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12.12.2 Hereditary periodic fever syndromes Helen J. Lachmann, Stefan Berg, and Philip N. Hawkins ESSENTIALS The hereditary periodic fever syndromes or hereditary auto inflammatory diseases are disorders of innate immunity that mostly present in childhood and are characterized by recurrent, self-limiting, seemingly unprovoked episodes of fever and systemic inflammation that occur in the absence of autoantibody production or identifiable infection. Disorders include (1) familial Mediterranean fever (FMF), due to mutations in the gene encoding pyrin; (2) tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), due to mu-

tations in a gene for a TNF receptor; (3) mevalonate kinase deficiency (MKD), caused by mutations in the mevalonate kinase gene; and (4) the cryopyrin-associated periodic syndromes (CAPS), which include (a) familial cold urticarial syndrome, (b) Muckle-Wells syndrome, and (c) chronic infantile neurological, cutaneous, and articular syndrome. With advances in genetics, further syndromes are continually being recognized. These are all extremely rare and in the majority are only known to affect a handful of kindred or individuals. Understanding of the molecular pathogenesis of these disorders provides unique insights into the regulation of innate immunity and inflammation. Diagnosis relies on recognition of suggestive clinical features (e.g. fever with peritonitis and/or pleurisy, arthralgia/arthritis) that are almost always accompanied by a substantial acute phase response, and is supported by genetic testing. With the exception of FMF, which is a common disease in certain geographic areas, hereditary periodic fever syndromes are rare and easily overlooked in the differential diagnosis of recurrent fevers. Clinical features and management—attacks can be mild to debilitating and short to prolonged, while their most feared complication is AA amyloidosis. Effective therapies are available for some syndromes, for example: (1) FMF—daily prophylactic colchicine prevents clinical attacks and susceptibility to AA amyloidosis, (2) CAPS—treatment with anti-IL-1 agents produces rapid and often complete clinical and serological remission, and (3) TRAPS—anti-IL therapies are extremely effective. Introduction The hereditary periodic fever syndromes are a group of multisystem disorders characterized by fluctuating or irregularly recurring episodes of fever and systemic inflammation, notably affecting the joints, eyes, skin, and serosal surfaces. More than 30 syndromes are now recognized; many of these are extremely rare and only affect a handful of individuals. Diseases affecting more than 1 per million, and therefore likely to be encountered in specialist practice, include familial Mediterranean fever (FMF), tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD, previously known as the hyperimmunoglobulin D and periodic fever syndrome (HIDS)), and the cryopyrin-associated periodic syndromes (CAPS). The latter are a spectrum of three hitherto apparently distinct disorders of increasing severity: familial cold urticarial syndrome (now known as familial cold autoinflammatory syndrome; FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurological, cutaneous, and articular syndrome (CINCA). The latter is also known in the United States of America as neonatal-onset multisystem inflammatory disorder (NOMID). Although many symptoms of these disorders are shared, there are clear distinctions in the pattern of their inheritance, the duration and frequency of attacks, and their overall clinical picture (Table 12.12.2.1). With a few exceptions, these diseases are usually compatible with normal life expectancy, though with the ever-looming grave threat of AA amyloidosis. Recent insights into their molecular pathogenesis have led to enhanced diagnosis through DNA analysis, the development of rational therapies, and have shed important new light on regulation of the innate immune system.

section 12 Metabolic disorders 2208 Table 12.12.2.1 Features of inherited periodic fever syndromes

Periodic fever syndrome	Gene, chromosome	OMIM	Mode of inheritance	Predominant population	Usual age at onset	Potential precipitants of attacks	Distinctive clinical features	Typical duration of attacks	Typical frequency of attacks	Characteristic laboratory abnormalities	Treatment	
FMF	MEFV, chromosome 16	249100	Autosomal recessive (dominant in rare families)	Eastern Mediterranean	Childhood/ early adulthood	Usually none	Occasionally menstruation, fasting, stress, or trauma	Short severe attacks of peritonitic and/or pleuritic pain, colchicine-responsive, erysipelas-like erythema	1–3 days	Variable	Marked acute phase response during attacks	Colchicine
TRAPS	TNFRSF1A, chromosome 12	142680	Autosomal dominant (can be de novo)	Northern								

European, but reported in many ethnic groups Childhood/ early adulthood Usually none Prolonged symptoms More than a week (may be very prolonged) Variable (may be continuous) Marked acute phase response during attacks Low levels of soluble TNFR1 when well Anti-IL-1 therapies High-dose corticosteroids MKD MVK, chromosome 12 260920 251170 Autosomal recessive Northern European, but reported in many ethnic groups Infancy Immunizations Diarrhoea and lymphadenopathy. 3–7 days 1–2 monthly Acute phase response, and mevalonate aciduria during attacks, elevated IgD and IgA Anti-IL-1 therapies, anti-TNF therapies, anti-IL-6 therapies FCAS NLRP3, chromosome 1 120100 606416 Autosomal dominant Northern but reported in many ethnic groups European, Neonatal/ infancy Exposure to cold environment Cold-induced fever, arthralgia, rash, and red eye 24–48 h Depends on environmental factors Acute phase response during attacks; to a lesser extent when well Cold avoidance, anti-IL-1 therapies MWS NLRP3, chromosome 1 191900 606416 Autosomal dominant, Northern European, but reported in many ethnic groups Neonatal/ infancy Marked diurnal variation Cold environment, but less marked than in FCAS Urticarial rash, red eye, sensorineural deafness Continuous (often worse in the evenings) Often daily Varying but marked acute phase response most of the time Anti-IL-1 therapies CINCA/ NOMID NLRP3, chromosome 1 607115 606416 Sporadic Northern European, but reported in many ethnic groups Neonatal/ infancy None Urticarial rash, aseptic meningitis, deforming arthropathy, sensorineural deafness, developmental damage Continuous Continuous Varying but marked acute phase response most of the time Anti-IL-1 therapies PAPA PSTPIP1 (CD2BP1), chromosome 15 604416 606347 Autosomal dominant Northern European, but reported in many ethnic groups Childhood None Pyogenic arthritis, pyoderma gangrenosum, and cystic acne Intermittent attacks with migratory arthritis Variable (may be continuous) Acute phase response during attacks Anti-TNF therapies

12.12.2 Hereditary periodic fever syndromes 2209 (continued) Blau's syndrome NOD2 (CARD15), chromosome 16 605956 186580 Autosomal dominant None Age <5 years None Granulomatous polyarthritis, iritis, and dermatitis Continuous Continuous Sustained modest acute phase response Corticosteroids, some reports of benefit from anti-TNF agents FCAS2 NLRP12, chromosome 19 611762 609648 Autosomal dominant South/Central American, but reported in other ethnic groups Neonatal Sometimes exposure to cold Urticarial rash, fever, arthralgia Intermittent Variable Acute phase response during attacks None know DIRA IL1RN, chromosome 2 612852 147679 Autosomal recessive Northern Europe and Central America Infancy None Pustular rash, sterile osteomyelitis of long bones Continuous Continuous Sustained acute phase response Anakinra (recombinant IL-1 receptor antagonist) Majeed's syndrome LIPN2, chromosome 18 609628 605519 Autosomal recessive Middle East Infancy None Recurrent multifocal osteomyelitis, congenital dyserythropoietic anaemia, neutrophilic dermatosis 2–7 days Variable Acute phase response during attacks NSAIDs and corticosteroids. Possible benefit from IL-1 blocking agents DITRA IL36RN, chromosome 2 614204 605507 Autosomal recessive None Variable— from infancy onwards Drug initiation or withdrawal, menstrual cycle, pregnancy Recurrent fever, generalized rash, and disseminated pustules often but not always on a background of psoriasis Intermittent Variable Acute phase response during attacks, typical spongiform pustules on skin biopsy Possible benefit from IL-1 blocking agents CANDLE/JMP PSMB8, chromosome 6 256040 177046 Autosomal recessive None Infancy None Lipodystrophy, characteristic rash, swollen lips, violaceous eyelids Continuous Continuous Acute phase response, typical appearances on skin biopsy None established? JAK inhibitors Early-onset inflammatory bowel disease/IL-10R deficiency IL10RA, chromosome 11, IL10RB, chromosome 21, or IL-10, chromosome 1 613148 612567 612381 Autosomal recessive

None Infancy None Very early-onset severe inflammatory bowel disease with perianal fistulae
Continuous Continuous Acute phase response, colitis with granulomas Stem cell transplantation
APLAID PLCG2, chromosome 16 614878 600220 Autosomal dominant Single family Infancy Rash
worse with heat or sun exposure Recurrent blistering rash and mild humoral immune deficiency
with sinopulmonary infections Continuous Continuous Acute phase response, dense inflammatory
infiltrate in skin, decreased IgM and IgA, no autoantibodies Partial response to IL-1 blockade and
corticosteroids

section 12 Metabolic disorders 2210 Periodic fever syndrome Gene, chromosome OMIM Mode of
inheritance Predominant population Usual age at onset Potential precipitants of attacks Distinctive
clinical features Typical duration of attacks Typical frequency of attacks Characteristic laboratory
abnormalities Treatment HOIL-1 deficiency RBCK1, chromosome 20 615895 Autosomal recessive
Two European families Infancy None Polyglucosan myopathy and cardiomyopathy with
immunodeficiency and bacterial infection and autoinflammation Intermittent Intermittent Acute
phase response, intracellular glycogen inclusions, on muscle biopsy All 4 cases died in childhood—
symptomatic improvement with corticosteroids, allogeneic stem cell transplantation attempted
DADA2 CECR1, chromosome 22 615688 Autosomal recessive None Childhood None Systemic and
local polyarteritis nodosa, livedo racemose, and early-onset stroke Intermittent Intermittent Acute
phase response during attacks Anti-TNF SAVI TMEM173, chromosome 5 615934 Autosomal
dominant None Infancy None Rash on cheeks, ears, nose, and digits with cartilage damage, failure
to thrive, interstitial lung disease Continuous Continuous Capillary inflammation, acute phase
response None established? JAK inhibitors APLAID, autoinflammation and PLCγ2-associated
antibody deficiency and immune dysregulation, CINCA/NOMID, chronic infantile neurological,
cutaneous, and articular syndrome/neonatal-onset multisystem inflammatory disorder; DADA2,
deficiency of adenosine deaminase 2; DIRA, deficiency of the IL-1 receptor antagonist; DITRA,
deficiency of the IL-36 receptor antagonist; FCAS, familial cold autoinflammatory syndrome; FMF,
familial Mediterranean fever; HOIL-1, haem-oxidized IRP2 ubiquitin ligase 1; IL-1, interleukin 1;
MKD, mevalonate kinase deficiency; MWS, Muckle-Wells syndrome; PAPA, pyogenic arthritis,
pyoderma gangrenosum, and acne syndrome; SAVI, STING-associated vasculopathy with onset in
infancy; TNF, tumour necrosis factor; TNFR1, tumour necrosis factor receptor 1; TRAPS, tumour
necrosis factor receptor-associated periodic syndrome. Table 12.12.2.1 Continued

12.12.2 Hereditary periodic fever syndromes 2211 Historical perspective Although the hereditary
periodic fever syndromes have only been identified as such during the last few decades, there are
various ancient references to them, particularly FMF. Perhaps the earliest extant clinical description
is found in William Heberden's 1802 Commentaries on History and Care of Disease: 'Pains which
are regularly intermittent, the fits of which return periodically as those of an ague; such as I have
known in the bowels, stomach, breast, loins, arms and hips, though it be but seldom that such
parts suffer in such a manner.' Familial Mediterranean fever Genetics FMF is predominantly
inherited in a recessive manner. The gene associated with FMF, MEFV, which encodes a protein
called pyrin, was identified through positional cloning in 1997. MEFV is expressed in neutrophils,
monocytes, dendritic cells, and fibroblasts. Expression is up-regulated in response to inflammatory
activators such as interferon-γ and TNFα. The more than 40 MEFV mutations that are associated
with FMF encode either single amino acid substitutions or small deletions. The mutations that
cause FMF are mostly in exon 10, but also occur elsewhere, particularly in exons 1, 3, 5, and
9. Mutations in each of the two MEFV alleles can be identified in most patients with FMF. Most

individuals with a single mutated allele remain healthy carriers but heterozygote FMF is well recognized and may account for up to 20% of cases. While it is inherently likely that different mutations will affect the function of a protein to differing extents, several findings suggest that the methionine residue at position 694 is especially important. Five different pathogenic exon 10 mutations involving Met694 have been identified, and individuals homozygous for Met694Val have particularly severe disease. Simple heterozygous deletion of this residue is associated with autosomal dominant FMF of variable penetrance in the British population. More extensive disruption of a single MEFV allele by one or more mutations may account for other rare reports of dominant FMF. Much more commonly, FMF affecting more than one generation of a family is pseudodominantly inherited, reflecting consanguinity or a high local prevalence of the heterozygous carrier state. One particular pyrin variant, E148Q encoded in exon 2, is extremely frequent in Asian populations, with an allele frequency of 10 to 20%, and occurs in other populations at a much lower frequency. Although pyrin E148Q can cause typical FMF when coupled with various exon 10 mutations, homozygosity for E148Q alone is thought not to be associated with disease in the vast majority of cases. There is, however, a suggestion that the presence of pyrin E148Q might intensify non-FMF types of inflammation. Pathology Unusually, given the recessive inheritance, the mutations underlying FMF appear to result in gain of function. Pyrin is a key component of an inflammasome which activates caspase-1 by autoproteolysis. Maturation of interleukin (IL)-1 β and IL-18 requires cleavage by caspase 1 which also induces macrophage pyroptosis. Assembly of inflammasomes is triggered by recognition of intracellular pathogen or damage-associated molecular patterns. Recent work suggests that pyrin is an indirect sensor of a wide variety of bacterial toxins; pyrin interacts, via its N-terminal death domain, with cytoskeleton microtubules and appears to detect pathological perturbation of actin polymerization dynamics caused by bacterial modification or inactivation of Rho GTPases. More than 20 other proteins that have homology with pyrin's N-terminal sequence are now classified generically to have a pyrin domain and are members of the death domain superfamily. They play important roles in the assembly and activation of apoptotic and inflammatory complexes through homotypic protein-protein interactions. Proteins with pyrin domains are involved in inflammation, apoptosis, and nuclear factor (NF)- κ B signalling and have been implicated in pathways in CAPS as well.

Epidemiology FMF occurs worldwide, though predominantly in populations arising from the eastern Mediterranean basin, particularly non-Ashkenazi Jews, Armenians, Turks, and Levantine Arabs. The prevalence of FMF has been estimated to be 1 in 250 to 1 in 500 among non-Ashkenazi Jews and 1 in 1000 in the Turkish population. The carrier frequency is as high as one in five among Armenian, Turkish, and North African Jewish populations, fuelling speculation that the FMF trait may have conferred survival benefit, most likely through enhanced resistance to microbial infection mediated by up-regulation of the innate inflammatory response. Males and females are equally affected. FMF usually presents in childhood, in 60% before the age of 10 years and in 90% by 20 years.

Clinical features Attacks of FMF occur irregularly at variable frequencies and may be precipitated by physical and emotional stress, menstruation, and diet. The onset is rapid and symptoms resolve spontaneously within 6 to 72 h. Fever with peritonitis and/or pleurisy are the hallmark features, but occur with widely varying intensity from very mild to severely incapacitating. The clinical picture may mimic an acute surgical abdomen with ileus and vomiting, and 40% of patients undergo laparoscopy before the diagnosis is made. Pleuritic attacks occur in 40% of patients, characteristically unilaterally, either alone or in association with peritonitis. Pericarditis is rare and cardiac tamponade extremely rare. Headache with meningism is reported, but generally the nervous system is not involved in attacks. Orchitis occurs in less than 5% of males, most commonly

in early childhood, when it can be confused with torsion of the testis. Transient arthralgia in lower-limb joints is not infrequent in acute attacks, and usually subsides within 2 to 4 days; dramatic acute oligoarthritis of the large joints of the lower limb can occur but chronic destructive inflammation is rare. There is a rare but genuine association between FMF associated with MEFV M694V and chronic sacroiliitis. A characteristic erysipelas-like erythematous rash occurs in 20% of patients (Fig. 12.12.2.1), usually on the lower extremities. Myalgia can be part of the constitutional upset during acute attacks, but up to one-fifth of patients complain of persistent muscle pain on exertion, usually affecting the calves. The rare but distinct syndrome of protracted febrile myalgia presents as severe pain, mainly affecting the lower limbs or abdominal musculature; symptoms may persist for weeks and be accompanied by a vasculitic rash, but usually respond to corticosteroids.

section 12 Metabolic disorders 2212 Clinical investigation Acute attacks are accompanied by a number of laboratory abnormalities including neutrophilia, raised ESR, and a dramatic acute phase response. Investigations may be required to exclude other potential causes of symptoms but, in general, imaging by radiography, ultrasonography, or echocardiography during acute attacks is unrewarding. The results of genetic testing must be interpreted with care, since some individuals with paired pathogenic MEFV mutations remain completely healthy, and others with apparent carrier status develop classical FMF. Furthermore, MEFV spans 10 exons, and most diagnostic laboratories offer only limited screening. However, in classical populations, the absence of a mutation in exon 10 makes a diagnosis of FMF unlikely. **Treatment** Supportive treatment, including analgesia, may be required in acute attacks, but the mainstay of therapy in FMF is prophylaxis with colchicine, a serendipitous discovery made by Goldfinger in 1972. Continuous treatment with colchicine 1 to 2 mg daily prevents or substantially reduces the symptoms of FMF in at least 95% of cases. Recent data also suggest that colchicine acts by a number of mechanisms including competition with pyrin for cleavage by caspase 1 thereby reducing the effect of N-terminal cleavage pyrin in enhancing NF- κ B activation in FMF. Long-term use of colchicine is advisable in every patient with FMF and mandatory in those with AA amyloidosis. Although colchicine is extremely toxic in large overdose, the small regular doses required for the treatment of FMF are very well tolerated. Particularly at dose initiation colchicine may cause diarrhoea which often responds to a lactose-free diet. Despite theoretical concerns about antimitotic potential, large cohort studies are very reassuring about the use of colchicine throughout conception and pregnancy. The concentration of colchicine in breast milk is sufficiently low to permit breastfeeding. Acute initiation or increase of the dose of colchicine does not usually ameliorate acute attacks. In the few patients who are genuinely resistant to colchicine, there have been reports of benefit in such patients following treatment with IL-1 blocking agents and a number of small trials have confirmed this. **Tumour necrosis factor receptor-associated periodic syndrome** **Genetics** TRAPS is an autosomal dominant disease associated with mutations in the 10-exon TNF receptor superfamily 1A gene (TNFRSF1A) on chromosome 12p13. A disproportionate number of the 50 or so associated mutations disrupt the coding of cysteine residues in the first and second extracellular domains. Pathology TNF is a key mediator in the inflammatory response, with several activities including increased expression of adhesion molecules, induction of cytokine secretion, and activation of leucocytes. TNF receptor 1 (TNFR1) is a member of the death domain superfamily and comprises an extracellular region containing four cysteine-rich domains, a transmembrane domain, and an intracellular death domain. Binding of TNF results in trimerization of the receptor and activation of NF- κ B, with downstream induction of inflammation or apoptosis. Under normal

circumstances, TNF signalling is terminated by cleavage of the extracellular domain; this results in the release of soluble TNFR1 into the plasma, competitively inhibiting the binding of circulating TNF to cell surface receptors. The mechanisms by which heterozygous TRFRSF1A mutations cause TRAPS are still unclear, and may well vary according to the specific mutation. Postulated explanations have included defective TNFR1 shedding from the cell surface, TNF-induced apoptosis, NF- κ B activation, aberrant activation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinases (MAPK), and mitochondrial reactive oxygen species inducing proinflammatory cytokine production. Recent work has focused on aberrant trafficking of the variant protein inducing an unfolded protein response and endoplasmic reticulum stress with production of reactive oxygen species. These intracellular stress responses appear to be mediated by inositol-requiring enzyme 1 α (IRE1 α), protein kinase-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6). Epidemiology TRAPS was first described in 1982, somewhat tongue-in-cheek, as 'familial Hibernian fever', reflecting a preponderance of patients from Ireland and Scotland in early reports. It is now clear that TRAPS occurs in diverse populations, including white, Jewish, Arab, and Central American populations, but the disease is rare with an estimated prevalence of 1 to 2 per million. Males and females are affected equally and the median age at presentation is 4 years. Most mutations are associated with high penetrance, but one variant that can be associated with TRAPS (R92Q) is present in approximately 2% of healthy chromosomes, and is thus variously regarded as a low-penetrance mutation or polymorphism. Clinical features Attacks of TRAPS are far less distinct than in FMF, sometimes lasting many weeks, and almost one-third of patients have fairly continuous symptoms. Approximately one-third of patients with pathogenic mutations report no family history. This is the case in more than 80% of patients carrying R92Q which tends to be associated with milder disease and older age at presentation. Symptoms are rather

Fig. 12.12.2.1 Typical erythematous erysipelas-like rash in a man with familial Mediterranean fever.

12.12.2 Hereditary periodic fever syndromes 2213 variable: more than 95% of patients experience fever and 80% complain of arthralgia or myalgia; abdominal pain occurs in 75%, and a rash (often overlying areas of myalgia) occurs in 50%. Other features include pleuritic pain, lymphadenopathy, conjunctivitis, and periorbital oedema. There are also reports of central nervous system manifestations resembling multiple sclerosis and TNFRSF1A R92Q confers a weak but significant genetic predisposition to multiple sclerosis. Clinical investigation Symptoms are almost universally accompanied by a very marked acute phase response. Genetic testing is pivotal in establishing the diagnosis. Interpretation of the significance of R92Q remains difficult and depends heavily on the clinical picture. Treatment Despite high hopes for anti-TNF biological agents, their effect in the treatment of TRAPS has proved disappointing in many patients. Acute attacks can be suppressed with corticosteroids, but prolonged treatment may be required at potentially harmful doses. IL-1 blockade is the most effective current option in severe TRAPS and in the majority of cases induces a complete disease response. Mevalonate kinase deficiency Genetics MKD is an autosomal recessive disease caused by mutations in the mevalonate kinase gene (MVK) on the long arm of chromosome 12. To date, 160 MKD-associated mutations have been described, spanning exons 2 to 11, the most common of which encode MVK variants V377I and I268T. The carriage frequency in the population of the Netherlands, in which MKD is most prevalent, is estimated to be 1 in 65. Pathology The MVK mutations associated with MKD result in 85 to 95% deficiency in mevalonate kinase activity. This enzyme is involved in cholesterol, farnesyl, and isoprenoid biosynthesis. It is not yet known how mevalonate kinase deficiency causes recurrent

inflammation, although there is speculation that reduced protein isoprenylation causes defective lymphocyte apoptosis. Other mutations in MVK result in even greater reduction in enzyme activity, and cause the much more severe disease known as mevalonic aciduria. Epidemiology MKD is most prevalent in the Netherlands, where it was first described as HIDS in 1984. It has subsequently been reported in other populations, including Arabs and South-East Asians, though is least rare among northern European white populations. The disease usually presents in the first year of life and occurs equally in both sexes. There are about 200 patients with MKD on the Dutch disease registry, and only some dozens recognized in the United Kingdom. Clinical features Symptoms are episodic and are often well circumscribed. Attacks are irregular, usually last 4 to 6 days, and can be provoked by vaccination, minor trauma, surgery, or stress. Fever, cervical lymphadenopathy, and abdominal pain with vomiting and diarrhoea are typical. Other common symptoms include headache, arthralgia, large joint arthritis, erythematous macules and papules, and aphthous ulcers. Rare complications include intellectual impairment, epilepsy, and retinitis pigmentosa. The disease sometimes ameliorates in early adult life and older patients may remain free of symptoms for years. Clinical investigation Diagnosis is supported by the presence of mevalonic acid in the urine during clinical attacks when there is an elevated acute phase response. Serum immunoglobulin (Ig)-D and IgA concentration are persistently elevated in 80% of patients although, particularly in the very young, this is nondiscriminative with respect to other autoinflammatory diseases. A mutation in both alleles of MVK can be identified in most patients, more than 80% of whom have the most common V337I variant. Treatment Treatment for milder disease remains largely supportive, including nonsteroidal anti-inflammatory drugs (NSAIDs) and on-demand corticosteroids. Colchicine and thalidomide have no convincing benefit. There is no evidence of benefit from treatment with simvastatin, an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (the enzyme before MKD in the cholesterol biosynthetic pathway). There are reports of responses to etanercept, tocilizumab, and anti-IL-1 agents; the latter are currently the most widely used biologics. In severe early-onset disease, bone marrow transplantation can be curative. Cryopyrin-associated periodic syndromes Genetics CAPS comprises a spectrum of disease associated with mutations in the gene NLRP3/CIAS1 on chromosome 1q44 that encodes the death domain protein variously known as NLRP3 (previously NALP3) and cryopyrin. Dominant inheritance is evident in about 75% of patients with MWS and FCAS, whereas CINCA, the most severe phenotype, is usually due to a de novo mutation. More than 140 single amino acid substitutions have been reported; the majority in exon 3. Somatic mosaicism is increasingly recognized in both early- and later-onset disease. The relationship between mutation and clinical phenotype can differ between individuals, even within a family, although some mutations are associated with a greater risk of neurological damage. Pathology NLRP3 is expressed in peripheral blood leucocytes and chondrocytes, and encodes a death domain protein that contains a pyrin domain, a nucleotide-binding site domain, and a leucine-rich repeat motif. Following recognition and binding, via its leucine-rich repeat, of an intracellular pathogen-associated molecular pattern, NLRP3 associates with other members of the death domain superfamily to form a multimeric cytosolic assembly, the inflammasome. This results in activation of caspase 1, which processes pro-IL-1 to produce the active cytokine; it also up-regulates NF- κ B expression, resulting

section 12 Metabolic disorders 2214 in increased IL-1 gene expression. IL-1 is a major proinflammatory cytokine involved in mediating local and systemic responses to infection and tissue injury. The remarkable response to IL-1 receptor blockade in CAPS confirms that the clinical features are substantially mediated by IL-1. Epidemiology So far, most reported patients have

European ancestry, but CAPS occurs worldwide. Onset of disease is in early infancy, and there is no sex bias. Clinical features FCAS was first described in 1940 as recurrent episodes of cold-induced fever, arthralgia, red eye (with inflammation at multiple levels), and rash. MWS was described in 1962 as a much more persistent urticaria-like rash, conjunctivitis, arthralgia, and fever, complicated by progressive sensorineural deafness and a high risk of AA amyloidosis (Fig. 12.12.2.2). CINCA was described as a sporadic severe inflammatory disorder that presents in the neonatal period with involvement of many organs including the skin, skeletal system, and central nervous system. Bony overgrowth and premature ossification may occur, particularly in the skull and knees, and chronic aseptic meningitis can result in severe developmental delay, optic atrophy, and deafness. It is now evident that FCAS, MWS (Fig. 12.12.2.3), and CINCA represent a spectrum of a single disease entity. Clinical investigation There is usually an acute phase response, and often leucocytosis and thrombocytosis that can vary substantially between measurements, and may not at times be present in some patients at the milder end of the disease spectrum (i.e. with FCAS and mild MWS). Audiometric evidence of sensorineural hearing loss should be sought, and characteristic bony abnormalities may be radiologically evident in CINCA. Features consistent with chronic meningitis may be evident on lumbar puncture, fundoscopy, and MRI. A mutation in NLRP3 can be readily identified in most patients with FCAS and MWS, though about half of those with CINCA are somatic mosaics. Treatment Treatment with anti-IL-1 agents produces rapid and often complete clinical and serological remission of CAPS. Three IL-1 inhibitors, anakinra, canakinumab and rilonacept, are licensed for the treatment of CAPS. There is hope that early treatment may prevent neurological and skeletal abnormalities. Other hereditary periodic fever syndromes Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome This autosomal dominant disease is caused by mutations in CD2BP1/PTSTIP1, the gene encoding CD2 binding protein 1. The underlying pathogenesis remains poorly understood, although there is evidence that CD2 binding protein 1 interacts with the pyrin pathway. It is characterized by early-onset recurrent sterile arthritis typically occurring after minor trauma, severe cystic acne, and pyoderma gangrenosum. Penetrance seems variable and asymptomatic gene carriage is recognized. There is no proven treatment, responses to steroids are usually partial, and early reports suggest variable responses to anti-TNF or anti-IL-1 agents. In general, skin disease is more treatment refractory than the arthritis. Blau's syndrome This was first described in 1985 as an autosomal dominant syndrome of sarcoid-like granulomatous infiltration causing a triad of arthritis, dermatitis, and uveitis. Sporadic disease in the absence of a family history is sometimes called early-onset sarcoidosis. The joint involvement is usually synovitis or tenosynovitis, sometimes causing camptodactyly (fixed flexion deformity of the proximal interphalangeal joint, usually most marked in the little finger). The rash is characteristically tan coloured and can be ichthyotic. Approximately a third of patients develop visual impairment from panuveitis and its complications. Other recognized features include fever, erythema nodosum, granulomatous hepatitis, and large vessel vasculitis. Fig. 12.12.2.2 Typical rash of mevalonate kinase deficiency. These lesions appear during febrile attacks. Fig. 12.12.2.3 Urticarial rash of Muckle-Wells syndrome. These lesions, accompanied by conjunctivitis, arthralgia, and fever, appeared daily in the early evenings.

12.12.2 Hereditary periodic fever syndromes 2215 Presentation is usually before the age of 5 years and is caused by missense mutations in NOD2/CARD15, another member of the death domain superfamily. NOD2 mutations have also been implicated in familial Crohn's disease but the gain-of-function mutations in Blau's syndrome occur in the NACTH domain whereas in Crohn's disease,

there are loss-of-function mutations in the LRR region. The NOD2 mutations associated with Blau's syndrome have not been found in adults with sarcoidosis. Most cases are steroid responsive but steroid-sparing agents and increasingly anti-TNF therapy may be required in more severe disease (Fig. 12.12.2.4). NALP12-associated periodic fever syndrome This autosomal dominant syndrome was described in 2008 in families from the Caribbean. Patients presented in infancy or the neonatal period with a syndrome with some features of cold induction, fever, arthralgia and myalgia, urticarial rash, and sensorineural deafness. The nonsense and splice site mutations identified in NALP12 appear to reduce its inhibitory effect on NF- κ B signalling. There is no established treatment. Deficiency of the IL-1 receptor antagonist (DIRA) This autosomal recessive disease was first described in 2009. It is due to mutations in the IL1RN gene that result in total deficiency of IL-1 receptor antagonist. The disease has been reported in only a handful of families of various ethnicities including Northern Europe and Central America. The disease presents in the immediate neonatal period with a pustular rash, joint swelling, multifocal osteitis of the ribs and long bones, heterotopic ossification, and periarticular soft tissue swelling. Treatment is replacement of the missing protein with recombinant IL-1Ra (anakinra), and good responses have been reported in all patients treated so far. Majeed's syndrome This autosomal recessive syndrome characterized by chronic recurrent multifocal osteomyelitis (CRMO), congenital dyserythropoietic anaemia, and inflammatory dermatosis was first described in 1989 in consanguineous Arab kindred. Onset is usually in the neonatal period and attacks consist of several days of fever, severe pain, and the appearance of periarticular soft tissue swelling. Long-term complications of growth retardation and flexion contractures are well recognized. The disease was found to be due to mutations in LPIN2, a widely expressed gene thought to play a role in lipid metabolism, in 2005. NSAIDs and corticosteroids can provide symptomatic relief. Recent case reports suggest IL-1 blockade may be effective although the long-term effect on dyserythropoiesis is not yet known Deficiency of interleukin-36 receptor

antagonist (DITRA) This rare disease is a recessively inherited autoinflammatory disease due to mutations in IL36RN resulting in unregulated signalling of IL-36 α , - β , and - γ . It is characterized by recurrent episodes of a generalized sterile pustular psoriasis accompanied with neutrophilia, a marked acute phase response, and fever. Age at onset varies from childhood to the sixth decade. Episodes may be precipitated by stress, pregnancy, or initiation or withdrawal of drugs and can be life-threatening. There is no established treatment but case reports suggest anakinra has been beneficial. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE syndrome) or proteasome-associated autoinflammatory syndrome (PRAAS), or joint contractures, muscular atrophy, microcytic anaemia, and panniculitis-induced lipodystrophy (JMP) This recessive disease is characterized by a neonatal onset of intermittent fevers, swollen violaceous eyelids, thickened lips, erythematous rash with a mixed myeloid, neutrophilic, and histiocytic infiltrate on skin biopsy, arthralgia/arthritis, and progressive lipodystrophy with later-onset joint contractures and raised acute phase response. Patients have been found to carry PSM8 mutations. This encodes an inducible subunit of the immune proteasome and deficiency is postulated to result in failure of proteolysis resulting in accumulation of damaged protein and intracellular stress. This appears to result in dysregulation of the interferon signalling pathway and early reports suggest treatment with Janus kinase inhibitors may be useful. IL-10 receptor deficiency This is also known as early-onset inflammatory bowel disease and presents with enterocolitis with perianal fistulae, recurrent fever, arthritis, and folliculitis in the first 3 months of life. It is a recessive disease caused by mutations in IL10RA, IL10RB, or IL10 resulting in decreased IL-10 signalling and macrophage activation. Conventional treatment of

inflammatory bowel disease is ineffective and bone marrow transplantation has been curative. Autoinflammation and PLC γ 2-associated antibody deficiency and immune dysregulation (APLAID) Only a single kindred is known with this autosomal dominant disease caused by gain-of-function mutations in PLCG2 which encodes phospholipase γ 2 (PLC γ 2). This enzyme is involved in several immunological pathways and in APLAID it may activate the NLRP3 inflammasome. Patients have low IgA and IgM and immunodeficiency with recurrent sinopulmonary infections. Autoinflammatory features include blistering rash, interstitial pneumonitis, ocular inflammation, and arthralgia. Deletions in Fig. 12.12.2.4 Camptodactyly due to Blau's syndrome.

section 12 Metabolic disorders 2216 PLCG2 are known to cause a different syndrome, PLC γ 2-associated antibody deficiency and immune dysregulation (PLAID) with an autoimmune phenotype. Haem-oxidized IRP2 ubiquitin ligase 1 deficiency (HOIL-1 deficiency) This fatal autosomal recessive disease has been reported in two families and is due to loss-of-function mutations in HOIL1 also known as RBCK. This encodes a component of the linear ubiquitin chain assembly complex, which adds polyubiquitin chains to substrate proteins and plays a role in NF- κ B induction. The phenotype is a combination of severe immunodeficiency and autoimmunity with recurrent fever, systemic inflammation, hepatosplenomegaly, and lymphadenopathy. The patients also developed amylopectinosis resulting in skeletal and cardiac myopathy. All four affected individuals died in childhood, corticosteroids were reported to be symptomatically helpful. Deficiency of ADA2 (DADA2) This was first described in 2014 as a monogenetic form of polyarteritis nodosa (PAN). It is a recessive disease caused by loss-of-function mutations in CECR1 encoding adenosine deaminase 2 (ADA2). ADA2 is thought to be a growth factor for endothelial cells as well as leucocytes and deficiency appears to induce an inflammatory vasculopathy. Clinical manifestations include childhood systemic and local PAN, recurrent fever, mild immunodeficiency, livedo racemose, and early-onset stroke. Treatment with anti-TNF agents has been reported to be effective and bone marrow transplantation has been reported to induce clinical benefit and improve ADA2 levels. A small study of fresh frozen plasma as a source of replacement ADA2 in acute attacks was not supportive. STING-associated vasculopathy with onset in infancy (SAVI) This autosomal dominant disease due to gain-of-function mutations in TMEM173 (encoding the stimulator of interferon genes (STING)) was first described in 2014 and results in increased interferon 1 signalling. Fewer than 20 patients are known and the disease is characterized by very early-onset facial and digital rash with scarring, cartilage destruction, and capillaritis on biopsy. Other features include failure to thrive, lymphadenopathy, fever, and interstitial lung disease. There is no proven treatment but treatment with Janus kinase inhibitors seems rational based on the apparent role of upregulated interferon signalling. Autoinflammatory diseases of unknown aetiology Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) First described in 1987, the diagnosis is suggested by a recurrent fever of early onset and one of the following associated symptoms: oral aphthous ulcers, cervical lymphadenopathy, or pharyngitis, in the absence of recurrent upper respiratory tract infections or cyclic neutropenia. Characteristically the children are entirely well between attacks. In a large case series, median age at presentation was 2.5 years and 83% of children presented before their fifth birthday with a slight male preponderance of 62%. The 'acronym symptoms' of aphthous oral ulcers, pharyngitis, and cervical lymphadenopathy are frequently not all present during a single attack. During attacks, the acute phase response is often strikingly elevated. In general the prognosis is good and most children will outgrow their symptoms within a decade. For many clinicians, the strongest diagnostic pointers are the extreme regularity of attacks (although attacks may be missed particularly in the

summer) and the response to a small dose of corticosteroids. Before diagnosis, recurrent infections and cyclic neutropenia must be excluded. The first-line treatment of PFAPA is a single dose of corticosteroid given at the start of the attack. Padeh et al. suggested that the dramatic response to a single oral dose of corticosteroids is sufficiently unique to PFAPA syndrome that it could be used as a diagnostic criterion. The H₂ receptor antagonist cimetidine and colchicine have been tried in PFAPA with variable reports of success. Tonsillectomy is the only treatment for which there is supportive evidence from clinical studies. Tonsillectomy can be curative in PFAPA; in general, more than 50% of children appear to have excellent long-term results. However, these data may be biased since many centres selectively refer children with persistently enlarged tonsils for surgery, and it is possible that responses may occur preferentially in this subgroup.

Schnitzler's syndrome This was first reported in 1974 and is characterized by a chronic urticarial-like rash, a monoclonal IgM (IgM kappa in 85%) gammopathy, and systemic inflammation usually presenting as fever. The median age at onset is 51 years and there is a slight male preponderance. The monoclonal protein appears central to the pathogenesis although the mechanism remains unclear. About a fifth of patients eventually progress to overt plasma cell malignancy.

Chemotherapy has been used in the past but does not appear to relieve the syndrome and should only be used for conventional haematological indications. The treatment of choice for Schnitzler's syndrome is IL-1 blockade which is highly effective. **Differential diagnosis of the hereditary periodic fever syndromes** These diseases have a broad differential diagnosis, particularly at first presentation, which is influenced by age and encompasses a vast spectrum of infectious, immune, and neoplastic disorders (Table 12.12.2.2). Conversely, symptoms such as fever, arthralgia, and rashes in a patient known to have a hereditary periodic fever syndrome may also result from an alternative intercurrent disorder. **Prognosis and complications** Although CINCA/NOMID can be sufficiently severe to cause death within the first few decades, life expectancy among most patients

12.12.2 Hereditary periodic fever syndromes 2217 with hereditary recurrent fever syndromes is relatively good, and excellent in those for whom there is now effective therapy. The most serious and life-threatening complication of these diseases generally is AA amyloidosis. AA amyloidosis This usually presents with proteinuric kidney dysfunction. AA amyloid fibrils are derived from the circulating acute phase protein serum amyloid A protein (SAA), which is synthesized by hepatocytes under the transcriptional regulation of IL-1, IL-6, and TNF α . The terminology is either serum amyloid A protein or SAA. The circulating concentration of SAA in health is less than approximately 3 mg/litre, but this can rise by up to 1000-fold in the presence of inflammation. In chronic inflammatory diseases generally, AA amyloidosis occurs in up to 5% of patients after a median duration of about 20 years, but is much more frequent among patients with untreated inherited periodic fever syndromes. This may reflect their lifelong nature and their capacity to stimulate remarkably high plasma concentrations of SAA, even when they seem clinically quiescent. Before the widespread introduction of colchicine prophylaxis, up to 60% of patients with FMF died of amyloidosis, and even recently it was reported in 13% of a large Turkish series. The incidence of AA amyloidosis in TRAPS and MWS is approximately 25%, but is less than 5% in MDK, perhaps because the disease often ameliorates in early adulthood. The natural course of AA amyloidosis is renal failure and early death, but this can be prevented by treatment of the underlying inflammatory disorder that substantially suppresses the production of serum amyloid A. Indeed, treatment such as colchicine in FMF and anakinra in CAPS can halt further deposition of AA amyloid, facilitate gradual regression of existing deposits, and lead to preservation or even improvement in renal function. Regular long-term measurement of serum amyloid A is vital in

patients with AA amyloidosis. Likely future developments The recent elucidation of the pathogenesis of these diseases has led to major advances in their treatment, most notably in CAPS. It is likely that continued studies will shed further light on aspects of the innate immune system and inflammation generally, and on strategies for the treatment of TRAPS and MKD in particular. The clinical significance of low-penetrance mutations and polymorphisms in the genes associated with inherited periodic fever syndromes will be sought. CAPS provides a powerful model of IL-1-driven disease, and a uniquely informative test bed for the early-phase development of novel IL-1 inhibitors that may have applications in many common inflammatory disorders, ranging from gout and rheumatoid arthritis to sepsis.

FURTHER READING Ben-Chetrit E, Levy M (2003). Reproductive system in familial Mediterranean fever: an overview. *Ann Rheum Dis*, 62, 916–19. Canna SW, Goldbach-Mansky R (2015). New monogenic auto inflammatory diseases—a clinical overview. *Semin Immunol*, 37, 387–94. Cowen EW, Goldbach-Mansky R (2012). DIRA, DITRA, and new insights into pathways of skin inflammation: what’s in a name? *Arch Dermatol*, 148, 381–4. Goldbach-Mansky R, et al. (2006). Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. *N Engl J Med*, 355, 581–92. Holzinger D, et al. (2015). From bench to bedside and back again: translational research in autoinflammation. *Nat Rev Rheumatol*, 10, 573–85. Lachmann HJ, et al. (2007). Natural history and outcome in systemic AA amyloidosis. *N Engl J Med*, 356, 2361–71. Lachmann HJ, et al. (2014). The phenotype of TNF receptor-associated autoinflammatory syndrome (TRAPS) at presentation: a series of 158 cases from the Eurofever/EUROTRAPS international registry. *Arthritis Rheum*, 73, 2160–7.

Table 12.12.2.2 Differential diagnosis of inherited periodic fever syndromes

Abdominal pain and fever	Thoracic pain and fever	Arthritis and fever	Fever, rash, and myalgia
Nonhereditary periodic fever syndromes	Acute surgical abdomen	Myocardial infarction	Septic arthritis
Viral illness	PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenopathy)	Acute cholecystitis	Pneumonia/pleurisy
Juvenile idiopathic arthritis	Systemic lupus erythematosus	Schnitzler’s syndrome	Pyelonephritis
Pericarditis	Rheumatic fever	Cellulitis/erysipelas	Pelvic inflammatory disease
Pulmonary embolism	Lyme disease	Behçet’s disease	Endometriosis
Palindromic arthritis	Cyclic neutropenia	Mesenteric adenitis	Crystalline arthritis (gout) and calcium pyrophosphate dihydrate crystal deposition disease
Malignancy	Systemic vasculitis	Adult-onset Stills disease and systemic-onset juvenile idiopathic arthritis	Dermatomyositis
Hereditary or acquired angio-oedema (not associated with fever)	Adult-onset Stills disease and systemic-onset juvenile idiopathic arthritis		

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