Rheumatology Advance Access published May 15, 2014

Review

doi:10.1093/rheumatology/keu170

Monogenic autoinflammatory diseases

Ricardo A. G. Russo[1] and Paul A. Brogan[2,3]

Abstract

During the past 15 years, a growing number of monogenic inflammatory diseases have been described and their respective responsible genes identified. The proteins encoded by these genes are involved in the regulatory pathways of inflammation and are mostly expressed in cells of the innate immune system. Diagnosis remains clinical, with genetic confirmation where feasible. Although a group of patients exhibit episodic systemic inflammation (periodic fevers), these disorders are mediated by continuous overproduction and release of pro-inflammatory mediators, such as IL-1 and IL-6, and TNF and are best considered as autoinflammatory diseases rather than periodic fevers. Treatment with biologic agents that block these cytokines, particularly IL-1, has proved to be dramatically effective in some patients. Still, in many cases of autoinflammation no genetic abnormalities are detected and treatment remains suboptimal, raising the question of novel pathogenic mutations in unexplored genes and pathways.

Key words: autoinflammatory, periodic fevers, familial Mediterranean fever, genetic, biologic agents.

Introduction

The monogenic autoinflammatory diseases are genetic disease orders characterized by episodic or persistent, seemingly unprovoked inflammation, without evidence of high-titre autoantibodies or antigen-specific T lymphocytes [1]. The concept of autoinflammation was introduced in the late 1990s, when the genetic causes of familial Mediterranean fever (FMF) and the TNF receptor-associated periodic syndrome (TRAPS) were identified [2–4]. In contrast to autoimmune diseases, in autoinflammatory diseases most abnormalities occur in the innate immune system components [5]. That said, the arbitrary distinction between dysregulation of the innate and adaptive immune systems and immunodeficiency is increasingly blurred with the discovery of novel monogenic autoinflammatory diseases. Typically these disorders result from dysregulation of the physiological alarm responses to foreign or endogenous danger signals, leading to abnormally increased inflammation, predominantly mediated by cells (neutrophils, monocytes) and molecules (IL-1β, IL-6 and TNF-α) of the innate immune system.

Significant advances in the knowledge of genetics, pathogenesis and treatment have occurred in the last few years. Autoinflammatory mechanisms (i.e. involving altered pathways in the innate immune system physiology) have been described in multifactorial, polygenic acquired inflammatory diseases such as gout and SLE [5]. Thus a new view of immune-mediated inflammatory diseases has arisen since the concept of autoinflammatory diseases was introduced [6]. This article will focus on the monogenic autoinflammatory diseases that are most relevant clinically to the rheumatologist.

Classification and generic clinical features

Different classifications have been attempted for this group of disorders. While a classification based on clinical features is useful for the practising physician (Table 1), a pathogenetically structured classification is mandatory for the conceptual understanding of the genetics and pathways involved in each entity (Table 2; see also http://fmf.igh.cnrs.fr/ISSAID/infevers/) [5].

Chronic, systemic inflammation is the common background for all autoinflammatory diseases. While patients with episodic diseases will typically experience recurrent bouts of fever followed by symptom-free periods (periodic fevers), individuals with autoinflammatory diseases may exhibit severe, continuous acute phase response, sometimes with periodic exacerbation. While the frequency, length and periodicity of the episodes are variable according to the mutated gene(s) and diagnosis, many other as

[1]Service of Immunology and Rheumatology, Hospital de Pediatría Garrahan, Buenos Aires, Argentina, [2]University College London Institute of Child Health and [3]Department of Paediatric Rheumatology, Great Ormond Street Hospital NHS Foundation Trust, London, UK.

Submitted 30 October 2013; revised version accepted 6 March 2014.

Correspondence to: Ricardo A. G. Russo, Service of Immunology and Rheumatology, Hospital de Pediatría Garrahan, Pichincha 1881, Buenos Aires 1245, Argentina. E-mail: rrusso@garrahan.gov.ar

Table 1 Clinical classification of autoinflammatory diseases

Group	Disease	Transmission	Main symptoms
Hereditary periodic fevers	FMF	AR (AD)	Recurrent fever, peritonitis, rash
	TRAPS	AD	Recurrent fever, rash, fasciitis, periorbital oedema, abdominal pain
	HIDS	AR	Recurrent fever, lymphadenopathy, rash, vomiting, diarrhoea
	CAPS	AD (spontaneous)	Recurrent or persistent fever, rash, hearing loss, conjunctivitis, arthralgia, arthropathy, cold-induced urticaria-like lesions
	NAPS	AD	Recurrent fever, cold-induced urticaria-like lesions, arthralgia
Granulomatous disorders	BS/EOS	AD (spontaneous)	Tan-coloured micropapular rash, uveitis, arthritis, granulomatous lesions
Pyogenic disorders	PAPA	AD	Pyoderma gangrenosum, sterile arthritis, acne
	DIRA	AR	Pustular psoriasis, osteitis
Autoinflammatory bone disorders	Majeed	AR	Recurrent fever, aseptic multifocal osteomyelitis, dyserythropoietic anaemia, neutrophilic dermatitis
	Cherubism	AD	Mandibular osseous lesions
Psoriasis-related monogenic disorders	DITRA	AR	Pustular psoriasis
	CAMPS	AD	Pustular psoriasis
Miscellaneous disorders	CANDLE	AR	Recurrent fever, joint contractures, panniculitis, lypodystrophy
	APLAID	AD	Blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, immunodeficiency
	Early IBD	AR	Infantile enterocolitis
	SLC29A3 related	AR	Recurrent fevers, hypertrychosis, hyperpigmentation, diabetes, short stature
	HOIL deficiency	AR	Invasive pyogenic bacterial infections, systemic autoinflammation, amylopectin-like deposits in muscle

AR: autosomal recessive; AD: autosomal dominant; FMF: familial Mediterranean fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; HIDS: hyperimmunoglobulin D and periodic fever syndrome; CAPS: cryopyrin-associated periodic syndromes; NAPS: NALP12-associated periodic syndrome; BS: Blau syndrome; EOS: early onset sarcoidosis; PAPA: pyogenic sterile arthritis, pyoderma gangrenosum and acne; DIRA: deficiency of the IL-1 receptor antagonist; DITRA: deficiency of IL-36 receptor antagonist; CAMPS: CARD-14-mediated pustular psoriasis; CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; APLAID: autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation.

yet poorly defined host and environmental factors contribute to the clinical phenotype of individual patients.

Due to their genetic nature, most individuals with a monogenic autoinflammatory disease start exhibiting manifestations of the disease early in life, although these may be dismissed initially as recurrent infections in early childhood. Inflammation usually manifests as fever; headache; abdominal, chest and limb pain and elevated acute phase responses such as elevated CRP, serum amyloid A (SAA), ESR, leucocytosis and thrombocytosis. While these features are common to most autoinflammatory diseases, there is wide clinical heterogeneity among the different disorders, and even between individuals with the same disease. Cold exposure, immunizations, concurrent infections, exposure to drugs and physical or emotional stress may precipitate an inflammatory episode. Often, no trigger is identified.

Finally, although many patients with autoinflammatory diseases have a normal life expectancy, their quality of life may be significantly hampered by recurrent/persistent inflammatory symptoms. Moreover, reactive systemic AA amyloidosis may develop in some individuals. The risk of amyloidosis is influenced by the diagnosis, type of mutation within disease subsets, environment (including the frequency of concurrent infections) and probably other undefined host factors [7].

Familial Mediterranean fever

FMF is considered the prototypical and most common monogenic autoinflammatory disease, and the first for which a genetic cause was identified [2, 3]. Individuals with FMF suffer from repeated, self-limiting acute attacks lasting 12–72 h, characterized by fever, peritoneal abdominal pain and/or pleuritic chest pain, arthritis,

Table 2 Pathophysiological classification of monogenic autoinflammatory diseases

Group	Disease	Gene	Mutation	Protein	Physiopathology
IL-1 activation disorders	FMF	*MEFV*	LF (GF)	Pyrin	Inflammasome activation
	HIDS	*MVK*	LF	MVK	Inflammasome activation
	CAPS	*NLRP3*	GF	Cryopyrin	Inflammasome activation
	PAPA	*PSTPIP1*	GF	PSTPIP1	Inflammasome activation
	DIRA	*IL1RN*	LF	IL-1Ra	Absence of IL-1 antagonism
NF-κB activation disorders	BS/EOS	*NOD2*	GF	NOD2	Increased NF-κB activation
	NAPS	*NLRP12*	GF	NLRP12	Increased NF-κB activation
Misfolded protein disorders	TRAPS	*TNFRSF1A*	GF	TNFR1 (p55)	Cellular stress
Proteasomopathies	CANDLE	*PSMB8*	LF	PSMB8	Cellular stress
Miscellaneous disorders	Majeed	*LPIN2*	LF	Lipin2	Unknown
	Cherubism	*SH3BP2*	GF	SH3BP2	Unknown
	DITRA	*IL36RN*	LF	IL-36Ra	Absence of IL-36 antagonism
	CAMPS	*CARD14*	GF	CARD14	Increased NF-κB activation
	HOIL-1 deficiency	*HOIL-1*	LF	HOIL-1	Increased NF-κB activation
	Early IBD	*IL10RA, IL10RB, IL-10*	LF	IL-10R	Absence of IL-10 signalling
	SLC29A3-related	*SLC29A3*	LF	SLC29A3	Unknown
	APLAID	*PLCγ2*	GF	PLCγ2	Unknown

LF: loss of function; GF: gain of function; FMF: familial Mediterranean fever; TRAPS: tumour necrosis factor receptor-associated periodic syndrome; HIDS: hyperimmunoglobulin D and periodic fever syndrome; CAPS: cryopyrin-associated periodic syndromes; NAPS: NALP12-associated periodic syndrome; BS: Blau syndrome; EOS: early onset sarcoidosis; PAPA: pyogenic sterile arthritis, pyoderma gangrenosum, and acne; DIRA: deficiency of the IL-1 receptor antagonist; DITRA: deficiency of IL-36 receptor antagonist; NF: nuclear factor; CAMPS: CARD-14-mediated pustular psoriasis; CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; APLAID: autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation.

splenomegaly and skin rashes, including erysipelas-like erythema of the lower limbs [8–10]. Although attacks may be mild, in many cases they will be disabling. Certain patients may even present with systemic vasculitis [11], albeit rarely.

Clinical presentation in the very early years of life can be non-specific and consist only of recurrent fever [12]. The disease is associated with mutations in the *MEFV* gene coding for the protein pyrin, involved in the regulation of inflammation and apoptosis [5]. Although considered to be an autosomal recessive disorder, patients with a classical clinical picture and mutations in only one allele, or even no mutations in the *MEFV* gene, have been described [13, 14]. A striking response to continuous prophylactic colchicine at 1–2 mg/day is an important diagnostic clue [15]. Amyloidosis may occur more frequently in patients who are non-compliant with prophylaxis, in those with severe attacks from childhood or in certain individuals who carry particular genetic variants (such as M694V homozygosity) [8, 16]. Environmental factors may also have an impact on the risk for amyloidosis [17].

TRAPS

TRAPS is an autosomal dominant disorder caused by mutations in the TNF receptor superfamily 1A (*TNFRSF1A*) gene coding for the p55TNF receptor [4, 18]. Although onset usually occurs in childhood, low suspicion and clinical mimicry of other more common entities may lead to late diagnosis in adult life. During febrile episodes, which may last from 5 days to several weeks, patients complain of myalgia, periorbital swelling, conjunctivitis, headache, abdominal and chest pain (secondary to pleuritis), scrotal pain, erythematous macular or serpiginous skin rash (often migratory), swollen plaques simulating cellulitis, lymphadenopathy and arthralgia or arthritis of the large joints [19–20]. The duration of symptom-free intervals is variable. Although no clear genotype–phenotype correlation exists, mutations leading to amino acid substitutions in the cysteine-rich domains of the protein have a higher penetrance and are associated with a more aggressive phenotype than mutations not related to cysteine substitutions [21, 22]. The R92Q variant (the most frequently observed) is associated with later onset and milder disease, sometimes resembling the periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome [23]. Healthy individuals without clinical features of TRAPS may also harbour this variant and therefore the diagnosis of TRAPS cannot be made purely by the finding of this variant in the absence of clinical features. Amyloidosis may develop in up to 25% of untreated patients, particularly in individuals with cysteine substitutions. Diagnostic indicators for the disorder have been proposed [19]. Recently the largest series of TRAPS patients has been described, providing a robust clinical description of the full spectrum of the disease [22].

Mevalonate kinase deficiency (hyperimmunoglobulinaemia D and periodic fever syndrome)

Mevalonate kinase deficiency (MKD), also known as hyperimmunoglobulin D and periodic fever syndrome (HIDS), is an autosomal recessive condition caused by mutations in the mevalonate kinase (*MVK*) gene resulting in deficiency of mevalonate kinase enzyme, involved in the isoprenoid biosynthesis pathway [24–26]. Initially thought to be predominantly a disease of individuals of Dutch ancestry, it is now recognized in many other ethnic groups. The clinical severity depends on the residual activity of the enzyme. Profound enzymatic deficiency leads to the severe metabolic disease, mevalonic aciduria, which shares some features with the periodic fever, MKD, at the milder end of the clinical spectrum. Genotype–phenotype correlation has been described: some variants are associated with a severe (V310M) or milder (V377I) phenotype [27, 28]. The disease usually manifests in the first months of life, with fever attacks typically characterized by abrupt onset, painful cervical lymphadenopathy and abdominal pain with vomiting and diarrhoea. Attacks usually last 4–7 days and are often precipitated by vaccination, minor physical trauma or stress. Arthralgia, headaches, irritability, erythematous or urticaria-like skin rash, hepatomegaly, splenomegaly and aphthous stomatitis may also occur during the attacks [29–31]. Urinary mevalonic acid is strongly elevated during the crisis, but may be normal when asymptomatic. Serum IgA is elevated in most patients, but despite its previous name of HIDS, IgD may be elevated or normal (very young patients do not usually exhibit high levels) [32, 33]. Decreased MVK enzymatic activity is a diagnostic clue, but its determination is confined to specialized laboratories. Although symptoms tend to ameliorate in adult life, a significant proportion of patients continue to suffer frequent febrile attacks into adulthood and may (rarely) develop amyloidosis [34]. Interestingly, individuals with MKD and hypogammaglobulinaemia [35] or macrophage activation syndrome [36] have been reported.

Cryopyrin-associated periodic syndromes

The cryopyrin-associated periodic syndromes (CAPS or cryopyrinopathies) comprise a group of autoinflammatory diseases classified as different clinical entities but have a common genetic defect. Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease (CINCA/NOMID), Muckle–Wells syndrome (MWS) and familial cold-induced autoinflammatory syndrome (FCAS) are autosomal dominant conditions that represent particular phenotypic expressions on a clinical continuum, with CINCA/NOMID at the severe end, FCAS at the milder end, and MWS with moderate severity [37–39] (Table 3). Individuals with intermediate clinical pictures (CAPS overlap) have been reported [40]. Mutations in the *NLRP3* gene, encoding cryopyrin, are the cause for all three of these clinical syndromes [41–44]. However, mutations in *NLRP3* can be found in only 60% of patients with the CINCA/NOMID phenotype using conventional Sanger sequencing. Somatic mosaicism, reported in patients with CAPS, may partly explain the mutation-negative cases [45, 46]; such patients have *NLRP3* mutations affecting a proportion of their leucocytes, enough to cause the disease, but too low to be detected by Sanger sequencing (used in standard genetic testing) [47]. While patients with the CINCA or severe CAPS phenotype exhibit a continuous inflammatory state, patients with milder MWS and FCAS usually have an episodic course. Common clinical features are fever, urticaria-like rash, conjunctivitis, arthralgia or arthritis and myalgia. Patients with CINCA/NOMID present an early disease onset (often at birth) and usually develop a severe, disabling arthropathy, bony overgrowth in the patellae and epiphyses of the long bones, facial dysmorphic features, short stature, hepatosplenomegaly and chronic meningitis leading to cerebral atrophy, progressive visual and sensorineural hearing loss and developmental delay [48]. Generalized exposure to cold frequently triggers inflammatory bouts, most strikingly in patients with FCAS. Amyloidosis may develop in individuals with MWS or CINCA/NOMID [49].

Table 3 Clinical features of cryopyrin-associated periodic syndromes

Clinical feature	FCAS	MWS	CINCA/NOMID
Onset	Neonatal/infancy	Infancy/adolescence	Neonatal period/infancy
Fever/rash duration	12–24 h	1–3 days	Continuous
Skin	Cold-induced urticaria-like rash	Urticaria-like rash	Urticaria-like rash
Articular	Arthralgia	Episodic arthritis	Progressive, deforming arthropathy with tumour-like bony and cartilaginous growth
Neurological	—	—	Chronic meningitis leading to cerebral atrophy, mental retardation
Deafness	—	Present	Present
Eyes	Conjunctivitis	Conjunctivitis	Conjunctivitis, uveitis, progressive visual loss
Amyloidosis	1–2%	25%	Present in some individuals

FCAS: familial cold-induced autoinflammatory syndrome; MWS: Muckle–Wells syndrome; CINCA/NOMID: chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease.

Pyogenic sterile arthritis, pyoderma gangrenosum and acne

Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome is a rare autosomal dominant disorder caused by mutations in the gene coding for CD2-binding protein 1 (CD2BP1), also known as proline serine threonine phosphatase interacting protein 1 (PSTPIP1) [50, 51]. Patients usually exhibit episodic, sterile arthritis beginning in childhood, which may resemble septic arthritis; repeated bouts of joint inflammation may lead to destructive cartilaginous and bony changes [52]. Recurrent ulcerative skin lesions, pyoderma gangrenosum, severe cystic acne and abscesses at the site of injections are less frequent manifestations. Mutations in the *PSTPIP1* gene can also cause a clinical picture of pyogenic arthritis, pyoderma gangrenosum, acne and hidradenitis suppurativa (PAPASH) [53].

Deficiency of the IL-1 receptor antagonist

Patients with deficiency of the IL-1 receptor antagonist (DIRA) were first described in unrelated families in 2010 [54–56]. Autosomal recessive mutations in the *IL-1RN* gene encoding the IL-1 receptor antagonist (IL-1Ra) are the cause of DIRA. Affected individuals exhibit a severe picture characterized by a chronic psoriasiform, pustular or icthyosiform rash, oral mucosal lesions and bone involvement with multifocal osteolytic lesions, epiphyseal overgrowth, widening of the rib ends and clavicles and periostitis. Presentation occurs in the neonatal period, with death in the first decade of life reported.

Deficiency of IL-36 receptor antagonist

Deficiency of IL-36 receptor antagonist (DITRA) is an autosomal recessive autoinflammatory disease caused by mutations in the IL-36 receptor antagonist gene [57]. Patients exhibit repeated bouts of generalized pustular psoriasis, fever, geographic tongue, nail dystrophy, arthritis and cholangitis. The disease may be life threatening.

Blau syndrome/early onset sarcoidosis

Since the discovery of a common genetic background, Blau syndrome (BS) and early onset sarcoidosis (EOS) are considered to be the familial and sporadic forms, respectively, of the same disorder. It is an autosomal dominantly inherited autoinflammatory disease characterized by chronic intermediate or panuveitis, icthyosiform tan-coloured skin rash, symmetrical polyarthritis with exuberant synovitis, tenosynovitis, camptodactyly and evidence of non-caseating epithelioid cell and giant cell granulomata [58]. Defects occurring in exon 4 of the gene *NOD2* (CARD15) are related to the disease [59–61]. Patients usually present in the first years of life with the classic triad of synovitis, uveitis and skin rash, but may also exhibit more severe manifestations such as large vessel vasculitis, interstitial lung disease, pericarditis, splenic involvement or hepatic granulomatous infiltration [58].

Guadeloupe-type fever syndrome (FCAS2)

Guadeloupe-type fever syndrome, also known as NALP12-associated periodic syndrome (NAPS) or FCAS2, is an autosomal dominant autoinflammatory disease with some clinical similarities to FCAS. Patients usually exhibit attacks of fever, urticaria-like rash, arthralgia and headaches upon generalized cold exposure [62]. Sensorineural hearing loss, aphthous stomatitis and abdominal pain may also occur. Mutations in the *NLRP12* gene [encoding for a protein acting as a negative regulator of inflammation through suppression of nuclear factor κB (NF-κB)] are associated with this syndrome [63].

Majeed syndrome

Majeed syndrome is a form of hereditary autoinflammatory disease of the bone considered to be a rare monogenic form of chronic recurrent multifocal osteomyelitis (CRMO) [64] (Table 4). Originally described in 1989, it is an autosomal recessive disorder caused by mutations in the *LPIN2* gene [65–67]. The role of *LPIN2* in the regulation of inflammation is unknown. Patients exhibit recurrent fever episodes, sterile multifocal osteomyelitis (persistent rather than recurrent), microcytic congenital dyserythropoietic anaemia, inflammatory neutrophilic dermatosis, pustulosis and growth failure. Unlike CRMO, Majeed syndrome usually starts in the very early years of life. Radiographs show large osteolytic areas in the metaphyses of the long bones, and joint deformities may occur.

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature

The syndrome chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) has been recently described [68]. CANDLE and other similar entities (such as Nakajo–Nikishima syndrome, and the joint contractures, muscle atrophy, microcytic anaemia, lipodystrophy and panniculitis syndrome) are now known to be caused by mutations in the same gene [68–70]. It is

Table 4 Autoinflammatory diseases of bone

Genetics	Disease	
	Predominantly bone disorders	Complex disorders
Monogenic	Majeed Cherubism	PAPA DIRA CAPS (CINCA/NOMID)
Polygenic	CRMO SAPHO	

PAPA: pyogenic sterile arthritis, pyoderma gangrenosum and acne; DIRA: deficiency of the IL-1 receptor antagonist; CAPS: cryopyrin-associated periodic syndromes; CINCA/NOMID: chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease; CRMO: chronic recurrent multifocal osteomyelitis; SAPHO: synovitis, acne, pustulosis, hyperostosis and osteitis.

an autosomal recessive disorder caused by mutations in genes encoding proteins of the immunoproteasome, with proteasome subunit type 8 (*PSMB8*) being the most frequently mutated gene. Other genes in the proteasome/immunoproteasome pathway can also cause CANDLE syndrome (P. Brogan *et al.*, unpublished results). The clinical picture includes fever, fixed purple plaques, arthritis, dactylitis, joint contractures, panniculitis, lipodystrophy, myositis, accumulation of abdominal fat, interstitial keratitis, intracranial calcification and intermittent cytopenias. The disorder usually develops in the first decade of life, but may be present from birth; severe anaemia and the presence of high-titre autoantibodies may occur.

Other recently described monogenic autoinflammatory syndromes

In the past few years, new syndromes have been added to the growing list of monogenic autoinflammatory diseases (http://fmf.igh.cnrs.fr/ISSAID/infevers/). Excellent reviews on the subject have recently been published [71–74]; a full description of all disorders is beyond the scope of this review. The following is a brief summary.

A gain of function mutation in *CARD14* is associated with the autosomal dominant syndrome of pustular psoriasis (CARD-14-mediated pustular psoriasis or CAMPS) [75].

Two recently described dominant monogenic disorders are related to gain of function defects in the phospholipase Cγ-2 (*PLCγ2*) gene, expressed in B cells, natural killer cells and mast cells. Deletions in the gene lead to a clinical picture of cold-induced urticaria-like lesions, atopy, granulomatous rash, autoimmune thyroiditis, sinopulmonary infections, antinuclear antibodies and common variable immunodeficiency called PCγ2-associated antibody deficiency and immune dysregulation (PLAID), also known as FCAS type 3 [76]. On the other hand, missense mutations in the same gene cause a syndrome characterized by blistering skin lesions, bronchiolitis, arthralgia, ocular inflammation, enterocolitis, absence of autoantibodies and mild immunodeficiency. This syndrome has been named autoinflammation and PLCγ2-associated antibody deficiency and immune dysregulation (APLAID) [77].

HOIL-1 [a component of the linear ubiquitination chain assembly complex (LUBAC)] deficiency provokes a clinical picture of immunodeficiency, autoinflammation and amylopectinosis [78].

A group of patients with mutations in the *SLC29A3* gene (causing a wide spectrum of clinical pictures spanning from the H syndrome to a Rosai Dorfman's-like histiocytosis) may carry an autoinflammatory phenotype [79–80].

Finally, mutations in the genes encoding the IL-10 receptors (IL-10RA and IL-10RB) [81] or the IL-10 gene itself [82] cause early IBD.

Pathogenesis

Although increased production and release of pro-inflammatory mediators is a final common abnormality, different mechanisms are involved in the pathogenesis of these conditions (Table 2). It is suggested that different levels of increased cellular stress and inflammatory signalling may be involved in most disorders [83]. The following is a short description of the main proposed pathogenic pathways (Table 2) [5].

IL-1 activation disorders

Description and characterization of the constituent and regulatory proteins of the NLRP3 inflammasome has shed light on the inflammatory pathways of the innate immune system cells, both in physiological and pathological settings [84, 85]. The inflammasome is a cytosolic multimolecular complex that links the innate immune system's ability to sense danger to the activation of the pro-inflammatory cytokine IL-1β as a rapid response [86]. Different proteins such as cryopyrin, pyrin or PSTPIP1 integrate or modulate the inflammasome [5, 87].

Gain of function mutations in the *NLRP3* gene (occurring in patients with CAPS) cause spontaneous oligomerization of cryopyrin and assembly of the inflammasome, resulting in activation of IL-1-converting enzyme (caspase 1) and subsequent cleavage of pro-IL-1β into active IL-1β [88].

The precise molecular mechanism by which MVK deficiency leads to inflammation remains obscure. A shortage of isoprenoid end products, such as the geranylgeranyl groups, could lead to inflammation through activation of caspase 1 in circulating monocytes and the consequent activation and liberation of IL-1β [89, 90]. In DIRA, competitive inhibition of the assembly of IL-1 and its receptor is deficient due to constitutive absence of IL-1Ra [54].

NF-κB activation disorders

The NF-κB disorders (BS and NAPS) do not seem to be as strongly related to increased activation of IL-1 as the previous entities, but more to activation of NF-κB [91, 92]. In CAMPS, mutations in CARD14, expressed mostly in keratinocytes, lead to up-regulation of NF-κB and transcription of pro-inflammatory proteins (i.e. CCL20, IL-8, and IL-36) [75].

Misfolded protein disorders

Various mechanisms have been proposed for the pathogenesis of TRAPS, including a shedding defect of TNFR1 due to the inability of metalloproteases to cleave it from the cell membrane, a defect of TNF-induced apoptosis, a defect in TNFR1 trafficking to the cell membrane and retention within the endoplasmic reticulum of mutant misfolded receptors that may lead to enhanced signalling [92–96]. Retained TNFR1 would lead to increased activation of pro-inflammatory mitogen-activated protein kinases secondary to stress-induced overproduction of mitochondrial reactive oxygen species.

Proteasomopathies

In CANDLE, mutations in the *PSMB8* gene lead to deficient assembly and activity of the immunoproteasome. The resulting intracellular accumulation of polyubiquitinated proteins results in a cell stress response with up-regulation of IFN-regulated genes and products [70].

Thus, unlike other autoinflammatory diseases, CANDLE is an interferonopathy associated with an IFN signature on microarray profiles [67].

Still unknown, possibly complex mechanisms are involved in other autoinflammatory diseases. Moreover, recent investigations have shed new light on the pathogenesis of FMF and other autoinflammatory diseases, with defects in autophagy as likely additional pathogenetic abnormalities [97, 98].

Diagnosis

The clinical diagnosis of autoinflammatory diseases may be guided by the recognition of symptoms, disease course pattern (recurrent or persistent), presence of acute phase reactants, pattern of inheritance and age at onset of symptoms. A question clinicians must ask themselves when faced with a patient with possible autoinflammatory disease is: Is the immune system overactive or underactive? In other words, is there autoinflammation/autoimmunity or immunodeficiency with or without immune dysregulation? Clinical history taking and investigations can then be tailored with these questions in mind. The clinician must also assess if acute phase responses are truly periodic (i.e. only coincident with fever attacks) or if there is evidence of subclinical inflammation between fever attacks, usually by measuring CRP or SAA when the patient is well.

Diagnostic criteria have been designed for FMF in countries where the disease is more prevalent, but their clinical utility in populations where the disease is less common remains uncertain [15, 99, 100]. There are no validated diagnostic criteria for the other monogenic autoinflammatory diseases. Therefore genetic testing is clearly of utmost importance for the monogenic autoinflammatory diseases, but is not always feasible, affordable or straightforward. Even in countries where genetic testing is widely available, it will usually only (routinely) cover a minority of the known genetic mutations. In fact, at least 50% of patients with a clinical picture of an autoinflammatory disease will show normal genetic results for the available tests. Diagnostic scores and decision trees may aid in selecting candidate individuals for a diagnostic genetic test and to differentiate them from polygenic autoinflammatory diseases such as PFAPA syndrome [99, 101–103]. Dedicated laboratories with accreditation in molecular biology and gene sequencing should be consulted for gene analysis. Techniques for gene analysis may vary, but standard recommendations for indications, strategy, interpretation and reporting of testing have been formulated to diminish variability [104, 105]. Certain gene variants have a high allelic frequency in the normal healthy population and should be treated cautiously, as they may represent coincidental bystanders: E148Q and R408Q for the *MEFV* gene, R92Q and P46L for the *TNFRSF1A* gene, and Q703K and V198M for the *NLRP3* gene [105]. Some patients with recessive diseases may exhibit only one mutated allele. Finally, genes related to a particular autoinflammatory disease may unexpectedly show pathogenic variants in patients with a clinical picture corresponding to another autoinflammatory disease. Different theories have been postulated to explain such findings [106–111]. Therefore diagnosis of the autoinflammatory diseases usually remains a clinically based one, sometimes confirmed by the genetic findings.

International registries and databases provide rich information about gene variants and associated phenotypes [112–114]. They may be consulted to compare the clinical and genetic picture of a given patient with others that have already been genotyped and described, keeping in mind that ethnic and environmental factors may impact the clinical expression of the same genetic defect.

Treatment

The objectives of treatment of the autoinflammatory diseases are to prevent acute flares, reduce chronic inflammation, normalize growth where possible for children and prevent amyloidosis and other late end-organ sequelae that result in impairment of patient quality of life. While most published reports are based on single cases/case series or experience in an open-label fashion, controlled clinical trials have demonstrated the efficacy of some agents in these conditions. For many patients, most therapeutic interventions are still based on the experience of the treating physician. Colchicine, the prophylactic therapy of choice in FMF, reduces (or abolishes) both the recurrence of attacks and the risk of developing amyloidosis [115–118]. Systemic corticosteroid therapy may be effective in the management of fever attacks in patients with TRAPS, MKD and Blau/EOS, but its continuous use frequently leads to unacceptable toxicity [119]. Simvastatin may decrease fever attacks in adult individuals with MKD [120].

Since the beginning of the last decade, biologics have been used in the treatment of patients with autoinflammatory diseases, delivering striking improvements in clinical symptoms, quality of life and long-term clinical course. Demonstration of a pivotal role of IL-1β in a number of autoinflammatory diseases has led to the introduction of anti-IL-1 strategies in the management of patients with autoinflammatory diseases. Patients with CAPS and DIRA benefit from therapy with anakinra, the recombinant receptor antagonist for IL-1 (blocking IL-1α and β), canakinumab, a longer-acting monoclonal antibody against IL-1β, and rilonacept (IL-1 trap), as reported in small case series and controlled trials, leading to approval of these latter drugs for the treatment of patients with CAPS [59, 121–140]. However, research into the safety and efficacy of anti-IL-1 agents in other autoinflammatory diseases is continuing. Case reports of their effectiveness in patients with TRAPS, MKD, refractory FMF, Blau and PAPA syndromes have increased optimism among physicians and patients [141–151].

However, a significant group of individuals do not respond to IL-1 blockade. In these cases, anti-TNF agents may be efficacious [152–159]. Tocilizumab, an IL-6 receptor antagonist, has been successfully used in the treatment of TRAPS [160]. IFN-α has been proposed as an alternative therapy for colchicine-resistant patients with FMF [161–164]. Lastly, the efficacy of Janus kinase

(JAK) inhibitors in patients with CANDLE is being tested in clinical trials [67, 165]. All these old and new therapies are associated with side effects, and clinicians must remain ever vigilant regarding opportunistic infection. We also advocate participation in registries of biologic therapy, where available, for ongoing prospective monitoring for potential toxicity.

Conclusions

The monogenic autoinflammatory diseases are rare, genetic diseases resulting in constitutive innate immune activation leading to dysregulation of inflammation pathways and excessive release of pro-inflammatory cytokines, notably IL-1β. Diagnosis remains clinical and is based on the different phenotypic features. Genetic diagnosis is of utmost importance, but must be performed judiciously and interpreted cautiously. IL-1 blocking agents and other biologic therapies are efficacious treatments for these patients. New therapies on the horizon for autoinflammatory diseases include JAK inhibitors. Challenges for the future include understanding the clinical significance of low-penetrance variants, the genetics and physiopathology of different autoinflammatory diseases and the long-term safety and efficacy of anti-IL-1 therapies. Additional yet unidentified genetic defects will continue to expand the horizons of autoinflammatory diseases, and will highlight novel therapeutic targets in the future. International registries will allow better characterization of these diseases and their response to therapy and monitoring of potential toxicity of treatments currently being used. Lastly, close interaction between clinicians and geneticists remains a prerequisite for ensuring new discoveries and therapeutic advances in this exciting and ever-expanding field.

Disclosure statement: P.A.B. has received an institutional grant (<£50 000) from Novartis to undertake an open-label trial of canakinumab in children <4 years of age (not included in this review). The other author has declared no conflicts of interest.

Rheumatology key messages

- The monogenic autoinflammatory diseases are rare inherited disorders resulting in constitutive innate immune activation.
- IL-1 is a central mediator in autoinflammatory diseases and IL-1 blocking agents have proved efficacious.
- Diagnosis of monogenic autoinflammatory diseases remains largely clinical, based on the phenotypic features, and genetic findings must be interpreted in the context of clinical features.

References

1 Kastner DL, Aksentijevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded: a clinical perspective. Cell 2010;140:784–90.

2 International FMF Consortium. Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever. Cell 1997;90:797–807.

3 French FMF Consortium. A candidate gene for familial Mediterranean fever. Nat Genet 1997;17:25–31.

4 McDermott MF, Aksentijevich I, Galon J *et al*. Germline mutations in the extracellular domains of the 55 kDa TNF receptor, TNFR1, define a family of dominantly inherited autoinflammatory syndromes. Cell 1999;97:133–44.

5 Masters SL, Simon A, Aksentijevich I, Kastner DL. Horror autoinflammaticus: the molecular pathophysiology of autoinflammatory disease. Annu Rev Immunol 2009;27:621–8.

6 McGonagle D, Aziz A, Dickie LJ, McDermott MF. An integrated classification of pediatric inflammatory diseases, based on the concepts of autoinflammation and immunological disease continuum. Pediatr Res 2009;65:38–45R.

7 Lachmann HJ, Hawkins PN. Developments in the scientific and clinical understanding of autoinflammatory disorders. Arthritis Res Ther 2009;11:212.

8 Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literature. Am J Med 1967;43:227–53.

9 Samuels J, Aksentijevich I, Torosyan Y *et al*. Familial Mediterranean fever at the millennium: clinical spectrum, ancient mutations, and a survey of 100 American referrals to the National Institutes of Health. Medicine 1998;77:268–97.

10 Tunca M, Akar S, Onen F *et al*. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine 2005;84:1–11.

11 Ozdogan H, Arisoy N, Kasapçapur O *et al*. Vasculitis in familial Mediterranean fever. J Rheumatol 1997;24:323–7.

12 Padeh S, Livneh A, Pras E *et al*. Familial Mediterranean fever in the first two years of life: a unique phenotype of disease in evolution. J Pediatr 2010;156:985–9.

13 Booty MG, Chae JJ, Masters SL *et al*. Familial Mediterranean Fever with a single MEFV mutation: where is the second hit? Arthritis Rheum 2009;60:1851–61.

14 Marek-Yagel D, Berkun Y, Padeh S *et al*. Clinical disease among patients heterozygous for familial Mediterranean fever. Arthritis Rheum 2009;60:1862–6.

15 Livneh A, Langevitz P, Zemer D *et al*. Criteria for the diagnosis of familial Mediterranean fever. Arthritis Rheum 1997;40:1879–85.

16 Gershoni-Baruch R, Brik R, Zacks N *et al*. The contribution of genotypes at the MEFV and SAA1 loci to amyloidosis and disease severity in patients with familial Mediterranean fever. Arthritis Rheum 2003;48:1149–55.

17 Touitou I, Sarkisian T, Medlej-Hashim M *et al*. Country as the primary risk factor for renal amyloidosis in familial Mediterranean fever. Arthritis Rheum 2007;56:1706–12.

18 Williamson LM, Hull D, Mehta R *et al*. Familial Hibernian fever. Q J Med 1982;51:469–80.

19 Hull KM, Drew E, Aksentijevich I *et al*. The TNF receptor-associated periodic syndrome (TRAPS): emerging

concepts of an autoinflammatory disorder. Medicine 2002; 81:349–68.

20 Aganna E, Hammond L, Hawkins PN *et al*. Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. Arthritis Rheum 2003;48:2632–44.

21 Ravet N, Rouaghe S, Dodé C *et al*. Clinical significance of P46L and R92Q substitutions in the tumor necrosis factor superfamily 1A gene. Ann Rheum Dis 2006;65:1158–62.

22 Lachmann HJ, Papa R, Gerhold K *et al*. The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases form the Eurofever/EUROTRAPS international registry. Ann Rheum Dis 2013, Aug 21. doi: 10.1136/annrheumdis-2013-204184. [Epub ahead of print].

23 Pelagatti MA, Meini A, Caorsi R *et al*. Long-term clinical profile of children with the low-penetrance R92Q mutation of the TNFRSF1A gene. Arthritis Rheum 2011;63:1141–50.

24 Drenth JPH, Haagsma CJ, van der Meer JWM. Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. Medicine 1994;73:133–44.

25 Drenth JP, Cuisset L, Grateau G *et al*. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. Nat Genet 1999;22:178–81.

26 Houten SM, Kuis W, Duran M *et al*. Mutations in MVK, encoding mevalonate kinase, cause hyperimmunoglobulinaemia D and periodic fever syndrome. Nat Genet 1999; 22:175–7.

27 Mandey SH, Schneiders MS, Koster J, Waterham HR. Mutational spectrum and genotype-phenotype correlations in mevalonate kinase deficiency. Hum Mutat 2006; 27:796–802.

28 Samkari A, Borzutzky A, Fermo E *et al*. A novel missense mutation in MVK associated with MK deficiency and dyserythropoietic anemia. Pediatrics 2010;125:e964–8.

29 Frenkel J, Houten SM, Waterham HR *et al*. Clinical and molecular variability in childhood periodic fever with hyperimmunoglobulinaemia D. Rheumatology 2001;40: 579–84.

30 van der Hilst JC, Bodar EJ, Barron KS *et al*. Long term follow-up, clinical features and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. Medicine 2008;87:301–10.

31 Bader-Meunier B, Florkin B, Sibilia J *et al*. Mevalonate kinase deficiency: a survey of 50 patients. Pediatrics 2011; 128:e152–9.

32 Saulsbury FT. Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) in a child with normal serum IgD, but increased serum IgA concentration. J Pediatr 2003; 143:127–9.

33 Ammouri W, Cuisset L, Rouaghe S *et al*. Diagnostic value of serum immunoglobulinaemia D level in patients with a clinical suspicion of hyper IgD syndrome. Rheumatology 2007;46:1597–600.

34 Lachmann HJ, Goodman HJB, Andrews PA *et al*. AA amyloidosis complicating hyperimmunoglobulinemia D with periodic fever syndrome. A report of two cases. Arthritis Rheum 2006;54:2010–4.

35 Sornsakrin M, Wenner K, Ganschow R. B cell cytopenia in two brothers with hyper-IgD and periodic fever syndrome. Eur J Pediatr 2009;168:825–31.

36 Rigante D, Capoluongo E, Bertoni B *et al*. First report of macrophage activation syndrome in hyperimmunoglobulinemia D with periodic fever syndrome. Arthritis Rheum 2007;56:658–81.

37 Muckle TJ, Wells M. Urticaria, deafness and amyloidosis: a new heredo-familial syndrome. Q J Med 1962;31: 235–48.

38 Prieur AM, Griscelli C. Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation. J Pediatr 1981;99:79–83.

39 Aksentijevich I, Putnam D, Remmers EF *et al*. The clinical continuum of cryopyrinopathies: novel CIAS1 mutations in North American patients and a new cryopyrin model. Arthritis Rheum 2007;56:1273–85.

40 Hentgen V, Despert V, Lepretre AC *et al*. Intrafamilial variable phenotypic expression of a CIAS1 from Muckle-Wells to chronic infantile neurological cutaneous and articular syndrome. J Rheumatol 2005;32:747–51.

41 Hoffman HM, Mueller JL, Broide DH, Wanderer AA, Kolodner RD. Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome. Nat Genet 2001; 29:301–5.

42 Feldmann J, Prieur AM, Quartier P *et al*. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. Am J Hum Genet 2002;71:198–203.

43 Aksentijevich I, Nowak M, Mallah M *et al*. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. Arthritis Rheum 2002;46:3340–8.

44 Aróstegui JI, Aldea A, Modesto C *et al*. Clinical and genetic heterogeneity among Spanish patients with recurrent autoinflammatory syndromes associated with the CIAS1/PYPAF1/NALP3 gene. Arthritis Rheum 2004;50:4045–50.

45 Aróstegui JI, Lopez Saldaña MD, Pascal M *et al*. A somatic NLRP3 mutation as a cause of sporadic case of chronic infantile neurologic, cutaneous, articular syndrome/neonatal-onset multisystem inflammatory disease. Arthritis Rheum 2010;62:1158–66.

46 Tanaka N, Izawa K, Saito MK *et al*. High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurological, cutaneous, articular syndrome. Arthritis Rheum 2011;63:3625–32.

47 Omoyinmi E, Melo Gomes S, Standing S *et al*. Whole exome sequencing revealing somatic *NLRP3* mosaicism in a patient with chronic infantile neurological cutaneous and articular syndrome. Arthritis Rheum 2014;66:197–202.

48 Prieur AM, Griscelli C, Lampert F *et al*. A chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome. A specific entity analysed in 30 patients. Scand J Rheumatol Suppl 1987;66:57–68.

49 Aganna E, Martinon F, Hawkins PN *et al*. Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad

phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. Arthritis Rheum 2002;46:2445–52.

50 Lindor NM, Arsenault TM, Solomon H, Seidman CE, McEvoy MT. A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum and acne: PAPA syndrome. Mayo Clin Proc 1997;72:611–5.

51 Wise CA, Gilium JD, Seidman CE *et al*. Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. Hum Mol Genet 2002;11:961–9.

52 Demidowich AP, Freeman AF, Kuhns DB *et al*. Genotype, phenotype, and clinical course in five patients with PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum, and acne). Arthritis Rheum 2012;64:2022–7.

53 Marzano AV, Trevisan V, Gattorno M *et al*. Pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis supurativa (PAPASH): a new autoinflammatory syndrome associated with a novel mutation of the PSTPIP1 gene. JAMA Dermatol 2013;149:762–4.

54 Aksentijevich I, Masters SL, Ferguson PJ *et al*. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med 2009;360:2426–37.

55 Reddy S, Jia S, Geoffrey R *et al*. An autoinflammatory disease due to homozygous deletion of the IL1RN locus. N Engl J Med 2009;360:2438–44.

56 Jesus AA, Osman M, Silva CS *et al*. A novel mutation of ILRN in the deficiency of interleukin-1 receptor antagonist syndrome. Description of two unrelated cases from Brazil. Arthritis Rheum 2011;63:4007–17.

57 Marrakchi S, Guigue P, Renshaw BR *et al*. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med 2011;365:620–8.

58 Rosé CD, Aróstegui JI, Martin TM *et al*. NOD2-associated pediatric granulomatous arthritis, an expanding phenotype. Study of an international registry and a national cohort in Spain. Arthritis Rheum 2009;60:1797–803.

59 Miceli-Richard C, Lesage S, Rybojad M *et al*. CARD15 mutations in Blau syndrome. Nat Genet 2001;29:19–20.

60 Kanazawa N, Okafuji I, Lambe N *et al*. Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-κB activation: common genetic etiology with Blau syndrome. Blood 2005;105:1195–7.

61 Rosé CD, Doyle TM, McIlvain-Simpson G *et al*. Blau syndrome mutation of CARD15/NOD2 in sporadic early onset granulomatous arthritis. J Rheumatol 2005;32:373–5.

62 Borghini S, Tassi S, Chiesa S *et al*. Clinical presentation and pathogenesis of cold induced autoinflammatory disease in a family with recurrence of an NLRP12 mutation. Arthritis Rheum 2011;63:830–9.

63 Jéru I, Duquesnoy P, Fernandes-Alnemri T *et al*. Mutations in NALP12 cause hereditary periodic fever syndromes. Proc Natl Acad Sci USA 2008;105:1614–9.

64 Ferguson PJ, El-Shanti HI. Autoinflammatory bone disorders. Curr Opin Rheumatol 2007;19:492–8.

65 Majeed HA, Kalaawi M, Mohanty D *et al*. Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. J Pediatr 1989;115:730–4.

66 Ferguson PJ, Chen S, Tayeh MK *et al*. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome). J Med Genet 2005;42:551–7.

67 Al-Mosawi ZS, Al-Saad KK, Ijadi-Maghsoodi R *et al*. A splice site mutation confirms the role of LPIN2 in Majeed syndrome. Arthritis Rheum 2007;56:960–4.

68 Liu Y, Ramot Y, Torrelo A *et al*. Mutations in preoteasome subunit β type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. Arthritis Rheum 2012;64:895–907.

69 Agarwal AK, Xing C, DeMartino G *et al*. PSMB8 encoding the β5i proteasome subunit is mutated in joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy syndrome. Am J Human Genet 2010;87:866–72.

70 Arima K, Kinoshita A, Mishima H *et al*. Proteasome assembly defect due to a proteasome subunit beta type 8 (PSMB8) mutation causes the autoinflammatory disorder, Nakajo-Nishimura syndrome. Proc Natl Acad Sci USA 2011;108:14914–9.

71 Standing A, Omoyinmi E, Brogan P. Gene hunting in autoinflammation. Clin Transl Allergy 2013;3:32.

72 Toiutou I, Galeotti C, Rossi-Semerano S *et al*. The expanding spectrum of rare monogenic autoinflammatory diseases. Orphanet J Rare Dis 2013;8:162.

73 Omenetti A, Federici S, Gattorno M. Inherited autoinflammatory diseases: a critical digest of the recent literature. Clin Exp Rheumatol 2013;31(Suppl 77):S118–26.

74 Ozen S, Bilginer Y. A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. Nat Rev Rheumatol 2014;10:135–47.

75 Jordan CT, Cao L, Roberson EDO *et al*. PSORS2 is due to mutations in CARD 14. Am J Hum Genet 2012;90:784–95.

76 Ombrello M, Remmers EF, Sun G *et al*. Cold urticaria, immunodeficiency, and autoimmunity related to PLCG2 deletions. N Engl J Med 2012;366:330–8.

77 Zhou Q, Lee GS, Brady J *et al*. A hypermorphic missense mutation in PLCG2, encoding phospholipase Cγ2, causes a dominantly inherited autoinflammatory disease with immunodeficiency. Am J Hum Genet 2012;91:713–20.

78 Boisson B, Laplantine E, Prando C *et al*. Immunodeficiency, auto-inflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency. Nat Immunol 2012;13:1178–86.

79 Melki I, Lambot K, Jonard L *et al*. Mutation in the SLC29A3 gene: a new cause of a monogenic, autoinflammatory condition. Pediatrics 2013;131:e1308.

80 Senniappan S, Hughes M, Shah P *et al*. Pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (PHID) syndrome is associated with severe chronic inflammation and cardiomyopathy, and represents a new monogenic autoinflammatory syndrome. J Pediatr Endocrinol Metab 2013;26:1–6.

81 Glocker EO, Kotlarz D, Boztug K *et al*. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med 2009;361:2033–45.

82 Kotlarz D, Beier R, Murugan D *et al*. Loss of interleukin-10 signaling and infantile inflammatory bowel disease: implications for diagnosis and therapy. Gastroenterology 2012; 143:347–55.

83 Park H, Bourla AB, Kastner DL *et al*. Lighting the fire within: the cell biology of autoinflammatory diseases. Nat Rev 2012;570–80.

84 Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-1. Mol Cell 2002;10: 417–26.

85 Agostini L, Martinon F, Burns K *et al*. NALP3 forms an IL-1-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. Immunity 2004; 20:319–25.

86 Mariathasan S, Monack DM. Inflammasome adaptors and sensors: intracellular regulators of infection and inflammation. Nat Rev Immunol 2007;7:31–40.

87 Shoham NG, Centola M, Mansfield E *et al*. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. Proc Natl Acad Sci USA 2003;100:13501–6.

88 Dinarello CA. Mutations in cryopyrin: bypassing roadblocks in the caspase 1 inflammasome for interleukin-1β secretion and disease activity. Arthritis Rheum 2007;56: 2817–22.

89 Mandey SH, Kuijk LM, Frenkel J, Waterham HR. A role for geranylgeranylation in interleukin-1beta secretion. Arthritis Rheum 2006;54:3690–5.

90 Pontillo A, Paoluzzi E, Crovella S. The inhibition of mevalonate pathway induces upregulation of NALP3 expression: new insight in the pathogenesis of mevalonate kinase deficiency. Eur J Hum Genet 2010;18:844–7.

91 Jéru I, Hentgen V, Normand S *et al*. Role of interleukin-1beta in NLRP12-associated autoinflammatory disorders and resistance to antiinterleukin-1 therapy. Arthritis Rheum 2011;63:2142–8.

92 Martin TM, Zhang Z, Kurz P *et al*. The NOD2 defect in Blau syndrome does not result in excess interleukin-1 activity. Arthritis Rheum 2009;60:611–8.

93 Huggins ML, Radford PM, McIntosh RS *et al*. Shedding of mutant tumor necrosis factor receptor superfamily 1A associated with tumor necrosis factor receptor-associated periodic syndrome: differences between cell types. Arthritis Rheum 2004;50:2651–9.

94 D'Osualdo A, Ferlito F, Prigione I *et al*. Neutrophils from patients with TNFRSF1A mutations display resistance to tumor necrosis factor-induced apoptosis: pathogenetic and clinical implications. Arthritis Rheum 2006;54: 998–1008.

95 Lobito AA, Kimberley FC, Muppidi JR *et al*. Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS). Blood 2006;108: 1320–7.

96 Bulua AC, Simon A, Maddipati R *et al*. Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). J Exp Med 2011;208: 519–33.

97 Mitroulis I, Kourtzelis I, Kambas K *et al*. Evidence for the involvement of mTOR inhibition and basal autophagy in familial Mediterranean fever phenotype. Hum Immunol 2011;72:135–8.

98 van der Burgh R, Nijhuis L, Pervolaraki K *et al*. Defects in mitochondrial clearance predispose human monocytes to interleukin-1β hypersecretion. J Biol Chem 2014;289: 5000–12.

99 Yalçinkaya F, Özen S, Özçakar ZB *et al*. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology 2009;48:395–8.

100 Kondi A, Hentgen V, Piram M *et al*. Validation of the new paediatric criteria for the diagnosis of familial Mediterranean fever: data from a mixed population of 100 children from the French reference centre for autoinflammatory disorders. Rheumatology 2010;49:2200–3.

101 Federici I, Rittore-Domingo C, Koné Paut I *et al*. A decision tree for genetic diagnosis of hereditary periodic fever in unselected patients. Ann Rheum Dis 2006;65: 1427–32.

102 Gattorno M, Sormani MP, D'Osualdo A *et al*. A diagnostic score for molecular analysis of hereditary autoinflammatory syndromes with periodic fever in children. Arthritis Rheum 2008;58:1823–32.

103 Gattorno M, Caorsi R, Meini A *et al*. Differentiating PFAPA syndrome from monogenic periodic fevers. Pediatrics 2009;124:e721–8.

104 Simon A, van der Meer JW, Vesely R *et al*. Approach to genetic analysis in the diagnosis of hereditary autoinflammatory syndromes. Rheumatology 2006;45:269–73.

105 Shinar Y, Obici L, Aksentijevich I *et al*. Guidelines for the genetic diagnosis of hereditary recurrent fevers. Ann Rheum Dis 2012;71:1599–605.

106 Touitou I. Inheritance of autoinflammatory diseases: shifting paradigms and nomenclature. J Med Genet 2013;50:349–59.

107 Koné-Paut I, Sanchez E, Le Quellec A, Manna R, Touitou I. Autoinflammatory gene mutations in Behçet's disease. Ann Rheum Dis 2007;66:832–4.

108 Berkun Y, Levy R, Hurwitz A *et al*. The familial Mediterranean fever gene as a modifier of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome. Semin Arthritis Rheum 2011;40:467–72.

109 Ozen S, Bakkaloglu A, Yilmaz E *et al*. Mutations in the gene for familial Mediterranean fever: do they predispose to inflammation? J Rheumatol 2003;30:2014–8.

110 Marek-Yagel D, Berkun Y, Padeh S *et al*. Role of the R92Q TNFRSF1A mutation in patients with familial Mediterranean fever. Arthritis Care Res 2010;62:1294–8.

111 Stojanov S, Lohse P, Lohse P *et al*. Molecular analysis of the MVK and TNFRSF1A genes in patients with a clinical presentation typical of the hyperimmunoglobulinemia D with periodic fever syndrome. Arthritis Rheum 2004;50: 1951–8.

112 Toplak N, Frenkel J, Ozen S *et al*. An international registry on autoinflammatory diseases: the Eurofever experience. Ann Rheum Dis 2012;71:1177–82.

113 De Menthiere CS, Terriere S, Pugnere D *et al*. INFEVERS: the registry for FMF and hereditary

inflammatory disorders mutations. Nucleic Acids Res 2003;31:282–5.

114 Lainka E, Bielak M, Hilger V *et al*. Translational research network and patient registry for auto-inflammatory diseases. Rheumatology 2011;50:237–42.

115 Goldstein RC, Schwabe AD. Prophylactic colchicine therapy in familial Mediterranean fever: a controlled, double-blind study. Ann Intern Med 1974;81:792–4.

116 Zemer D, Revach M, Pras M *et al*. A controlled trial of colchicine in preventing attacks of familial Mediterranean fever. N Engl J Med 1974;291:932–4.

117 Dinarello CA, Wolff SM, Goldfinger SE *et al*. Colchicine therapy for familial Mediterranean fever. A double-blind trial. N Engl J Med 1974;291:934–7.

118 Kallinich T, Haffner D, Niehues T *et al*. Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. Pediatrics 2007;119:e474–83.

119 ter Haar N, Lachmann H, Özen S *et al*. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. Ann Rheum Dis 2013;72:678–85.

120 Simon A, Drewe E, van der Meer JW *et al*. Simvastatin treatment for inflammatory attacks of the hyperimmunoglobulinemia D and periodic fever syndrome. Clin Pharmacol Ther 2004;75:476–83.

121 Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. N Engl J Med 2003;348:2583–4.

122 Hoffman HM, Rosengren S, Boyle DL *et al*. Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. Lancet 2004;364:1779–85.

123 Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. Arthritis Rheum 2004;50:607–12.

124 Goldbach-Mansky R, Dailey NJ, Canna SW *et al*. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1β inhibition. N Engl J Med 2006;355:581–92.

125 Metyas SK, Hoffman HM. Anakinra prevents symptoms of familial cold autoinflammatory syndrome and Raynaud's disease. J Rheumatol 2006;33:2085–7.

126 Leslie KS, Lachmann HJ, Bruning E *et al*. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. Arch Dermatol 2006;142:1591–7.

127 Neven B, Marvillet I, Terrada C *et al*. Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurological, cutaneous, articular syndrome. Arthritis Rheum 2010;62:258–67.

128 Kuemmerle-Deschner JB, Tyrrell PN, Koetter I *et al*. Efficacy and safety of anakinra therapy in pediatric and adult patients with the autoinflammatory Muckle-Wells syndrome. Arthritis Rheum 2011;63:840–9.

129 Sibley CH, Plass N, Snow J *et al*. Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease (NOMID) treated with anakinra. Arthritis Rheum 2012;64:2375–86.

130 Alten R, Gram H, Joosten LA *et al*. The human anti-IL-1 beta monoclonal antibody ACZ885 is effective in joint inflammation models in mice and in a proof-of-concept study in patients with rheumatoid arthritis. Arthritis Res Ther 2008;10:R67.

131 Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB *et al*. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009;360:2416–25.

132 Kuemmerle-Deschner JB, Ramos E, Blank N *et al*. Canakinumab (ACZ885, a fully human IgG1 anti-IL-1β mAb) induces sustained remission in pediatric patients with cryopyrin-associated periodic syndrome (CAPS). Arthritis Res Ther 2011;13:R34.

133 Kuemmerle-Deschner JB, Hachulla E, Cartwright R *et al*. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis 2011;70:2095–102.

134 Koné-Paut I, Lachmann HJ, Kuemmerle-Deschner JB *et al*. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. Arthritis Res Ther 2011;13:R202.

135 Kuemmerle-Deschner JB, Lohse P, Koetter I *et al*. NLRP3 E311K mutation in a large family with Muckle-Wells syndrome—description of a heterogeneous phenotype and response to treatment. Arthritis Res Ther 2011;13:R196.

136 Caorsi R, Lepore L, Zulian F *et al*. The schedule of administration of canakinumab in cryopyrin associated periodic syndrome is driven by the phenotype severity rather than the age. Arthritis Res Ther 2013;15:R33.

137 Imagawa T, Nishikomori R, Takada H *et al*. Safety and efficacy of canakinumab in Japanese patients with phenotypes of cryopyrin-associated periodic syndrome as established in the first open-label, phase-3 pivotal study (24-week results). Clin Exp Rheumatol 2013;31:302–9.

138 Russo RA, Melo-Gomes S, Lachmann HJ *et al*. Efficacy and safety of canakinumab therapy in paediatric patients with cryopyrin-associated periodic syndrome: a single-centre, real world experience. Rheumatology 2014;53:665–70.

139 Goldbach-Mansky R, Shroff SD, Wilson M *et al*. A pilot study to evaluate the safety and efficacy of the long-acting interleukin-1 inhibitor rilonacept (interleukin-1 trap) in patients with familial cold autoinflammatory syndrome. Arthritis Rheum 2008;58:2432–42.

140 Hoffman HM, Throne ML, Amar NJ *et al*. Efficacy and safety of rilonacept (interleukin-1 trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum 2008;58:2443–52.

141 Simon A, Bodar EJ, van der Hilst JC *et al*. Beneficial response to interleukin 1 receptor antagonist in TRAPS. Am J Med 2004;117:208–10.

142 Gattorno M, Pelagatti MA, Meini A *et al*. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum 2008;58:1516–20.

143 Obici L, Meini A, Cattalini M *et al*. Favourable and sustained response to anakinra in tumor necrosis factor receptor-associated periodic syndrome (TRAPS) with or without AA amyloidosis. Ann Rheum Dis 2011;70:1511–2.

144 Bodar EJ, Kuijk LM, Drenth JP *et al*. On-demand anakinra treatment is effective in mevalonate kinase deficiency. Ann Rheum Dis 2011;70:2155–8.

145 Galeotti C, Meinzer U, Quartier P *et al*. Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. Rheumatology 2012;51:1855–9.

146 Ozen S, Bilginer Y, Aktay Ayaz N *et al*. Anti-interleukin 1 treatment for patients with familial Mediterranean fever resistant to colchicine. J Rheumatol 2011;38:516–8.

147 Meinzer U, Quartier P, Alexandra JF *et al*. Interleukin-1 targeting drugs in familial Mediterranean fever: a case series and a review of the literature. Semin Arthritis Rheum 2011;41:265–71.

148 Dierselhuis MP, Frenkel J, Wulffraat NM, Boelens JJ. Anakinra for flares of pyogenic arthritis in PAPA syndrome. Rheumatology 2005;44:406–8.

149 Brenner M, Ruzicka T, Plewig G, Thomas P, Herzer P. Targeted treatment of pyoderma gangrenosum in PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) syndrome with the recombinant human interleukin-1 receptor antagonist anakinra. Br J Dermatol 2006;161:1199–201.

150 Aróstegui JI, Arnal C, Merino R *et al*. NOD2 gene-associated pediatric granulomatous arthritis: clinical diversity, novel and recurrent mutations, and evidence of clinical improvement with interleukin-1 blockade in a Spanish cohort. Arthritis Rheum 2007;56:3805–13.

151 Simonini G, Xu Z, Caputo R *et al*. Clinical and transcriptional response to the long-acting Interleukin-1 blocker canakinumab in Blau syndrome-related uveitis. Arthritis Rheum 2013;65:513–8.

152 Drewe E, McDermott EM, Powell PT *et al*. Prospective study of anti-tumor necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumor necrosis factor receptor superfamily 1A fusion protein, in tumor necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients. Rheumatology 2003;42:235–9.

153 Nowlan ML, Drewe E, Bulsara H *et al*. Systemic cytokine levels and the effects of etanercept in TNF receptor-associated periodic syndrome (TRAPS) involving a C33Y mutation in TNFRSF1A. Rheumatology 2006;45:31–7.

154 Stojanov S, Dejaco C, Lohse P *et al*. Clinical and functional characterisation of a novel TNFRSF1A c.605T>A/V173D cleavage site mutation associated with tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS), cardiovascular complications and excellent response to etanercept treatment. Ann Rheum Dis 2008;67:1292–8.

155 Bulua AC, Mogul DB, Aksentijevich I *et al*. Efficacy of etanercept in the tumor necrosis factor receptor-associated periodic syndrome: a prospective, open-label, dose-escalation study. Arthritis Rheum 2012;64:908–13.

156 Arkwright PD, McDermott MF, Houten SM *et al*. Hyper IgD syndrome (HIDS) associated with in vitro evidence of defective monocyte TNFRSF1A shedding and partial response to TNF receptor blockade with etanercept. Clin Exp Immunol 2002;130:484–8.

157 Takada K, Aksentijevich I, Mahadevan V *et al*. Favorable preliminary experience with etanercept in two patients with the hyperimmunoglobulinemia D and periodic fever syndrome. Arthritis Rheum 2003;48:2645–51.

158 Bilgen SA, Kilic L, Akdogan A *et al*. Effects of anti-tumor necrosis factor agents for familial Mediterranean fever patients with chronic arthritis and/or sacroiliitis who were resistant to colchicine treatment. J Clin Rheumatol 2011;17:358–62.

159 Cortis E, De Benedetti F, Insalaco A *et al*. Abnormal production of the tumor necrosis factor and clinical efficacy of the tumor necrosis factor inhibitor etanercept in a patient with PAPA syndrome. J Pediatr 2004;145:851–5.

160 Vaitla PM, Radford PM, Tighe PJ *et al*. Role of interleukin-6 in a patient with tumor necrosis factor receptor-associated periodic syndrome: assessment of outcomes following treatment with the antiinterleukin-6 receptor monoclonal antibody tocilizumab. Arthritis Rheum 2011;63:1151–5.

161 Tunca M, Tankurt E, Akbaylar Akpinar H *et al*. The efficacy of interferon alpha on colchicine-resistant familial Mediterranean fever attacks: a pilot study. Br J Rheumatol 1997;36:1005–8.

162 Tweezer-Zaks N, Rabinovich E, Lidar M *et al*. Interferon-alpha as a treatment modality for colchicine-resistant familial Mediterranean fever. J Rheumatol 2008;35:1362–5.

163 Tunca M, Akar S, Soytürk M *et al*. The effect of interferon alpha administration on acute attacks of familial Mediterranean fever: a double-blind, placebo-controlled trial. Clin Exp Rheumatol 2004;22(Suppl 34):S37–40.

164 Calguneri M, Apras S, Ozbalkan Z *et al*. The efficacy of continuous interferon alpha administration as an adjunctive agent to colchicine-resistant familial Mediterranean fever patients. Clin Exp Rheumatol 2004;22(Suppl 34):S41–4.

165 NIH Clinical Center. Compassionate Use Treatment Protocol I4V-MC-JAGA; Treatment of Autoinflammatory Syndromes Expected to Benefit from JAK Inhibition. http://clinicalstudies.info.nih.gov/cgi/detail.cgi?A_2012-AR-8001.html (20 October 2013, date last accessed).