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Monogenic autoinflammatory disorders: beyond the periodic fever

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Abstract

The past two decades have seen an exponential increase in the number of monogenic autoinflammatory disorders described, coinciding with improved genetic sequencing techniques. This group of disorders has evolved to be heterogeneous and certainly more complex than the original four 'periodic fever syndromes' caused by innate immune over-activation. This review aims to provide an update on the classic periodic fever syndromes as well as introducing the broadening spectrum of clinical features seen in more recently described conditions.

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Since the coinage of the term '*autoinflammatory disease'* in 1999 (1), over 40 syndromes have been added to this category of immunological disorders by the International Union of Immunological Societies (IUIS) and the International Society for Systemic Autoinflammatory Diseases (ISSAID) (2, 3). Originally used to describe a discrete group of conditions characterised by innate immune dysregulation without markers of adaptive immune dysfunction, such as high titres of autoantibodies or self-reactive T-cells (1), it now encompasses an increasingly heterogeneous group of disorders that have features of both innate and adaptive dysregulation, as well as immune deficiency. There is therefore a need for clinicians to recognise that autoinflammatory diseases can present beyond the periodic fever. This review provides a brief overview of autoinflammatory disorders from a symptom-based perspective and details a few issues adult physicians face in the diagnosis of these conditions.

1 Periodic fever

The traditional autoinflammatory disorders, familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), tumour necrosis factor receptor associated periodic syndrome (TRAPS) and cryopyrin associated periodic syndrome (CAPS), are characterised by periodic or cyclic fever with a constellation of symptoms that prompt consideration of a specific diagnosis (**Figure 1**). Indeed, diagnostic algorithms have been developed to aid clinicians in determining when molecular testing should be considered for a child presenting with a

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periodic fever (4, 5). Clinical variables of participants in the Eurofever project have been collated (6) and proposed classification guidelines have recently been published, taking into account both clinical features and molecular testing (7).

1.1 Familial Mediterranean Fever

FMF was the first described and is the most common monogenic autoinflammatory disease (8, 9). The majority of cases of FMF are caused by autosomal recessive mutations in exon 2 or 10 of *MEFV* that result in a decrease in the activation threshold of the inflammasome forming protein pyrin (10-12). In health, pyrin is activated by an event downstream of RhoA inactivation, induced by bacteria such as *Clostridium difficile* and *Burkholderia cenocepacia.* In response, pyrin forms an inflammasome and induces inflammatory cell death (pyroptosis) and the release of active cytokines IL-1β and IL-18 (11, 13). The recent linking of pyrin with an effector mechanism of *Yersenia pestis* has provided interesting theories about the high prevalence of carrier rates in certain ethnic populations, and the possibility that FMF associated variants may have provided a survival advantage during plague epidemics (14, 15).

FMF is characterised by periodic fevers of 12-72 h duration associated with polyserositis and high acute phase reactants. Over half of patients with FMF have their first episode of serositis prior to the age of 10 years and the vast majority before the age of 20 years (16, 17). Poorly controlled inflammation, either overt or subclinical, may result in accumulation and renal deposition of serum amyloid A (SAA) leading to chronic renal insufficiency.

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A number of *clinical* diagnostic criteria for FMF exist, including the Tel-Hashomer, Livneh simplified (18) and the Yalçinkaya-Ozen criteria (19). The performances of these criteria were retrospectively compared using a cohort of patients with childhood-onset and genetically confirmed FMF registered with the Eurofever project. In this select population, the Yalçinkaya-Ozen criteria yielded higher sensitivity, but lower specificity compared with the other diagnostic criteria (20). The response to colchicine is included as a major criterion in the Tel-Hashomer and a minor criterion in the Livneh criteria (18). The therapeutic effectiveness of the microtubule polymerization inhibitor colchicine in this population has been reported for decades (21), with a number of more recent publications documenting *in vitro* evidence of effect on pyrin inflammasome formation (11, 12, 22).

Renal amyloidosis remains the leading cause of increased mortality in adults with FMF even after the introduction of routine colchicine therapy (23, 24). Whether this is the result of poor adherence to treatment or true 'colchicine-resistance' is unclear (25, 26). The response of patients with colchicine-resistant FMF (CR-FMF) to the neutralizing anti-IL-1β antibody canakinumab suggests that IL-1β is a key cytokine in this disorder (27). The recent randomized controlled CLUSTER trial strengthened this idea, with the demonstration of the effectiveness of canakinumab at controlling flares and disease control compared with standard of care in CR-FMF (28).

1.2 Mevalonate Kinase Deficiency

MKD, also known as hyper-IgD syndrome (HIDS), is an autosomal recessive disorder caused by loss-of-function mutations in *MVK* encoding mevalonate kinase, resulting in approximately 10% residual enzyme function (29). Mevalonate kinase plays an important

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role in the production of isoprenoids from acetate and is involved in a number of cellular processes including cholesterol synthesis (30). In recent years, mevalonate kinase and its pathway have been shown to have the physiological role of maintaining pyrin in an inactive state, and MKD may be considered a pyrin dependent disorder (11).

MKD is characterised by fever duration of 3-7 days occurring every 4-8 weeks with symptom onset typically early in life (median 6 months) (31). Flares are associated with hepatosplenomegaly, lymphadenopathy, arthralgia and gastrointestinal symptoms and are possibly triggered by infections, vaccinations, or stress (31). Mevalonate aciduria (MA), on the severe end of MKD spectrum with almost no detectable enzyme activity, is associated with developmental delay, ataxia and failure to thrive and is considered a metabolic disorder.

Despite its conventional name, the utility of serum IgD levels in the diagnosis of MKD has been criticized. A high serum IgD level is not specific for the diagnosis of MKD nor does the level of IgD correlate with disease severity in patients with MKD (32, 33). In contrast, urine mevalonic acid has clinical utility. A diagnosis of MKD is unlikely with normal urine mevalonic acid excretion during a flare, most recently shown to have a negative predictive value of 98% (34). However, with a positive predictive value of 71% for positive urine mevalonic acid, *MVK* sequencing is still required for the diagnosis of MKD (34).

Although the frequency of episodes decreases with age, the majority of patients with MKD still experience symptoms in adulthood (31). Prior to the introduction of biologic therapy acute episodes were treated symptomatically with non-steroidal and steroidal anti-inflammatory medications. Initial small prospective trials suggested that on-demand anakinra therapy commenced within 24 hours of symptom onset reduced the severity and duration of

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the attack (35). More recently the use of canakinumab in MKD was addressed in the CLUSTER study, with 57% of patients with MKD experiencing complete response (as determined by absence of attack in a 4-month period) with a high dose of canakinumab (28). Those patients who did not achieve a complete response experienced reduced frequency and severity of attacks.

1.3 Tumor necrosis factor receptor associated periodic syndrome

TRAPS is an autosomal dominant condition caused by heterozygous mutations in *TNFRSF1A.*

Typical attacks are prolonged, lasting several weeks to near-continuous, and the majority are associated with fever, abdominal pain, rash and periorbital oedema. The incidence of amyloidosis in a European cohort study of 158 patients with TRAPS was 10% (36).

It was previously thought that disease associated mutations result in defective shedding of the TNF-receptor TNFR1, but the pathogenesis of TRAPS is proving to be more complicated than increased signalling through this receptor to the NF-κB pathway. This is highlighted with the eventual failure of etanercept, a dimeric fusion protein that binds TNF, to completely abate symptoms of individuals with TRAPS (37, 38). Likewise, the administration of infliximab, a chimeric anti-TNF monoclonal antibody, has resulted in severe inflammatory reactions in this population (39, 40). The therapeutic benefit afforded by IL-1β targeted therapy raises the possibility of cytoplasmic aggregates of abnormal receptor triggering inflammasome activation (28, 41).

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1.4 Cryopyrin-associated periodic syndrome

CAPS encompasses a spectrum of clinical manifestations caused by gain-of-function mutations in *NLRP3*, from familial cold urticarial syndrome (FCAS), Muckle-Wells syndrome (MWS) to neonatal onset multisystemic inflammatory disease (NOMID). FCAS is characterized by episodic fever as well as cold induced urticaria and conjunctival injection (42). Individuals with MWS may have complications such as late onset sensorineural hearing loss and renal amyloidosis in addition to more persistent features of FCAS (43). Individuals with NOMID are on the severe end of the CAPS spectrum, with a broad range of symptoms stemming from widespread inflammation, with classic features including chronic aseptic meningitis as well as dermatological and articular manifestations. From the clinical manifestations described, it is understandable that these three conditions were originally considered to be distinct disease entities. However, subsequent genetic evaluation of symptomatic families determined the cause of all three syndromes to be heterozygous mutations in *NLRP3* (43-46).

The pathophysiological basis of CAPS is augmented NLRP3 inflammasome formation (47). Unlike FMF, where patients have a *lowered threshold* for pyrin inflammasome formation, patients with CAPS have *constitutive* NLRP3 inflammasome formation. Peripheral blood mononuclear cells (PBMCs) from patients with CAPS demonstrate spontaneous secretion of IL-1β. The introduction of IL-1β targeted therapy, whether in the form of recombinant IL-1 receptor antagonist anakinra (48-50), human monoclonal antibody specific for IL-1β canakinumab (51) or anti-IL-1 dimeric fusion protein rilonacept (52), has completely altered the morbidity and mortality previously associated with this condition.

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Today in Australia, anakinra is available on the Pharmaceutical Benefits Scheme for moderate to severe CAPS.

2 Dermatological presentation

Although each of the periodic fever syndromes described may have dermatological manifestations, there are certain monogenic autoinflammatory diseases in which the skin involvement is likely to be a prominent feature.

The initial manifestation of Blau syndrome, a granulomatous inflammatory condition caused by heterozygous mutations in *NOD2*, is usually dermatological in the form of a fine maculo-(micro)papular rash (53, 54). This rash, however, may be overlooked and almost all children have polyarticular arthritis by the time they present to a paediatric rheumatologist (55). Uveitis develops next, making up the triad of symptoms classically seen in Blau syndrome (55, 56). All symptoms tend to present prior to the age of 5 years. Despite the impressiveness of the 'boggy' arthritis, the skin rash is important in the diagnosis of this condition as biopsy is more sensitive at detecting non-caseating granulomatous inflammatory infiltrate in patients who are eventually diagnosed with Blau Syndrome than biopsy of affected synovium (55).

Although caused by mutations in *MEFV*, the recently described Pyrin Associated Autoinflammation with Neutrophilic Dermatosis (PAAND) is clinically distinct from FMF, characterized by pustular acne, pyoderma gangrenosum, recurrent fevers, myalgia and arthralgia (57). PAAND is caused by heterozygous mutations in the 14-3-3 binding sites of pyrin (57, 58), although a recent case description suggests a homozygous form exists (59).

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The 14-3-3 family of proteins is required to keep pyrin in its autoinhibited conformation, and mutations disrupting this interaction result in an auto-activated pyrin (11, 57, 58).

Similarly, patients with Pyogenic Arthritis-Pyoderma gangrenosum-Acne (PAPA) syndrome, have pyoderma gangrenosum as a key manifestation. Unlike PAAND, however, the presentation of pyogenic arthritis usually precedes the dermatological manifestations (60). PAPA syndrome is caused by heterozygous mutations in *PSTPIP1* and although it is understood that the inflammatory manifestations in PAPA syndrome are pyrin dependent (61, 62), the exact mechanism of disease is unclear. The optimal treatment regimen for these patients is also uncertain, with case reports of both anti-IL-1β therapy and anti-TNF therapy having some efficacy (63).

Two rare dermatological conditions, multiple self-healing palmoplantar carcinoma (MSPC) and familial keratosis lichenoides chronica (FKLC), have recently been linked to activating heterozygous mutations in *NLRP1* (64). Uncontrolled inflammasome activation and subsequent paracrine signalling in the skin was proposed as the patho-mechanism of malignant transformation in these patients. The clinical response to targeting IL-1β or NLRP1 was not examined in this small cohort. Interestingly, soon after this publication, a more systemic disease attributed to increased NLRP1 activity was described (65). Three individuals were initially considered to have systemic onset juvenile idiopathic arthritis, but all had the distinct feature of skin dyskeratosis and features of autoimmunity. The disparate disease presentations, and whether an important genotype-phenotype correlation exists has not been explored. Recently, a specific endogenous inhibitor of NLRP1, DPP9, has been

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identified and it will be interesting to see whether treatment options based on this protein are developed (66-69).

An autosomal recessive form of generalised pustular psoriasis (GPP) has also been described. Homozygous missense mutations in *IL36RN*, causing deficiency in IL-36 receptor antagonist (IL-36Ra, DITRA), lead to unregulated signalling through the IL-36 receptor (70). There are a broad range of therapeutic agents that have shown some efficacy in symptom management, including biologics targeting IL-1β, TNF, IL-17 and IL-12/23 (71-81). Therapeutic targeting of the IL-36 receptor specifically is currently being investigated (82).

3 Bone involvement

Deficiency of IL-1Ra (DIRA) is a rare neonatal disorder characterized by multifocal sterile osteomyelitis, pustular dermatosis as well as biochemical evidence of systemic inflammation. It is caused by homozygous truncation mutations in or complete deletion of *ILRN* encoding IL-1Ra (83, 84). The prompt and complete clinical and biochemical response to anakinra in DIRA is not surprising as the therapy is essentially replacing the deficient protein in patients.

Early onset multifocal osteomyelitis is certainly not unique to DIRA. The initial description of Majeed Syndrome included cousins with chronic recurrent multifocal osteomyelitis, congential dyserythropoietic anaemia and neutrophilic dermatosis. The eponymous syndrome was determined to be caused by homozygous mutations in *LPIN2*, encoding LIPIN2, a phosphatidate phosphatase (85-87). Although the exact mechanism of inflammatory disease is unclear, the clinical response to IL-1β targeted therapy suggests that this is a key cytokine in disease pathogenesis (88).

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4 Gastrointestinal presentation

Similar to the disorders presented above, those that present with dominant gastrointestinal manifestations tend to do so in very early life. This is certainly true for disorders associated with homozygous mutations in *IL10*, *IL10RA* or *IL10RB* resulting in deficiencies in IL-10, IL-10Rα or IL-10Rβ respectively (89, 90). IL-10, acting via its receptor comprising of IL-10Rα and IL-10Rβ, exerts a STAT3-mediated regulatory effect on inflammation (91-93). Individuals with deficiencies in this pathway present with severe and early onset inflammatory bowel disease that is often refractory to treatment with immunomodulatory agents (94).

The first two publications describing NLRC4-associated autoinflammatory diseases (NLRC4-AIDs) reported enterocolitis as a key clinical feature of the condition, along with macrophage activation syndrome (MAS) (95, 96). Caused by gain-of-function heterozygous mutations in *NLRC4*, this condition was distinct from other inflammasomopathies (for example CAPS, FMF and PAAND) in that the key driving cytokine was determined to be IL-18. Indeed, there has been a report of the successful use of recombinant human IL-18 binding protein (rhIL18BP) in a patient with NLRC4-associated MAS (97) and a Phase 3 clinical trial (NCT03113760) is currently underway looking at rhIL18BP in NLRC4-associated MAS. Since these first reports, the phenotypic spectrum of patients with NLRC4-AIDs has broadened significantly, with the report of a large pedigree with dominantly inherited cold-induced urticaria and arthritis without gastrointestinal manifestations or MAS, and another of a patient with possible immunodeficiency in addition to inflammatory manifestations (98-100).

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5 Vasculitis

The original back to back publications describing patients with Deficiency of ADA2 (DADA2) described two distinct syndromes associated with loss-of-function mutations in *CECR1* (now known as *ADA2*). The first documented 19 subjects of Georgian Jewish heritage with polyarteritis nodosa (101), the second 9 individuals with early onset stroke, vasculopathy and febrile episodes (102). Most individuals presented in the first decade of life. Since this time, a number of reports published suggest that the phenotypic spectrum is broad, and the penetrance of disease is variable, with cytopaenias, lymphoproliferative disease and immune deficiencies being reported (103-107). Although an interferon gene signature has been noted in these patients (108, 109), the response to TNF inhibition has been impressive (101, 110, 111) and is now recommended therapy (112).

Gain-of-function mutations in *TMEM137* encoding the cytosolic innate immune sensor STING result in an autoinflammatory diseases characterised by peripheral vascular inflammation, nail dystrophy and interstitial lung disease termed STING associated vasculopathy with onset in infancy (SAVI) (113). Like DADA2, patients with SAVI have an interferon gene signature but in this disorder, it appears to be causing, at least in part, clinical disease as evidenced by the response to JAK/STAT inhibition (113-115). Interestingly, some clinical manifestations may persist despite treatment. For example, the lividinous rash in one case did not respond to ruxolitinib, suggesting that the interferon pathway may not be the only pathway involved in disease (116).

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6 Neurological presentation

A number of autoinflammatory disorders have the dominant clinical feature of intracranial calcification and developmental delay. The classic 'interferonopathy', Aicardi-Goutières syndrome (AGS), was described as a disorder of the CNS mimicking intrauterine infection, associated CSF lymphocytosis and bilateral basal ganglia calcifications (117). The genetic causes of AGS determined to date involve the processing or sensing of cytoplasmic nucleic acid (118-122). Patients may also present with chilblains or variable degrees of autoimmunity or autoantibody positivity. Likewise, USP18 deficiency is also associated with intracranial calcification as well as microcephaly, cerebral haemorrhage and hepatosplenomegaly (123). This autosomal recessive disorder is caused by defective downregulation of interferon signalling. Similarly, mutations in *POLA1* that cause X-linked reticulate pigmentary disorder (XLPDR) are associated with upregulated interferon gene signature and intracranial calcifications in addition to hyperpigmentation, abnormal hair, amyloid deposits and hyperkeratosis (124). Although not a key manifestation, intracranial calcifications are also seen in some patients with SAVI and Systemic Lupus Erythematosus (125, 126), suggesting that this feature may be linked to interferon upregulation.

7 Immunological overlap

Over the past 5 or so years, a number of conditions have been described that have brought in to question the original definition of autoinflammatory disorders. The presence of autoinflammation in patients with evidence of autoimmunity and/or immunodeficiency highlights that the divide between the innate and adaptive immune system is not strict. (103). A complex immunological phenotype is seen in PLCγ2-associated antibody deficiency and

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immune dysregulation (PLAID) and autoinflammation and PLAID (APLAID), caused by mutations in *PLCG2* (127, 128). PLCγ2 is a phospholipase involved in immune signalling pathways and intracellular calcium release (129). The initial description of PLAID investigated three families with dominantly inherited cold-induced urticaria, antibody deficiency and autoimmunity (128). APLAID, on the other hand, was diagnosed in individuals with prominent inflammatory manifestations involving the skin, gut, bronchioles and uvea (127). The immune deficiency manifests in the form of hypogammaglobulinemia resulting in recurrent bacterial infection (127). In both PLAID and APLAID, there have been reports of non-caseating granuloma on skin biopsy. Despite the distinct clinical entities, it is unclear if a genotype-phenotype exists or if there are broader clinical phenotypes associated with PLCγ2 variants.

The immune features of monogenic disorders involving the linear ubiquitination of components the NF-κB pathway are similarly complex. Homozygous mutations in either *HOIL1* or *HOIP*, resulting in loss-of-function of the linear ubiquitin chain assembly complex (LUBAC), result in a syndrome of amylopectinosis, autoinflammation as well as immunodeficiency (130, 131). In investigating the range of immunological manifestations in these individuals, Bossoin et al. performed *ex vivo* stimulation experiments on a range of cells and determined that the NF-κB pathway was differentially affected depending on the cell type examined (131). Although B cells and fibroblasts from patients with HOIL-1 deficiency had an attenuated NF-κB response to stimulation, monocytes had an enhanced response to stimulation. This has provided key insight in to how a variety of immunological manifestations can exist in one individual, and how a mutation in a single gene may

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differentially affect a pathway depending on the cell type. The immunological spectrum seen in autoinflammatory disorders is represented in **Figure 2**.

8 Diagnosis of monogenic autoinflammatory diseases in the adult

Monogenic autoinflammatory diseases generally present in childhood and as such the index of suspicion for this diagnosis in a patient presenting in adulthood is not high. There is a paucity of data on the incidence these disorders in the adult population. The experience of a single American adult autoinflammatory clinic was published in 2016 (132). Of the 266 patients suspected of a monogenic autoinflammatory diseases, 13 were diagnosed with FMF, 5 with CAPS, 6 with TRAPS and 1 with HIDS. Four of the 5 CAPS cases and the single HIDS case had symptoms since very early childhood and experienced a large diagnostic delay. In cases not fitting in to the classic periodic fevers, there may be even more of a delay, as shown in the initial description of PAAND. Most individuals were diagnosed in adulthood but had symptoms onset in childhood (57). Likewise, despite the early onset of NLRC4-AID, the initial description documented an affected adult. The father of the index case was determined to have a *de novo* variant in *NLRC4* and presented later in life with a severe febrile episode complicated by acute respiratory distress syndrome, disseminated intravascular coagulation and subarachnoid haemorrhage associated with elevated ferritin and soluble IL-2R. On further questioning, however, the patient had been admitted with fever, diarrhea and failure to thrive during the first year of life without a specific diagnosis, and the recurrent fevers had persisted through to adulthood.

Having said this, symptom onset may indeed occur in adulthood. An Italian tertiary centre published results of 195 patients referred to an autoinflammatory clinic with the

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possible diagnosis of periodic fever syndrome (133). Over half (64.6%) were adults and of these, 24 (12.7%) were genetically defined as FMF (12 individuals), TRAPS (6), MKD (3) or CAPS (3). Interestingly, a number of these individuals experienced symptom onset in the third decade of life. Furthermore, with improvements in genetic sequencing techniques and widespread use of next-generation sequencing, monogenic autoinflammatory disorders caused by somatic mutations have been diagnosed in individuals with symptom onset in adulthood. An individual presenting with symptoms typical of CAPS from the age 56 years was diagnosed with a somatic *NLRP3* mosaicism restricted to myeloid cells (134). Similarly, 8 adults with symptoms consistent with CAPS other than onset in mid-adulthood harbored pathogenic mutations in *NLRP3* with an allele frequency of 5.1% to 21.2% in DNA from whole blood (135). This highlights the importance of considering the possible diagnosis, and if the index of suspicion is high, enquiring further if initial genetic testing does not detect a pathogenic variant.

9 Conclusion

The field of autoinflammatory diseases has expanded such that consideration of the diagnosis should be made even in patients presenting beyond the periodic fever, including by clinicians other than paediatric rheumatologists and immunologists. Newer and widely available genetic sequencing techniques, either through diagnostic laboratories or collaboration with research projects, may allow for diagnosis in patients who present later in life, or with an atypical clinical presentation. **Figure 3** categorises autoinflammatory disease based on their presenting or primary clinical feature and the cytokine or pathway implicated in disease. Although these conditions are rare and as such comprehensive data on incidence and

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prevalence is difficult to ascertain, appropriate diagnosis may lead to the institution of effective targeted biologic therapy and reduction in long term complications of uncontrolled inflammation, such as amyloidosis.

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Figure 1: Clinical symptoms associated with periodic fever syndromes. Schematic representation of symptoms in the four key periodic fever syndromes.

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Figure 2: Spectrum of immunological overlap seen in autoinflammatory disorders.

AGS Aicardi-Goutières syndrome, AIADK autoinflammation with arthritis and dyskeratosis, AIFEC autoinflammation with infantile enterocolitis, AILJK autoimmune interstitial lung, joint, and kidney disease, APLAID autoinflammation, antibody deficiency, and immune dysregulation syndrome, DADA2 deficiency of ADA2, DIRA interleukin 1 receptor antagonist deficiency, DITRA interleukin 36 receptor antagonist deficiency, EOIBD early onset inflammatory bowel disease, FMF familial Mediterranean fever, H+ syndrome histiocytosis-lymphadenopathy plus syndrome, HA20 haploinsufficiency of A20, HS hidradenitis suppurtiva, HYDM1 hydatidiform mole, recurrent 1, JIA juvenile idiopathic arthritis, MKD mevalonate kinase deficiency, MSPC multiple self-healing palmoplantar carcinoma, ORAS otulin-related autoinflammatory syndrome, PAAND pyrin associated autoinflammation with neutrophilic dermatosis, PAPA syndrome pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome, PFIT autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia, PLAID PLCG2 associated antibody deficiency and immune dysregulation, PRAAS proteasome-associated autoinflammatory syndrome, PRP pityriasis rubra pilaris, SAVI STING-associated vasculopathy, infantile-onset, SIFD sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay, SPENCDI spondyloenchondrodysplasia with immune dysregulation, TRAPS tumor necrosis factor receptor-associated periodic syndrome, XLPDR X-linked pigmentary disorder, reticulate, with systemic manifestations. (137-140)

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Figure 3: Main clinical manifestation and cytokine/pathway implicated in disease. Autoinflammatory disorders as listed in IUIS and Infevers database classified based on main clinical feature and pathway implicated in disease.

AGS Aicardi-Goutières syndrome, AIADK autoinflammation with arthritis and dyskeratosis, AIFEC autoinflammation with infantile enterocolitis, AILJK autoimmune interstitial lung, joint, and kidney disease, APLAID autoinflammation, antibody deficiency, and immune dysregulation syndrome, DADA2 deficiency of ADA2, DIRA interleukin 1 receptor antagonist deficiency, DITRA interleukin 36 receptor antagonist deficiency, EOIBD early onset inflammatory bowel disease, FMF familial Mediterranean fever, H+ syndrome histiocytosis-lymphadenopathy plus syndrome, HA20 haploinsufficiency of A20, HS hidradenitis suppurtiva, HYDM1 hydatidiform mole, recurrent 1, JIA juvenile idiopathic arthritis, MKD mevalonate kinase deficiency, MSPC multiple self-healing palmoplantar carcinoma, ORAS otulin-related autoinflammatory syndrome, PAAND pyrin associated autoinflammation with neutrophilic dermatosis, PAPA syndrome pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome, PFIT autoinflammatory periodic fever, immunodeficiency, and thrombocytopenia, PLAID PLCG2 associated antibody deficiency and immune dysregulation, PRAAS proteasome-associated autoinflammatory syndrome, PRP pityriasis rubra pilaris, SAVI STING-associated vasculopathy, infantile-onset, SIFD mes, periodic fevers, and developmental delay, SPENCDI

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spondyloenchondrodysplasia with immune dysregulation, TRAPS tumour necrosis factor receptor-associated periodic syndrome, XLPDR X-linked pigmentary disorder, reticulate, with systemic manifestations.

[*]Response to canakinumab suggests IL-1β implicated in disease. [^]Associated with congenital dyserythropoietic anaemia. [#]Variable additional features including vasculitis and hepatosplenomegaly. [&]Response of vascular events to TNF inhibition suggests this is a key cytokine however not all features respond, and the pathway implicated in disease is thus far unclear. [+] Associated with inflammatory skin disease.

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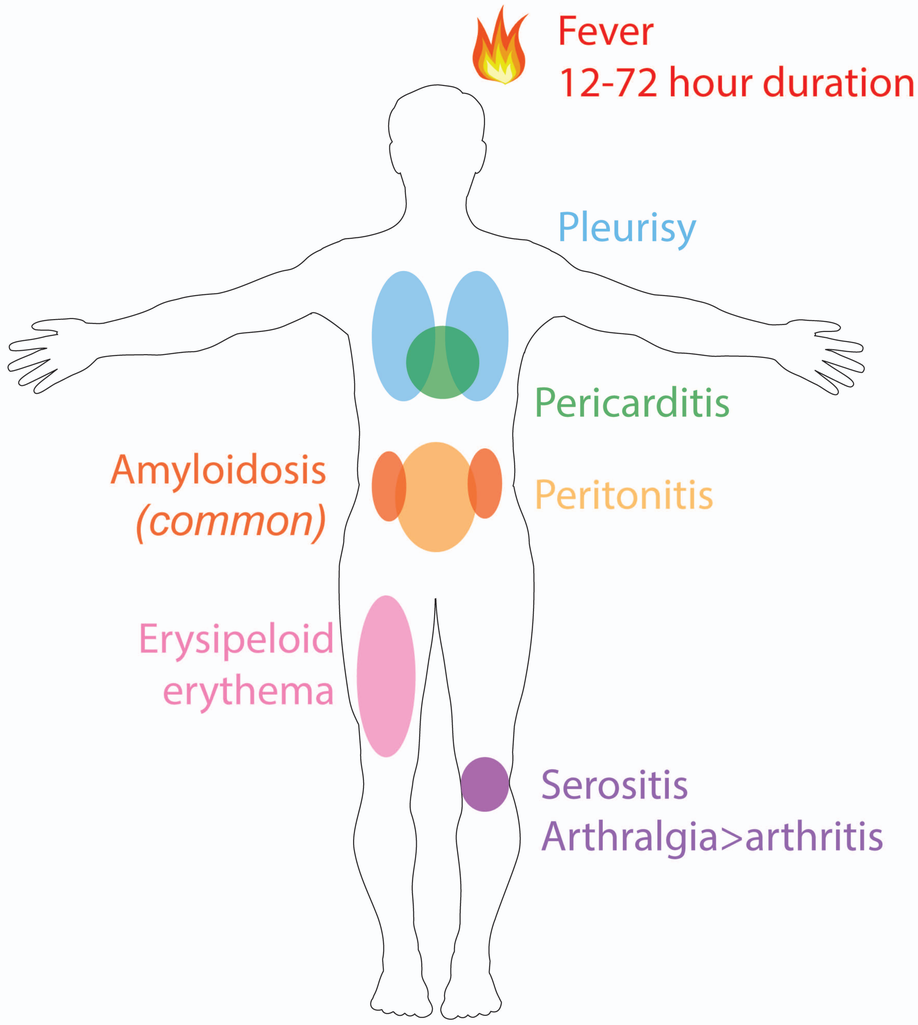
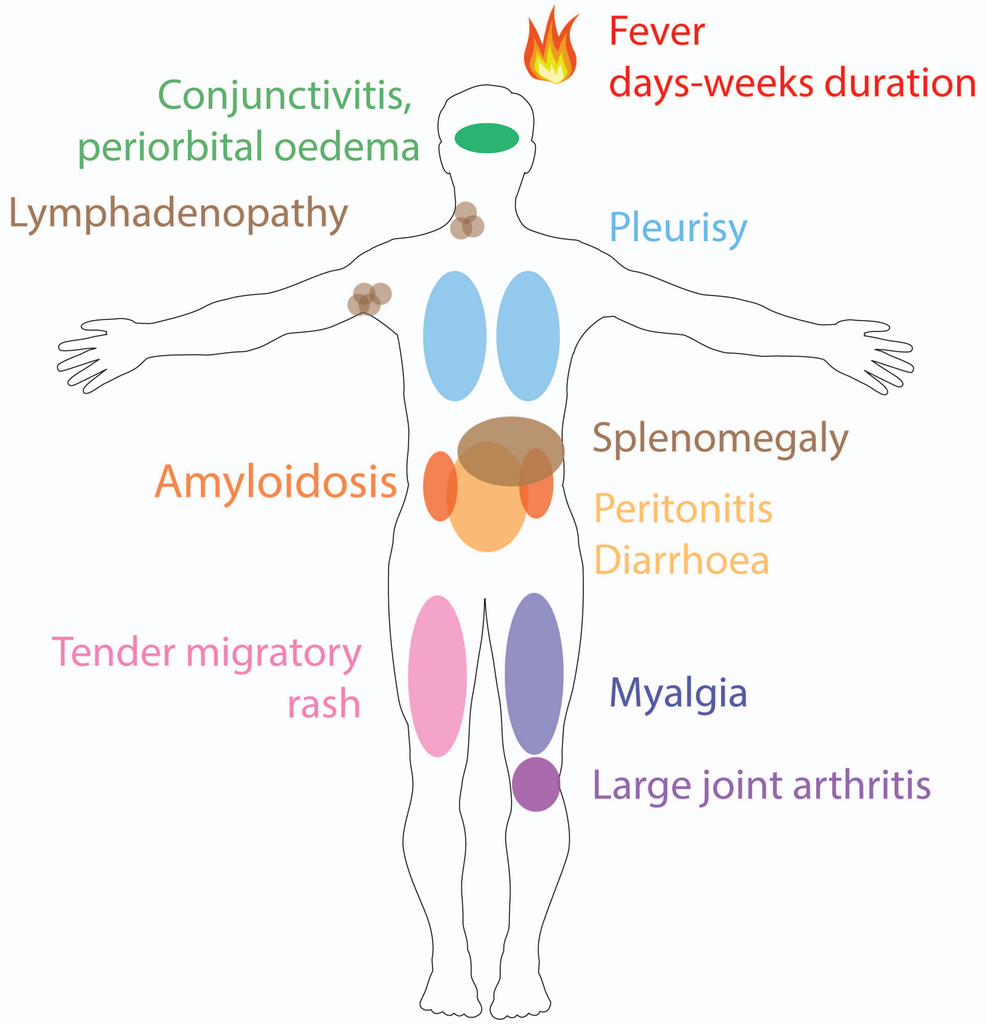
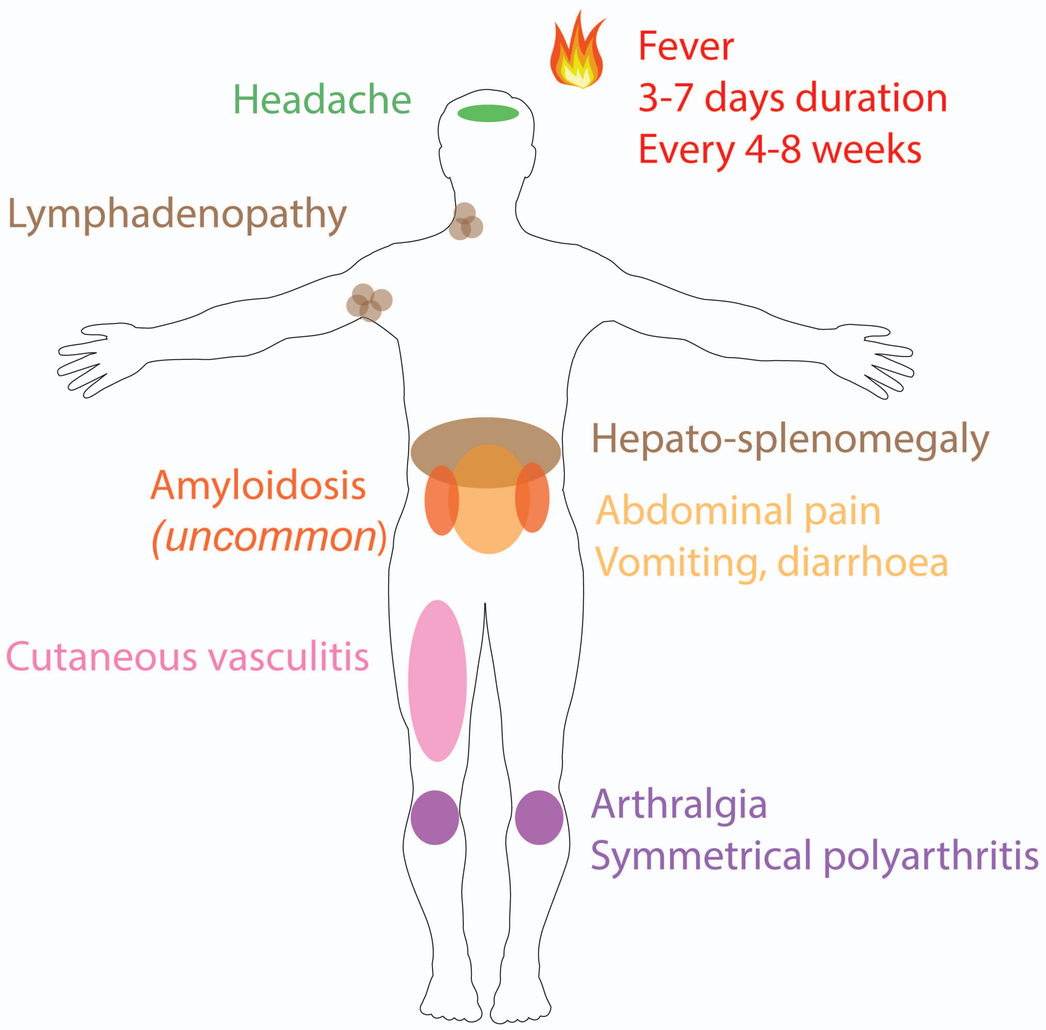


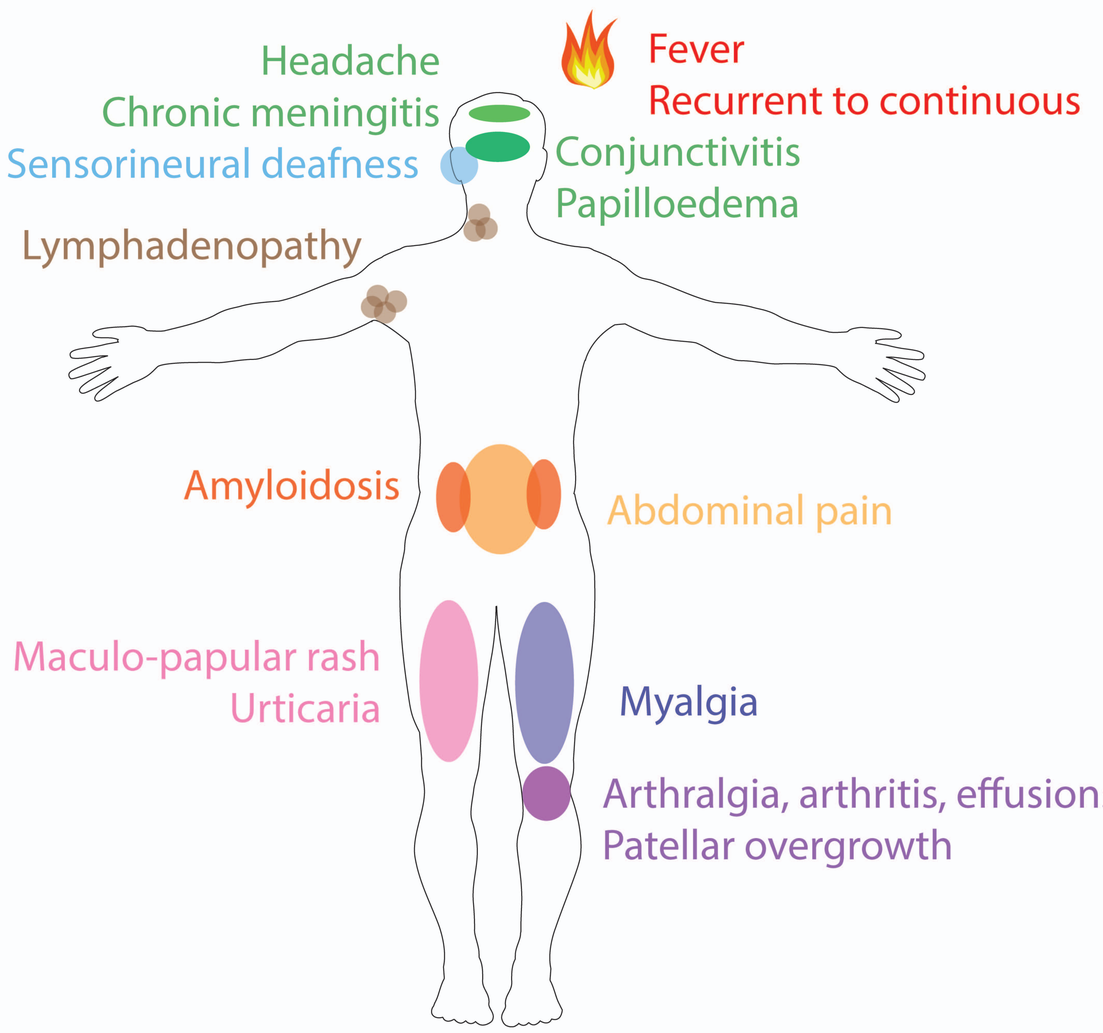
Familial Mediterranean Fever



TNF-receptor associated periodic syndrome



Mevalonate Kinase Deficiency
(formerly known as HyperIgD syndrome)



Cryopyrin Associated Periodic Syndrome

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Autoinflammation

Blau syndrome
CAPS
Cherubism
DIRA
DITRA
EOIBD
Familial HS
FCAS2
FMF
Familial JIA
Majeed syndrome
PAAND
PAPA syndrome
PRP
Pustular psoriasis
TRAPS
USP18 deficiency
XLPDR

MKD
MSPC
HYDM1

Immune dysregulation

AGS1-7
HA20
ORAS
PRAAS

AILJK
H syndrome
SAVI

Autoimmunity

ADAM17 deficiency
HOIL1 deficiency
HOILP deficiency
PFIT
SIFD

PLAID
SPENCD

DADA2

AIEFC
APLAID

Immune deficiency

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	IL-1	IL-18	IL-36	IL-10	IFN	NF-kB	Multiple	Unknown
Periodic fevers	CAPS FMF MKD* TRAPS*							
Multisystem	AIADK PAAND PAPA syndrome				PRAAS SAVI SPENCD XLPDR	Blau syndrome FCAS2 HA20 HOIL1 deficiency HOIP deficiency ORAS	AILJK	APLAID DADA2[&] H+ syndrome PFIT PLAID SIFD
Neurological					AGS[#] USP18 deficiency[#]			
Gastro-intestinal		AIEFC		EOIBD				ADAM17 deficiency[+]
Musculo-skeletal	DIRA Majeed Syndrome[^]							Cherubism Familial JIA
Dermatol-ogical	MSPC		DITRA			PRP		Familial HS
Gynaecol-ogical								HYDM1

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