685>
- 171 Janssen, R., Verhard, E., Lankester, A., Ten Cate, R. and van Dissel, J.T. (2004) Enhanced interleukin-1beta and interleukin-18 release in a patient with chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum.* **50**, 3329–3333, <https://doi.org/10.1002/art.20494>
- 172 Feldmann, J., Prieur, A.M., Quartier, P., Berquin, P., Certain, S., Cortis, E. et al. (2002) 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.* **71**, 198–203, <https://doi.org/10.1086/341357>
- 173 Hoffman, H.M., Mueller, J.L., Broide, D.H., Wanderer, A.A. and Kolodner, R.D. (2001) Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. *Nat. Genet.* **29**, 301–305, <https://doi.org/10.1038/ng756>
- 174 Ueki, Y., Lin, C.Y., Senoo, M., Ebihara, T., Agata, N., Onji, M. et al. (2007) Increased myeloid cell responses to M-CSF and RANKL cause bone loss and inflammation in SH3BP2 “cherubism” mice. *Cell* **128**, 71–83, <https://doi.org/10.1016/j.cell.2006.10.047>
- 175 Mukai, T., Ishida, S., Ishikawa, R., Yoshitaka, T., Kittaka, M., Gallant, R. et al. (2014) SH3BP2 cherubism mutation potentiates TNF- $\alpha$ -induced osteoclastogenesis via NFATc1 and TNF- $\alpha$ -mediated inflammatory bone loss. *J. Bone Miner. Res.* **29**, 2618–2635, <https://doi.org/10.1002/jbmr.2295>
- 176 Horai, R., Saijo, S., Tanioka, H., Nakae, S., Sudo, K., Okahara, A. et al. (2000) Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin 1 receptor antagonist-deficient mice. *J. Exp. Med.* **191**, 313–320, <https://doi.org/10.1084/jem.191.2.313>
- 177 Aksentijevich, I., Masters, S.L., Ferguson, P.J., Dancy, P., Frenkel, J., van Royen-Kerkhoff, A. et al. (2009) An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N. Engl. J. Med.* **360**, 2426–2437, <https://doi.org/10.1056/NEJMoa0807865>
- 178 Skendros, P., Chrysanthopoulou, A., Rousset, F., Kambas, K., Arampatzioglou, A., Mitsios, A. et al. (2017) Regulated in development and DNA damage responses 1 (REDD1) links stress with IL-1beta-mediated familial Mediterranean fever attack through autophagy-driven neutrophil extracellular traps. *J. Allergy Clin. Immunol.* **140**, 1378.e13–1387.e13, <https://doi.org/10.1016/j.jaci.2017.02.021>
- 179 Apostolidou, E., Skendros, P., Kambas, K., Mitroulis, I., Konstantinidis, T., Chrysanthopoulou, A. et al. (2016) Neutrophil extracellular traps regulate IL-1beta-mediated inflammation in familial Mediterranean fever. *Ann. Rheum. Dis.* **75**, 269–277, <https://doi.org/10.1136/annrheumdis-2014-205958>
- 180 Messaed, C., Chebaro, W., Di Roberto, R.B., Rittore, C., Cheung, A., Arseneau, J. et al. (2011) NLRP7 in the spectrum of reproductive wastage: rare non-synonymous variants confer genetic susceptibility to recurrent reproductive wastage. *J. Med. Genet.* **48**, 540–548, <https://doi.org/10.1136/jmg.2011.089144>
- 181 Singer, H., Biswas, A., Zimmer, N., Messaed, C., Oldenburg, J., Slim, R. et al. (2014) NLRP7 inter-domain interactions: the NACHT-associated domain is the physical mediator for oligomeric assembly. *Mol. Hum. Reprod.* **20**, 990–1001, <https://doi.org/10.1093/molehr/gau060>
- 182 Onoufriadis, A., Simpson, M.A., Pink, A.E., Di Meglio, P., Smith, C.H., Pullabhatla, V. et al. (2011) Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am. J. Hum. Genet.* **89**, 432–437, <https://doi.org/10.1016/j.ajhg.2011.07.022>
- 183 Zigmund, E., Bernshtein, B., Friedlander, G., Walker, C.R., Yona, S., Kim, K.W. et al. (2014) Macrophage-restricted interleukin-10 receptor deficiency, but not IL-10 deficiency, causes severe spontaneous colitis. *Immunity* **40**, 720–733, <https://doi.org/10.1016/j.immuni.2014.03.012>
- 184 Jéru, I., Duquesnoy, P., Fernandes-Alnemri, T., Cochet, E., Yu, J.W., Lackmy-Port-Lis, M. et al. (2008) Mutations in NALP12 cause hereditary periodic fever syndromes. *Proc. Natl. Acad. Sci. U.S.A.* **105**, 1614–1619, <https://doi.org/10.1073/pnas.0708616105>
- 185 Jeru, I., Hentgen, V., Normand, S., Duquesnoy, P., Cochet, E., Delwail, A. et al. (2011) Role of interleukin-1beta in NLRP12-associated autoinflammatory disorders and resistance to anti-interleukin-1 therapy. *Arthritis Rheum.* **63**, 2142–2148, <https://doi.org/10.1002/art.30378>
- 186 Jeru, I., Le Borgne, G., Cochet, E., Hayrapetyan, H., Duquesnoy, P., Grateau, G. et al. (2011) Identification and functional consequences of a recurrent NLRP12 missense mutation in periodic fever syndromes. *Arthritis Rheum.* **63**, 1459–1464, <https://doi.org/10.1002/art.30241>
- 187 Ibrahim, J.N., Jounblat, R., Delwail, A., Abou-Ghoch, J., Salem, N., Chouery, E. et al. (2014) Ex vivo PBMC cytokine profile in familial Mediterranean fever patients: involvement of IL-1beta, IL-1alpha and Th17-associated cytokines and decrease of Th1 and Th2 cytokines. *Cytokine* **69**, 248–254, <https://doi.org/10.1016/j.cyto.2014.06.012>

- 188 Van Gorp, H., Saavedra, P.H., de Vasconcelos, N.M., Van Opendenbosch, N., Vande Walle, L., Matusiak, M. et al. (2016) Familial Mediterranean fever mutations lift the obligatory requirement for microtubules in Pyrin inflammasome activation. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 14384–14389, <https://doi.org/10.1073/pnas.1613156113>
- 189 Molho-Pessach, V., Lerer, I., Abeliovich, D., Agha, Z., Abu Libdeh, A., Broshtilova, V. et al. (2008) The H syndrome is caused by mutations in the nucleoside transporter hENT3. *Am. J. Hum. Genet.* **83**, 529–534, <https://doi.org/10.1016/j.ajhg.2008.09.013>
- 190 Melki, I., Lambot, K., Jonard, L., Couloigner, V., Quartier, P., Neven, B. et al. (2013) Mutation in the SLC29A3 gene: a new cause of a monogenic, autoinflammatory condition. *Pediatrics* **131**, e1308–13, <https://doi.org/10.1542/peds.2012-2255>
- 191 Drenth, J.P., Goertz, J., Daha, M.R. and van der Meer, J.W. (1996) Immunoglobulin D enhances the release of tumor necrosis factor-alpha, and interleukin-1 beta as well as interleukin-1 receptor antagonist from human mononuclear cells. *Immunology* **88**, 355–362, <https://doi.org/10.1046/j.1365-2567.1996.d01-672.x>
- 192 Drenth, J.P., van der Meer, J.W. and Kushner, I. (1996) Unstimulated peripheral blood mononuclear cells from patients with the hyper-IgD syndrome produce cytokines capable of potent induction of C-reactive protein and serum amyloid A in Hep3B cells. *J. Immunol.* **157**, 400–404
- 193 Drenth, J.P., van Deuren, M., van der Ven-Jongekrijg, J., Schalkwijk, C.G. and van der Meer, J.W. (1995) Cytokine activation during attacks of the hyperimmunoglobulinemia D and periodic fever syndrome. *Blood* **85**, 3586–3593
- 194 Stoffels, M., Jongekrijg, J., Remijn, T., Kok, N., van der Meer, J.W. and Simon, A. (2015) TLR2/TLR4-dependent exaggerated cytokine production in hyperimmunoglobulinaemia D and periodic fever syndrome. *Rheumatol. (Oxf.)* **54**, 363–368, <https://doi.org/10.1093/rheumatology/keu341>
- 195 Jurczyk, J., Munoz, M.A., Skinner, O.P., Chai, R.C., Ali, N., Palendira, U. et al. (2016) Mevalonate kinase deficiency leads to decreased prenylation of Rab GTPases. *Immunol. Cell Biol.* **94**, 994–999, <https://doi.org/10.1038/icb.2016.58>
- 196 Messaëd, C., Akoury, E., Djuric, U., Zeng, J., Saleh, M., Gilbert, L. et al. (2011) NLRP7, a nucleotide oligomerization domain-like receptor protein, is required for normal cytokine secretion and co-localizes with Golgi and the microtubule-organizing center. *J. Biol. Chem.* **286**, 43313–43323, <https://doi.org/10.1074/jbc.M111.306191>
- 197 Hayward, B.E., De Vos, M., Talati, N., Abdollahi, M.R., Taylor, G.R., Meyer, E. et al. (2009) Genetic and epigenetic analysis of recurrent hydatidiform mole. *Hum. Mutat.* **30**, E629–E639, <https://doi.org/10.1002/humu.20993>
- 198 Kou, Y.C., Shao, L., Peng, H.H., Rosetta, R., del Gaudio, D., Wagner, A.F. et al. (2008) A recurrent intragenic genomic duplication, other novel mutations in NLRP7 and imprinting defects in recurrent biparental hydatidiform moles. *Mol. Hum. Reprod.* **14**, 33–40, <https://doi.org/10.1093/molehr/gam079>
- 199 El-Maarri, O., Seoud, M., Coullin, P., Herbiniaux, U., Oldenburg, J., Rouleau, G. et al. (2003) Maternal alleles acquiring paternal methylation patterns in biparental complete hydatidiform moles. *Hum. Mol. Genet.* **12**, 1405–1413, <https://doi.org/10.1093/hmg/ddg152>
- 200 Herlin, T., Fiirgaard, B., Bjerre, M., Kerndrup, G., Hasle, H., Bing, X. et al. (2013) Efficacy of anti-IL-1 treatment in Majeed syndrome. *Ann. Rheum. Dis.* **72**, 410–413, <https://doi.org/10.1136/annrheumdis-2012-201818>
- 201 Donkor, J., Zhang, P., Wong, S., O'Loughlin, L., Dewald, J., Kok, B.P.C. et al. (2009) A Conserved Serine residue is required for the phosphatidate phosphatase activity but not the transcriptional coactivator functions of Lipin-1 and Lipin-2. *J. Biol. Chem.* **284**, 29968–29978, <https://doi.org/10.1074/jbc.M109.023663>
- 202 Ferguson, P., Chen, S., Tayeh, M., Ochoa, L., Leal, S., Pelet, A. et al. (2005) Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *J. Med. Genet.* **42**, 551–557, <https://doi.org/10.1136/jmg.2005.030759>
- 203 Lorden, G., Sanjuan-Garcia, I., de Pablo, N., Meana, C., Alvarez-Miguel, I., Perez-Garcia, M.T. et al. (2017) Lipin-2 regulates NLRP3 inflammasome by affecting P2X7 receptor activation. *J. Exp. Med.* **214**, 511–528, <https://doi.org/10.1084/jem.20161452>
- 204 Zhong, F.L., Mamai, O., Sborgi, L., Boussofara, L., Hopkins, R., Robinson, K. et al. (2016) Germline NLRP1 mutations cause skin inflammatory and cancer susceptibility syndromes via inflammasome activation. *Cell* **167**, 187–202.e17, <https://doi.org/10.1016/j.cell.2016.09.001>
- 205 Damgaard, R.B., Walker, J.A., Marco-Casanova, P., Morgan, N.V., Titheradge, H.L., Elliott, P.R. et al. (2016) The deubiquitinase OTULIN is an essential negative regulator of inflammation and autoimmunity. *Cell* **166**, 1215–1230.e20, <https://doi.org/10.1016/j.cell.2016.07.019>
- 206 Zhou, Y., Zhang, Y., Moorman, J.P., Yao, Z.Q. and Jia, Z.S. (2014) Viral (hepatitis C virus, hepatitis B virus, HIV) persistence and immune homeostasis. *Immunology* **143**, 319–330, <https://doi.org/10.1111/imm.12349>
- 207 Masters, S.L., Lagou, V., Jeru, I., Baker, P.J., Van Eyck, L., Parry, D.A. et al. (2016) Familial autoinflammation with neutrophilic dermatosis reveals a regulatory mechanism of pyrin activation. *Sci. Transl. Med.* **8**, 332ra45, <https://doi.org/10.1126/scitranslmed.aaf1471>
- 208 Moghaddas, F., Llamas, R., De Nardo, D., Martinez-Banaclocha, H., Martinez-Garcia, J.J., Mesa-Del-Castillo, P. et al. (2017) A novel pyrin-associated autoinflammation with neutrophilic dermatosis mutation further defines 14-3-3 binding of pyrin and distinction to Familial Mediterranean Fever. *Ann. Rheum. Dis.* <https://doi.org/10.1136/annrheumdis-2017-211473>
- 209 Cortesio, C.L., Wernimont, S.A., Kastner, D.L., Cooper, K.M. and Huttenlocher, A. (2010) Impaired podosome formation and invasive migration of macrophages from patients with a PSTPIP1 mutation and PAPA syndrome. *Arthritis Rheum.* **62**, 2556–2558, <https://doi.org/10.1002/art.27521>
- 210 Geusau, A., Mothes-Luksch, N., Nahavandi, H., Pickl, W.F., Wise, C.A., Pourpak, Z. et al. (2013) Identification of a homozygous PSTPIP1 mutation in a patient with a PAPA-like syndrome responding to canakinumab treatment. *JAMA Dermatol.* **149**, 209–215, <https://doi.org/10.1001/2013.jamadermatol.717>
- 211 Demidowich, A.P., Freeman, A.F., Kuhns, D.B., Aksentijevich, I., Gallin, J.I., Turner, M.L. et al. (2012) Brief report: genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). *Arthritis Rheum.* **64**, 2022–2027, <https://doi.org/10.1002/art.34332>
- 212 Shoham, N.G., Centola, M., Mansfield, E., Hull, K.M., Wood, G., Wise, C.A. et al. (2003) Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc. Natl. Acad. Sci. U.S.A.* **100**, 13501–13506, <https://doi.org/10.1073/pnas.2135380100>

- 213 Omenetti, A., Carta, S., Caorsi, R., Finetti, M., Marotto, D., Lattanzi, B. et al. (2016) Disease activity accounts for long-term efficacy of IL-1 blockers in pyogenic sterile arthritis pyoderma gangrenosum and severe acne syndrome. *Rheumatol. (Oxf.)* **55**, 1325–1335, <https://doi.org/10.1093/rheumatology/kew031>
- 214 Fehling, H.J., Swat, W., Laplace, C., Kuhn, R., Rajewsky, K., Muller, U. et al. (1994) MHC class I expression in mice lacking the proteasome subunit LMP-7. *Science* **265**, 1234–1237, <https://doi.org/10.1126/science.8066463>
- 215 Fuchs-Telem, D., Sarig, O., van Steensel, M.A., Isakov, O., Israeli, S., Nousbeck, J. et al. (2012) Familial pityriasis rubra pilaris is caused by mutations in CARD14. *Am. J. Hum. Genet.* **91**, 163–170, <https://doi.org/10.1016/j.ajhg.2012.05.010>
- 216 Jordan, C.T., Cao, L., Roberson, E.D., Pierson, K.C., Yang, C.F., Joyce, C.E. et al. (2012) PSORS2 is due to mutations in CARD14. *Am. J. Hum. Genet.* **90**, 784–795, <https://doi.org/10.1016/j.ajhg.2012.03.012>
- 217 Mahil, S.K., Twelves, S., Farkas, K., Setta-Kaffetzi, N., Burden, A.D., Gach, J.E. et al. (2016) AP1S3 Mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36p production. *J. Invest. Dermatol.* **136**, 2251–2259, <https://doi.org/10.1016/j.jid.2016.06.618>
- 218 Setta-Kaffetzi, N., Simpson, M.A., Navarini, A.A., Patel, V.M., Lu, H.C., Allen, M.H. et al. (2014) AP1S3 mutations are associated with pustular psoriasis and impaired Toll-like receptor 3 trafficking. *Am. J. Hum. Genet.* **94**, 790–797, <https://doi.org/10.1016/j.ajhg.2014.04.005>
- 219 Briggs, T.A., Rice, G.I., Adib, N., Ades, L., Barete, S., Baskar, K. et al. (2016) Spondyloenchondrodysplasia due to mutations in ACP5: a comprehensive survey. *J. Clin. Immunol.* **36**, 220–234, <https://doi.org/10.1007/s10875-016-0252-y>
- 220 Briggs, T.A., Rice, G.I., Daly, S., Urquhart, J., Gornall, H., Bader-Meunier, B. et al. (2011) Tartrate-resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. *Nat. Genet.* **43**, 127–131, <https://doi.org/10.1038/ng.748>
- 221 An, J., Briggs, T.A., Dumax-Vorzet, A., Alarcon-Riquelme, M.E., Belot, A., Beresford, M. et al. (2017) Tartrate-resistant acid phosphatase deficiency in the predisposition to systemic lupus erythematosus. *Arthritis Rheumatol.* **69**, 131–142, <https://doi.org/10.1002/art.39810>
- 222 Bune, A.J., Hayman, A.R., Evans, M.J. and Cox, T.M. (2001) Mice lacking tartrate-resistant acid phosphatase (Acp 5) have disordered macrophage inflammatory responses and reduced clearance of the pathogen, *Staphylococcus aureus*. *Immunology* **102**, 103–113, <https://doi.org/10.1046/j.1365-2567.2001.01145.x>
- 223 Lobito, A.A., Kimberley, F.C., Muppidi, J.R., Komarow, H., Jackson, A.J., Hull, K.M. et al. (2006) Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS). *Blood* **108**, 1320–1327, <https://doi.org/10.1182/blood-2005-11-006783>
- 224 Bachetti, T., Chiesa, S., Castagnola, P., Bani, D., Di Zanni, E., Omenetti, A. et al. (2013) Autophagy contributes to inflammation in patients with TNFR-associated periodic syndrome (TRAPS). *Ann. Rheum. Dis.* **72**, 1044–1052, <https://doi.org/10.1136/annrheumdis-2012-201952>
- 225 Nedjai, B., Hitman, G.A., Church, L.D., Minden, K., Whiteford, M.L., McKee, S. et al. (2011) Differential cytokine secretion results from p65 and c-Rel NF-kappaB subunit signaling in peripheral blood mononuclear cells of TNF receptor-associated periodic syndrome patients. *Cell. Immunol.* **268**, 55–59, <https://doi.org/10.1016/j.cellimm.2011.02.007>
- 226 Nedjai, B., Hitman, G.A., Yousaf, N., Chernajovsky, Y., Stjernberg-Salmela, S., Pettersson, T. et al. (2008) Abnormal tumor necrosis factor receptor I cell surface expression and NF-kappaB activation in tumor necrosis factor receptor-associated periodic syndrome. *Arthritis Rheum.* **58**, 273–283, <https://doi.org/10.1002/art.23123>
- 227 Rebelo, S.L., Bainbridge, S.E., Amel-Kashpaz, M.R., Radford, P.M., Powell, R.J., Todd, I. et al. (2006) Modeling of tumor necrosis factor receptor superfamily 1A mutants associated with tumor necrosis factor receptor-associated periodic syndrome indicates misfolding consistent with abnormal function. *Arthritis Rheum.* **54**, 2674–2687, <https://doi.org/10.1002/art.21964>
- 228 Yousaf, N., Gould, D.J., Aganna, E., Hammond, L., Mirakian, R.M., Turner, M.D. et al. (2005) Tumor necrosis factor receptor I from patients with tumor necrosis factor receptor-associated periodic syndrome interacts with wild-type tumor necrosis factor receptor I and induces ligand-independent NF-kappaB activation. *Arthritis Rheum.* **52**, 2906–2916, <https://doi.org/10.1002/art.21268>
- 229 D’Ossualdo, A., Ferlito, F., Prigione, I., Obici, L., Meini, A., Zulian, F. et al. (2006) Neutrophils from patients with TNFRSF1A mutations display resistance to tumor necrosis factor-induced apoptosis: pathogenetic and clinical implications. *Arthritis Rheum.* **54**, 998–1008, <https://doi.org/10.1002/art.21657>
- 230 Kamata, H., Honda, S., Maeda, S., Chang, L., Hirata, H. and Karin, M. (2005) Reactive oxygen species promote TNFalpha-induced death and sustained JNK activation by inhibiting MAP kinase phosphatases. *Cell* **120**, 649–661, <https://doi.org/10.1016/j.cell.2004.12.041>
- 231 Miscia, S., Marchisio, M., Grilli, A., Di Valerio, V., Centurione, L., Sabatino, G. et al. (2002) Tumor necrosis factor alpha (TNF-alpha) activates Jak1/Stat3-Stat5B signaling through TNFR-1 in human B cells. *Cell Growth Differ.* **13**, 13–18
- 232 Negm, O.H., Mannsperger, H.A., McDermott, E.M., Drewe, E., Powell, R.J., Todd, I. et al. (2014) A pro-inflammatory signalome is constitutively activated by C33Y mutant TNF receptor 1 in TNF receptor-associated periodic syndrome (TRAPS). *Eur. J. Immunol.* **44**, 2096–2110, <https://doi.org/10.1002/eji.201344328>
- 233 Meuwissen, M.E., Schot, R., Buta, S., Oudesluijs, G., Tinschert, S., Speer, S.D. et al. (2016) Human USP18 deficiency underlies type 1 interferonopathy leading to severe pseudo-TORCH syndrome. *J. Exp. Med.* **213**, 1163–1174, <https://doi.org/10.1084/jem.20151529>
- 234 Starokadomskyy, P., Gemelli, T., Rios, J.J., Xing, C., Wang, R.C., Li, H. et al. (2016) DNA polymerase- $\alpha$  regulates type I interferon activation through cytosolic RNA:DNA synthesis. *Nat. Immunol.* **17**, 495–504, <https://doi.org/10.1038/ni.3409>
- 235 Gazzo, A., Raimondi, D., Daneels, D., Moreau, Y., Smits, G., Van Dooren, S. et al. (2017) Understanding mutational effects in digenic diseases. *Nucleic Acids Res.* **45**, e140, <https://doi.org/10.1093/nar/gkx557>
- 236 Lupski, J.R. (2012) Digenic inheritance and Mendelian disease. *Nat. Genet.* **44**, 1291–1292, <https://doi.org/10.1038/ng.2479>
- 237 Cordell, H.J. (2002) Epistasis: what it means, what it doesn’t mean, and statistical methods to detect it in humans. *Hum. Mol. Genet.* **11**, 2463–2468, <https://doi.org/10.1093/hmg/11.20.2463>
- 238 Gazzo, A.M., Daneels, D., Cilia, E., Bonduelle, M., Abramowicz, M., Van Dooren, S. et al. (2016) DIDA: a curated and annotated digenic diseases database. *Nucleic Acids Res.* **44**, D900–D907, <https://doi.org/10.1093/nar/gkv1068>

- 239 Ameratunga, R., Woon, S.T., Bryant, V.L., Steele, R., Slade, C., Leung, E.Y. et al. (2017) Clinical implications of digenic inheritance and epistasis in primary immunodeficiency disorders. *Front. Immunol.* **8**, <https://doi.org/10.3389/fimmu.2017.01965>
- 240 Ben-Zvi, I., Brandt, B., Berkun, Y., Lidar, M. and Livneh, A. (2012) The relative contribution of environmental and genetic factors to phenotypic variation in familial Mediterranean fever (FMF). *Gene* **491**, 260–263, <https://doi.org/10.1016/j.gene.2011.10.005>
- 241 Rodríguez-Cortez, V.C., del Pino-Molina, L., Rodríguez-Ubreva, J., Ciudad, L., Gómez-Cabrero, D., Company, C. et al. (2015) Monozygotic twins discordant for common variable immunodeficiency reveal impaired DNA demethylation during naïve-to-memory B-cell transition. *Nat. Commun.* **6**, <https://doi.org/10.1038/ncomms8335>
- 242 Kirectepe, A.K., Kasapcopur, O., Arisoy, N., Celikyapi Erdem, G., Hatemi, G., Ozdogan, H. et al. (2011) Analysis of MEFV exon methylation and expression patterns in familial Mediterranean fever. *BMC Med. Genet.* **12**, 105, <https://doi.org/10.1186/1471-2350-12-105>
- 243 Vento-Tormo, R., Álvarez-Errico, D., Garcia-Gomez, A., Hernández-Rodríguez, J., Buján, S., Basagaña, M. et al. (2017) DNA demethylation of inflammasome-associated genes is enhanced in patients with cryopyrin-associated periodic syndromes. *J. Allergy Clin. Immunol.* **139**, 202.e6–211.e6, <https://doi.org/10.1016/j.jaci.2016.05.016>
- 244 Zuo, T., Tycko, B., Liu, T.M., Lin, J.J. and Huang, T.H. (2009) Methods in DNA methylation profiling. *Epigenomics* **1**, 331–345, <https://doi.org/10.2217/epi.09.31>