# The Spectrum of Monogenic Autoinflammatory Syndromes: Understanding Disease Mechanisms and Use of Targeted Therapies

*Rachel L. Glaser, MD, and Raphaela Goldbach-Mansky, MD, MHS*

**Corresponding author**
Raphaela Goldbach-Mansky, MD, MHS
National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health Building 10, Room 6N-216A, 10 Center Drive, Bethesda, MD 20892, USA.
E-mail: goldbacr@mail.nih.gov

**Current Allergy and Asthma Reports** 2008, **8:**288–298
Current Medicine Group LLC ISSN 1529-7322


Monogenic autoinflammatory diseases encompass a distinct and growing clinical entity of multisystem inflammatory diseases with known genetic defects in the innate immune system. The diseases present clinically with episodes of seemingly unprovoked inflammation (fever, rashes, and elevation of acute phase reactants). Understanding the genetics has led to discovery of new molecules involved in recognizing exogenous and endogenous danger signals, and the inflammatory response to these stimuli. These advances have furthered understanding of innate inflammatory pathways and spurred collaborative research in rheumatology and infectious diseases. The pivotal roles of interleukin (IL)-1β in cryopyrin-associated periodic syndromes, tumor necrosis factor (TNF) in TNF receptor-associated periodic syndrome, and links to inflammatory cytokine dysregulation in other monogenic autoinflammatory diseases have resulted in effective therapies targeting proinflammatory cytokines IL-1β and TNF and uncovered other new potential targets for anti-inflammatory therapies.

## Introduction

Discovery of mutations in the previously unknown gene, *MEFV*, as the cause of familial Mediterranean fever (FMF) in 1997, spearheaded an era of new gene discovery leading to the identification of novel inflammatory pathways [1,2]. Over the past 10 years, a poorly characterized category of periodic fever syndromes developed into a series of success stories by new technologies of molecular genetics and cell biology. Facilitated by the Human Genome Project, single-gene defects associated with several periodic fever syndromes were identified over the ensuing 5 years from 1997 to 2002. In 1999, mutations in the tumor necrosis factor (TNF) receptor 1, *TNFRSF1A*, were demonstrated in families with the dominantly inherited TNF receptor–associated periodic syndrome (TRAPS) [3]. Shortly thereafter, two groups in the Netherlands independently described mutations in the mevalonate kinase gene in hyperimmunoglobulin D syndrome (HIDS) [4,5]. In 2001 and 2002, defects in cryopyrin were found to cause familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID) (also called chronic infantile neurologic, cutaneous, and arthritis [CINCA] syndrome) [6–8].

Discovery of genetic causes for pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) [9], Blau syndrome [10], early-onset sarcoidosis [11•], and Majeed syndrome [12•] led to their recognition as monogenic autoinflammatory syndromes and expanded the spectrum to include diseases in which fever is uncommon. Table 1 lists the currently recognized monogenic autoinflammatory disorders, clinical features, and genetic bases.

## Clinical Presentations and Genetics of Monogenic Autoinflammatory Diseases

### Familial Mediterranean fever

*Clinical presentation*

FMF is the most common periodic fever syndrome and affects more than 100,000 people worldwide [13]. FMF is most prevalent in ethnic groups around the Mediterranean Sea including Sephardic Jews, Armenians, North Africans, Italians, and Turks, but has been described in other ethnic groups, including Japanese and Ashkenazi Jews. FMF most commonly presents with 1- to 3-day episodes of fever, serositis, and arthralgia or arthritis. Erysipeloid erythema, particularly on the extensor

**Table 1. Clinical and genetic features of the monogenic autoinflammatory diseases**

| Disease | Historical description | Clinical features/manifestations | | | | | Gene | Protein | Inheritance pattern |
|---|---|---|---|---|---|---|---|---|---|
| | | Flare/fever pattern | Skin | Ocular | Musculoskeletal | Distinguishing features | | | |
| FMF (MIM 249100) | 1945 | 1–3 d | Erysipeloid erythema of lower extremity | Rare | Arthralgia, oligoarthritis, myalgia | Serosal inflammation, amyloidosis | *MEFV* (16p13) | Pyrin | Autosomal recessive |
| TRAPS (MIM 191190) | 1982 | 1–4 wk | Migratory rash | Conjunctivitis, periorbital edema | Arthralgia, arthritis | Serosal inflammation, amyloidosis | *TNFRSF1A* (12p13) | Tumor necrosis factor receptor 1 | Autosomal dominant |
| CAPS: | | | | | | | | | |
| FCAS (MIM 120100) | 1940 | < 24 h | Cold-induced urticaria | Conjunctivitis | Arthralgia | | *CIAS1* (1q44) Exon 3 | Cryopyrin | Autosomal dominant |
| MWS (MIM 191900) | 1961 | 2–3 d to continuous | Urticarial rash | Conjunctivitis, episcleritis | Arthralgia | Sensorineural hearing loss, amyloidosis (30%) | *CIAS1* (1q44) Exon 3 | Cryopyrin | Autosomal dominant |
| NOMID (MIM 607115) | 1975 | Continuous with flares | Urticarial rash | Conjunctivitis, episcleritis, uveitis, papilledema | Arthralgia, arthropathy secondary to osseous overgrowth | Chronic meningitis, sensorineural hearing loss; characteristic facies, amyloidosis (rare) | *CIAS1* (1q44) Exon 3 | Cryopyrin | Autosomal dominant/ de novo |
| HIDS (MIM 260920) | 1984 | 4–7 days | Erythema macular rash | Rare | Arthralgia | Some with elevated IgD, diarrhea, lymphadenopathy | *MVK* (12q24) | Mevalonate kinase | Autosomal recessive |
| PGA* (MIM 186580) | 1985 | Continuous with flares/remission | Erythematous or tan scaly rash | Panuveitis | Granulomatous polyarthritis | Camptodactyly | *NOD2* (16q12) | Nod2 | Autosomal dominant |
| PAPA (MIM 604416) | 1997 | Weeks-months | Cystic acne, pyoderma gangrenosum | None | Sterile neutrophilic arthritis | | *CD2BP1* (15q24) | Pstpip1 | Autosomal dominant |
| Majeed's syndrome (MIM 609628) | 1989 | Variable | | | Bone pain, osteitis | Cultures negative, organomegaly, microcytic anemia | *LPIN2* (18p11) | Lipin2 | Autosomal recessive |

*Including Blau syndrome (MIM 186580) and early-onset sarcoidosis (MIM 609464).
CAPS—cryopyrin-associated periodic syndromes; FCAS—familial cold autoinflammatory syndrome; FMF—familial Mediterranean fever; HIDS—hyperimmunoglobulin D syndrome; MIM—Mendelian Inheritance in Man number; MWS—Muckle-Wells syndrome; NOMID—neonatal-onset multisystem inflammatory disease; PAPA—pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PGA—pediatric granulomatous arthritis; TRAPS—tumor necrosis factor receptor–associated periodic syndrome.

surfaces of the lower extremities, may also be present. Patients are typically asymptomatic between attacks; however, elevations in inflammatory markers (leukocyte count, sedimentation rate, C-reactive protein, and serum amyloid A) may persist. Prolonged elevated serum amyloid A levels can lead to amyloid deposition, primarily in the kidneys, which is present in 11.4% of patients with FMF and associated with kidney failure [14•]. A threefold higher risk of developing amyloidosis is conferred by living in Armenia, Turkey, and other Arab countries. Other risk factors include homozygosity for the *M694V* mutation, presence of the serum amyloid A1 alpha allele, and disease duration [14•,15].

*Genetics*

FMF is caused by mutations in the *MEFV* gene on chromosome 16p13, which encodes the protein pyrin, also known as marenostrin. Forty-nine mutations in the *MEFV* gene have been associated with clinical symptoms of FMF [16]. Although FMF is inherited in an autosomal recessive mode, patients with only a single mutation, and a few patients with clinical FMF without genetic mutations, have been described [4]. Several genetic variants, including E148Q, are present in pyrin; however, whether these variants constitute functional polymorphisms of FMF or have a proinflammatory role in other diseases is not yet known [17].

*Pathophysiology*

*MEFV* encodes the protein pyrin, which is composed of a PYRIN, B-box, coiled-coiled, and B30.2 (PRYSPRY) domain. The role of mutated pyrin in FMF is not fully understood; however, increased interleukin (IL)-1 secretion is observed in a murine pyrin-knockout model. Transfection of wild-type murine pyrin into murine monocytes suppresses IL-1β [18]. These observations led to the notion that pyrin has an anti-inflammatory role. This is further supported by in vitro studies demonstrating that pyrin interacts with the NALP3 inflammasome, a molecular complex containing cryopyrin and the adaptor proteins ASC (apoptotic speck-like protein with a caspase recruitment domain) and CARDINAL, and two pro-caspase-1 molecules. The assembly of the NALP3 inflammasome leads to caspase-1–mediated activation and release of the proinflammatory cytokine and pyrogen, IL-1β (Fig. 1) [19]. Pyrin's binding to ASC may lead to sequestration of ASC and may prevent formation of a functional NALP3 inflammasome complex. Pyrin can also bind to caspase-1 directly and inhibit its ability to cleave pro–IL-1β into its biologically active form [20•].

Many of the *MEFV* mutations have been found in the caspase binding area of the B30.2 or PRYSPRY domain, and lead to decreased pyrin binding to ASC. Because ASC is not sequestered, it can assemble with cryopyrin, and activate the NALP3 inflammasome to secrete proinflammatory cytokines.

Although most evidence currently suggests that wild-type pyrin has an anti-inflammatory effect, a recent transfection model suggests that in certain in vitro conditions, wild-type protein may be proinflammatory by forming an IL-1β–activating platform similar to the NALP3 inflammasome [21•]. Although the relevance of the latter model in human disease remains to be determined, the changing role of pyrin may depend on its cellular context.

*Treatment*

Colchicine decreases the frequency of FMF attacks. Prophylactic colchicine therapy leads to complete remission or significant improvement in 85% of patients with FMF, and it prevents amyloidosis [22]. In case reports and small series of patients in whom colchicine is not tolerated or is ineffective, thalidomide, etanercept, and anakinra have been shown to decrease inflammation markers and frequency of attacks [22].

### TNF receptor–associated periodic syndrome

*Clinical presentation*

Febrile attacks associated with abdominal pain, pleuritis, myalgia, arthritis, and rash are characteristic of TRAPS. This syndrome was originally described as familial Hibernian fever in an Irish/Scottish family with symptoms similar to FMF; however, unlike FMF, the disease exhibits a dominant inheritance pattern and response to steroids [23]. Contrary to initial assumptions, TRAPS is prevalent in diverse ethnic populations. Attacks are usually more protracted than those seen in FMF, lasting 1 to 4 weeks. The myalgia typically migrates centrifugally out to the distal extremities, and the accompanying rash is caused by a monocytic fasciitis [24].

*Genetics*

The disease was renamed "tumor necrosis factor receptor–associated periodic syndrome" in 1999 to indicate that it is caused by autosomal dominant mutations of the *TNFRSF1A* gene located on chromosome 12p13, which encodes the TNF receptor type 1 (TNFR1, p55 receptor). Forty-six mutations, most of which are cysteine substitutions in the extracellular domain of the TNF receptor, have been described in patients with clinical disease [16]. Mutations resulting in loss of a cysteine residue correlate with clinically more severe disease and a higher risk of amyloidosis [24]. Several mechanisms leading to the proinflammatory role of the TNF receptor mutations have been described.

*Pathophysiology*

Wild-type TNFR1 is transported to the cell surface, where it complexes upon TNF binding to form active signaling units. TNFR1 can be cleaved from the cell surface, leading to decreased cell surface binding sites and increased buffering of unbound soluble TNF. Mutations in the TNFR1 receptor lead to decreased binding of TNF to the mutated receptor and decreased receptor signaling, which has created controversy in explaining the proinflammatory effect

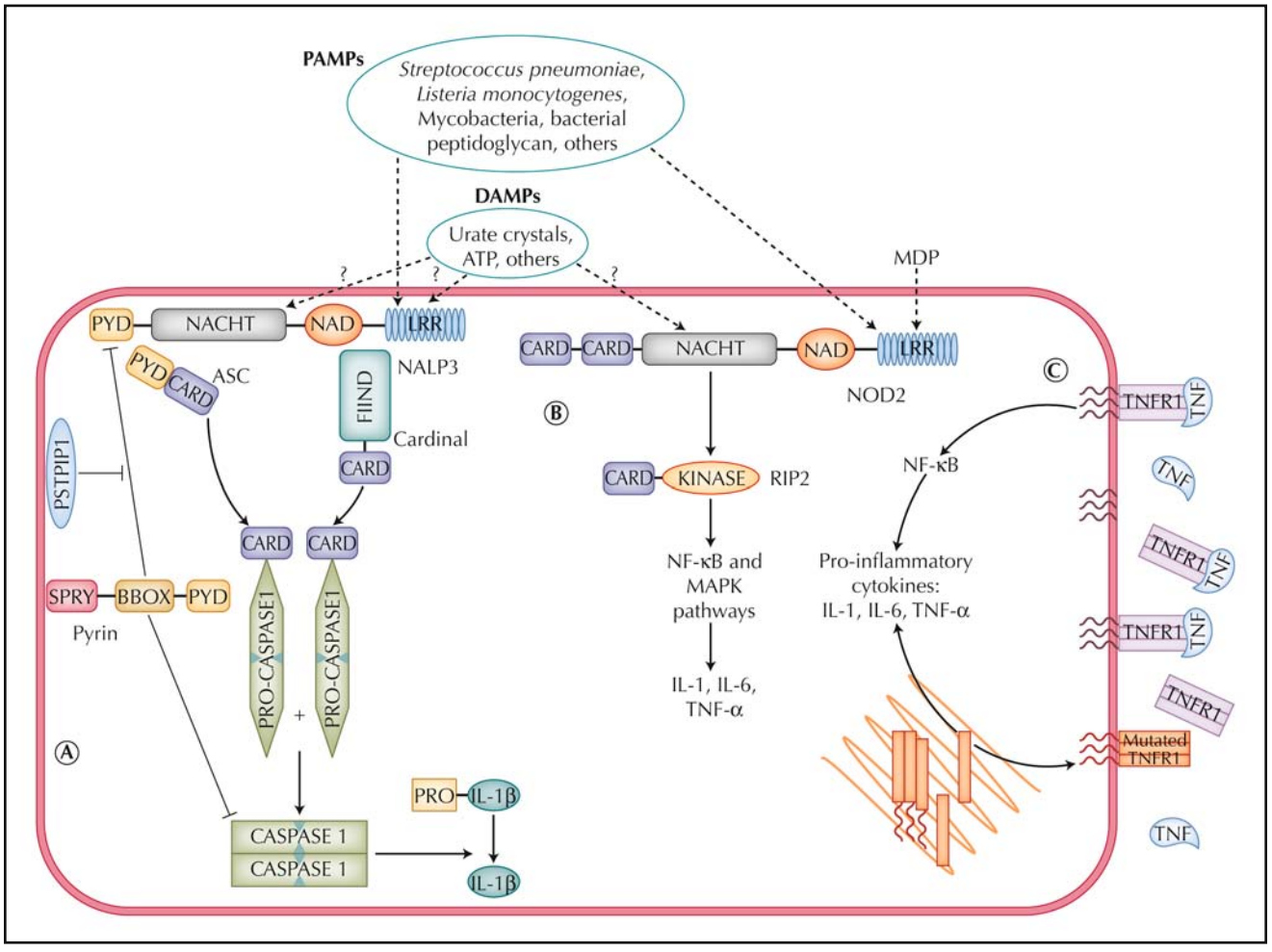


**Figure 1.** Proposed mechanisms of activation of proinflammatory signaling pathways in cryopyrin-associated periodic syndromes (CAPS); familial Mediterranean fever (FMF); pediatric granulomatous arthritis (PGA); pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome; and tumor necrosis factor (TNF) receptor–associated periodic syndrome (TRAPS). **A**, Unlike wild-type NALP3, mutated NALP3 (which causes CAPS) is constitutively activated and thought to oligomerize and bind to adaptor molecules ASC and CARDINAL to form an active catalytic complex with two pro–caspase-1 molecules. Via autocatalysis, this complex generates active caspase-1, which cleaves inactive pro–interleukin (IL)-1β to its active form, IL-1β. Wild-type pyrin can inhibit inflammasome activation by sequestration of ASC or by direct binding to caspase-1. Mutated pyrin (which causes FMF) cannot exert its inhibitory effect on the inflammasome, leading to unopposed inflammasome activation. Wild-type PSTPIP1, another regulatory molecule of the NALP3 inflammasome, binds to pyrin. Mutated PSTPIP1 (which causes PAPA) cannot dissociate from its binding to pyrin, leading to uninhibited inflammasome activity. **B**, Bacterial peptidoglycans stimulate the NOD2 inflammasome. RIP2 is recruited, leading to activation of nuclear factor (NF)-κB and mitogen-activated protein kinase (MAPK) signaling pathways. Mutations in the NACHT domain (which cause PGA) lead to presumed autoactivation of NOD2 and constitutive activation of NF-κB and proinflammatory cytokines. **C**, TNFR1 molecules are transported from endoplasmic reticulum (ER) to the Golgi and then to the cell surface. Wild-type TNFR1 complexes are bound to extracellular TNF, leading to NF-κB activation. Receptor cleavage from the cell surface abrogates receptor signaling, and the soluble receptor can buffer soluble TNF. Mutated TNFR1 (which causes TRAPS) is misfolded and cannot be transported to the cell surface. Misfolded TNFR1 is sequestered in the ER, where it may lead to abnormal signaling.

of TNFR1 mutations. Early results in patients with TRAPS showed reduced shedding of mutated TNF receptor from the cell surface after activation, resulting in decreased plasma levels of soluble TNFR1 [3,25•]. This supported the hypothesis of increased wild-type receptor signaling and reduced buffering of free TNF. Because the shedding defect is not seen universally in patients with TRAPS, alternative mechanisms were sought. Recent data indicate that misfolding of the mutated receptor is a common finding. The misfolded protein aggregates in the endoplasmic reticulum, and cannot be transported to the cell surface, which may cause ligand-independent TNFR1 signaling through formation of intracellular signaling complexes and lead to induction of proinflammatory cytokines and other inflammatory pathways [25•].

*Treatment*

Corticosteroids, although effective in treating the symptoms of TRAPS, are associated with significant long-term side effects. Colchicine is better tolerated, but generally ineffective. Several small studies or case reports have shown that the TNF inhibitor etanercept decreases the

frequency, intensity, and duration of flares and has been used to improve renal amyloid A (AA) amyloidosis in patients with nephrotic syndrome [26]. Treatment with the IL-1 receptor antagonist anakinra, an IL-1 signaling blocker, has also shown clinical benefit [27].

**Cryopyrin-associated periodic syndromes**

*Clinical presentation*

The cryopyrin-associated periodic syndromes (CAPS)—which include FCAS, MWS, and NOMID—present with episodes of fever, urticarial rash, and elevations in acute phase reactants, but differ in the spectrum of multiorgan disease manifestations and in long-term morbidity and mortality. Patients with MWS or NOMID typically present with an urticarial rash at birth, whereas the first manifestations of FCAS may present later in life.

FCAS was first described in a young woman with a lifelong history of urticarial eruption that occurred after 30 minutes of cold exposure and was accompanied by fever, chills, and joint stiffness, which resolved 6 to 48 hours later. Similar symptoms occurred in 23 of 47 relatives of both genders [28]. Cold-induced episodes of inflammation may also present with conjunctivitis and headaches. Although patients suffer from these attacks, in most cases long-term outcome is favorable and amyloidosis is rarely reported.

In MWS, episodes of fever, urticarial rash, and arthritis are continuous and, in most instances, are not provoked by cold. The original reports of a family with MWS described nine members with "aguey bouts" and an urticarialike rash, with progressive perceptive hearing loss and nephropathy [29]. Conjunctivitis, episcleritis, and optic disc edema are also seen; in a European cohort, amyloidosis was reported in up to 25% of patients [30].

NOMID was first described in two siblings with a continuous rash from birth, lymphadenopathy, uveitis, and mental retardation [31]. This was followed by the definition of the disease as CINCA syndrome in three unrelated children with symptoms similar to those previously reported. In addition, abnormal bony overgrowth of the knees and chronic meningitis were seen [32]. The characteristic arthropathy is caused by uncontrolled overgrowth of the patella and epiphyses of the long bones, and presents in up to 60% of patients [33]. Disability in patients with NOMID is caused by joint contractures at affected sites, but most devastating are the central nervous system (CNS) manifestations, which include chronic aseptic meningitis, increased intracranial pressure, ventriculomegaly, cerebral atrophy, seizures, and mental retardation. Sensorineural hearing loss develops in most patients in childhood, and progressive vision loss can be a consequence of optic nerve atrophy caused by chronically increased intracranial pressures [34•,35•,36]. Other findings include short stature, frontal bossing of the skull, and rarely, flattening of the nasal bridge. If untreated, the reported mortality is 20% before adulthood [36].

*Genetics*

Although originally described as separate disease entities, the discovery of autosomal dominant mutations in the same gene, *CIAS1* (also *NLRP3, NALP3,* or *PYPAF1*), which is located on chromosome 1q44 and encodes the protein cryopyrin, led to the recognition that these diseases form a clinical spectrum, with NOMID having the most severe phenotype and FCAS the mildest [6,37]. More than 50 missense mutations in exon 3 of *CIAS1* have been identified [16]. Most of the FCAS cases described share an ancestral haplotype that carries a single heterozygous missense mutation, L353P in exon 3 of *CIAS1*, suggesting a founder effect of this mutation [38]. Most of the reported patients with FCAS and MWS have *CIAS1* mutations, whereas disease occurs sporadically in patients with NOMID. De novo cryopyrin mutations are found in only 50% of patients with clinical disease [6], but patients with and without *CIAS1* mutations have similar clinical phenotypes and respond equally well to IL-1 blockade [35•]. A subset of patients, who were *CIAS1* mutation negative when typed by standard DNA sequencing methods, had somatic *CIAS1* mutations in peripheral blood cells when molecular cloning techniques were used [39].

Although phenotype/genotype correlations cannot be understood on a structural basis because FCAS, MWS, and NOMID mutations are seen in the same cluster positions on the gene, some mutations are associated with mild and others with severe clinical phenotypes. Three *CIAS1* mutations have been associated with more than one disorder: R260W with both MWS and FCAS; D303N with MWS and NOMID; and T436I with FCAS and NOMID [7,35•,40]. Few mutations, such as R488K, are found in unaffected relatives, suggesting incomplete penetrance in only rare cases [34•].

*Pathophysiology*

Cryopyrin has three structural domains (Fig. 1). The leucine-rich repeat (LRR) domain is found on Toll-like receptors that bind to extracellular microbial triggers [41]. The NACHT/NACHT-associated domain (NAD) and LRR domain are found in related receptors recently characterized as the NOD-like receptor (NLR) family, whose role in sensing exogenous and endogenous "danger signals" is emerging. Cryopyrin shares the PYRIN domain with pyrin, the protein mutated in patients with FMF.

Upon stimulation with bacterial triggers and molecules released during cell injury or stress (adenosine triphosphate and uric acid), the cryopyrin or NALP3 inflammasome activates the enzyme caspase-1 that cleaves the proinflammatory cytokine IL-1β into its active form [42•]. The inflammasome containing wild-type cryopyrin is autoinhibited by a putative conformational interaction between the LRR domain and the NACHT domain. The majority of *CIAS1* mutations are thought to disrupt the inactive closed ring conformation of wild-type cryopyrin and facilitate oligomerization of cryopyrin [34•] and inflammasome activation (Fig. 1).

The hypothesis of constitutive inflammasome activation in patients with CAPS could explain the high IL-1β levels measured in unstimulated peripheral blood mononuclear cells from patients with CAPS as compared with controls [35•]. Mutations in cryopyrin have been associated with activation of nuclear factor (NF)-κB and macrophage necrosis in in vitro models [43,44]. The role of these pathways in clinical disease needs to be determined.

*Treatment*

Although several reports using disease-modifying antirheumatic drugs, including TNF inhibitors, indicated partial responses to these treatments [35•], the impressive clinical results with IL-1–blocking agents in patients with FCAS, MWS, and NOMID have clearly linked these diseases to IL-1β overproduction and instituted IL-1 blockade as the treatment of choice for CAPS. Anakinra, a recombinant IL-1 receptor antagonist approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, competitively inhibits binding of IL-1α and IL-1β to the IL-1 receptor type 1. Within hours of administration of anakinra to patients with CAPS, the rash disappears, and inflammatory markers, including C-reactive protein and serum amyloid A levels, drop rapidly [35•,45•,46,47]. In NOMID, the effect of IL-1 blockade extends to the CNS manifestations. Reduced intracranial pressure, pleocytosis, and cerebrospinal fluid protein are observed with treatment, and hearing loss is stabilized [35•]. Although bony lesions seen in patients with NOMID continue to grow in children with open growth plates, the development of new lesions has not been observed with treatment [33]. More recently, the FDA approved rilonacept, a fusion protein of the extracellular IL-1 receptor 1 and the IL-1 receptor accessory protein linked to the Fc portion of human IgG1, which also acts as an IL-1 inhibitor in the treatment of CAPS. In a double-blind randomized trial, rilonacept, 160 mg, administered weekly rapidly suppressed clinical symptoms and normalized laboratory markers of inflammation in patients with FCAS and MWS for 24 weeks [48•]. In five patients, the response was durable for up to 2 years, and the drug was well tolerated at doses up to 320 mg/wk [49].

## Hyperimmunoglobulin-D syndrome

*Clinical presentation*

HIDS was first described in 1984. It is an autosomal recessive disorder characterized by episodes of fever, rash, abdominal pain, and arthralgia or arthritis, typically of large joints. Marked lymphadenopathy and splenomegaly help to distinguish HIDS from FMF clinically. Most patients with HIDS are of Western European (particularly Danish and French) ancestry, suggesting a founder gene effect in these populations [4]. Febrile episodes can occur spontaneously or following vaccinations, trauma, or stress. They last several days and recur every 4 to 8 weeks. Patients may have elevated urine mevalonic acid levels during attacks, and elevated serum IgD and IgA levels both during and between attacks. Despite the name, patients may have normal serum IgD levels, particularly those younger than 3 years of age [4].

When HIDS was found to be caused by mutations in the mevalonate kinase gene, it was recognized that defects in this gene were already known to cause mevalonic aciduria, a "classic" metabolic disorder. Similar to HIDS, patients with mevalonic aciduria present with febrile episodes and systemic inflammation, but other features include developmental delay, facial dysmorphism, ataxia, hypotonia, myopathy, cataracts, and failure to thrive, which can contribute to significant morbidity [4]. Both diseases represent different phenotypes along a spectrum of increasing severity.

*Genetics*

Sixty-two mutations associated with the HIDS phenotype and 15 with the mevalonic aciduria phenotype have been described in the mevalonate kinase gene on chromosome 12, which encodes mevalonate kinase, an enzyme involved in the cholesterol biosynthesis pathway [16]. The disease spectrum is inherited in an autosomal recessive fashion and most patients carry two missense mutations. V377I is the most common mutation in patients with HIDS, present in 80% of patients, followed by mutations in I268T [4,50].

*Pathophysiology*

In the cholesterol biosynthesis pathway, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the enzyme targeted by statin drugs, converts HMG-CoA to mevalonate, which then undergoes phosphorylation to mevalonate phosphate. Conversion from mevalonate to mevalonate phosphate by the enzyme mevalonate kinase is the rate-limiting step. End products of this pathway include cholesterol and several compounds known as isoprenoids, which include ubiquinone-10, dolichol, isopentenyl transfer RNA, and other isoprenylated proteins that participate in cellular processes related to cell growth and differentiation, cytoskeletal function, and vesicle trafficking [51].

Mevalonate kinase mutations create a block in the pathway, preventing the conversion to mevalonate phosphate. The lack of negative feedback by end products downstream in the pathway leads to an increase in HMG-CoA reductase activity with accumulation of mevalonate in serum and tissues, and increased urinary excretion of mevalonate [4,52•]. Severity of the clinical phenotype correlates with residual mevalonate kinase activity; patients with mevalonic aciduria have no kinase activity, but in patients with HIDS, kinase activity decreases to 1% to 10% of that seen in unaffected individuals [52•]. In an in vitro model with peripheral blood mononuclear cells from patients with HIDS, the shortage of isoprenoid end products, but not the excess of mevalonate, contributed to increased IL-1β production [53]. The search for pathways linking the enzymatic defect to inflammation is the subject of ongoing research.

*Treatment*
NSAIDs are administered for fever and arthralgia. Short courses of corticosteroids may be effective in some patients, but colchicine is generally not. Based on the assumption that mevalonate accumulation is pathogenic, simvastatin, an HMG-CoA reductase inhibitor, was given to six patients, of whom five had a nonstatistically significant decrease in number of febrile days [54]. Treatment with etanercept has also yielded variable results [55–57]. The successful treatment of a small case series of patients with HIDS with IL-1 inhibition lends support to its role in the pathophysiology [55]. Lastly, leukotriene inhibitors are used in some centers, but clinical studies have not been performed. Further research is needed to determine optimal treatment for HIDS.

**Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome**
*Clinical presentation*
PAPA is a rare dominantly inherited disorder characterized by skin lesions and variable expression of pauciarticular, nonaxial, erosive corticosteroid-responsive arthritis with recurrent sterile effusions. It was first described in 1997 [58], and five affected families have subsequently been identified. Skin manifestations are severe cystic acne, pyoderma gangrenosum, and sterile abscess formation at injection sites. Less common features include adult-onset insulin-dependent diabetes mellitus and proteinuria. Similar to other autoinflammatory diseases, a nonspecific predominantly neutrophilic infiltrate is found in the inflammatory lesions of PAPA.

*Genetics*
Missense mutations have been identified in the *PSTPIP1* gene (also known as CD2 binding protein 1) on chromosome 15q24. To date, four gain-of-function mutations have been associated with clinical disease [16].

*Pathophysiology*
Wild-type dephosphorylated PSTPIP1 can bind to pyrin, the protein central to the pathogenesis of FMF, thought to prevent pyrin's anti-inflammatory effect on the NALP3 inflammasome. PSTPIP1 undergoes phosphorylation by PTP-PEST, a protein tyrosine phosphatase that inhibits its ability to bind to pyrin (Fig. 1). Mutations in PSTPIP1 prevent its phosphorylation and lead to a prolonged pyrin and mutated PSTPIP1 complex formation. This complex prevents the inhibitory function of pyrin on the NALP3 inflammasome, with a presumed net effect of increased IL-1β production and inflammation [21•,59].

In an alternative model, mutated PSTPIP1 may increase pyrin's proinflammatory role through a conformational change enabling pyrin to oligomerize with adaptor proteins that lead to increased production of IL-1β [21•]. Although the clinical relevance of these models remains to be explored, both models link the PAPA-causing mutations in *PSTPIP1* to excessive IL-1β production, and suggest the possibility of effective therapy with an IL-1 inhibitor.

*Treatment*
Intra-articular and oral glucocorticoids have been effective in treating the joint and skin manifestations of PAPA, but some initially responsive patients become refractory. There are promising case reports of benefit from more targeted therapy with TNF inhibitors or the IL-1 receptor antagonist, anakinra [60].

**Pediatric granulomatous arthritis**
*Clinical presentation*
Pediatric granulomatous arthritis (PGA) is the term now applied to the syndromes formerly described as Blau syndrome, a familial form of granulomatous disease, and early-onset sarcoidosis, a sporadic form [61•]. PGA is a chronic granulomatous disease of the skin, eyes, and joints, first described in 1985 [62]. It affects young children of both genders without ethnic or racial predilection [63]. Patients typically present before age 4 with a tan, scaly ichthyosiform rash and symmetric polyarticular arthritis or tenosynovitis. Ocular findings, including recurrent bilateral uveitis, conjunctivitis, synechiae, cataracts, and glaucoma, may be seen later in the disease course. In one series, 88% of affected patients displayed the classic dermatitis, whereas 41% had severe visual impairment [61•]. Noncaseating granulomas are present on synovial and skin biopsies, and in the liver. Other features include camptodactyly, fever, and cranial neuropathies [64•]. Persistent leukocytosis, thrombocytosis, and elevated inflammatory markers may be present. Large-vessel vasculitis is a rare manifestation.

*Genetics*
PGA is caused by autosomal dominant missense mutations in the NACHT domain of the *NOD2* or *CARD15* gene, located on chromosome 16. *NOD2* encodes the cytosolic protein, NOD2, a member of the pathogen recognition receptors—the NLRs. NOD2 is highly expressed on monocytes, macrophages, and in intestinal Paneth cells [64•]. Twelve mutations have been reported in patients with Blau syndrome or early-onset sarcoidosis [16]. Mutations in *NOD2* are found in 50% to 90% of patients with the triad of arthritis, dermatitis, and uveitis [61•]. All mutations identified suggest complete penetrance [61•,64•]. Variants in the LRR domain of *NOD2* have also been associated with a subset of patients with Crohn's disease, a granulomatous disease affecting the bowel.

*Pathophysiology*
NOD2 functions as an intracellular sensor triggered by peptidoglycan components from the cell wall of gram-positive and gram-negative bacteria, such as muramyl dipeptide. NOD2 activation results in complex, incompletely characterized downstream responses. These include activation of NF-κB and mitogen-activated

protein kinase signaling pathways that upregulate levels of antimicrobial peptides, proinflammatory cytokines, and chemokines, which recruit immune cells to the sites of microbial invasion. Similar to the loss of autoinhibition caused by mutations in cryopyrin, mutations in the NACHT domain of NOD2 are postulated to cause constitutive activation of the NOD2 inflammasome. Mutations in the pathogen-sensing LRR domain seen in Crohn's disease are thought to be associated with impaired recognition of bacterial pathogens; how these mutations lead to granulomatous inflammation is currently under investigation.

*Treatment*

Less severely affected patients respond to NSAIDs, whereas more significant manifestations require systemic corticosteroid therapy. Other treatment regimens include methotrexate, cyclosporine, and etanercept [64•]. Ocular disease can be more difficult to treat, and worsening of uveitis has been reported in patients treated with infliximab [63]. Anakinra has improved symptoms and decreased plasma cytokine levels in case reports, suggesting a possible relationship with IL-1β [64•].

### Majeed syndrome: a monogenic form of chronic recurrent multifocal osteomyelitis?

*Clinical presentation*

Majeed syndrome was first described in 1989 as a severe infantile form of chronic recurrent multifocal osteomyelitis (CRMO) in a family of consanguineous parents in two brothers and a female cousin. The patients presented with chronic recurrent multifocal osteomyelitis, neutrophilic dermatosis, and congenital dyserythropoietic anemia not seen in other CRMO presentations. Skin manifestations in the original report were Sweet syndrome; however, psoriasis and pustulosis have also been described [12•]. Sterile bone lesions resembling osteomyelitis are the hallmark of CRMO and can develop in clavicles, sternum, long bones, and, less commonly, mandible and vertebrae. Radiographs reveal osteolytic lesions with surrounding sclerosis. Bacterial and fungal cultures from blood and bone biopsies are negative, and the granulocytic infiltrate seen on histology of affected lesions is nonspecific.

Majeed syndrome and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome have been hypothesized to represent more severe phenotypes in the clinical spectrum of CRMO. The Majeed phenotype presents in early infancy, whereas the more common CRMO phenotype presents in school-age children, and SAPHO is mainly seen in young adults. In patients with CRMO and in their close relatives, prevalence of inflammatory skin lesions, inflammatory bowel disease, and arthritis is increased [65•]. CRMO can be self-limited in patients with isolated bone lesions, but may be associated with significant morbidity in very severe cases.

*Genetics*

The autosomal recessive infantile form of CRMO, Majeed syndrome, is caused by mutations in *LPIN2*, which encodes the protein lipin2 [12•]. Three *LPIN2* mutations have been described in patients with Majeed syndrome [16]. Mutations in *LPIN2* have not been found in the sporadic cases of CRMO. However, clues to a possible pathway may come from two murine models of CRMO with different disease severity. In both models, the disease is caused by autosomal recessive missense mutations in the *pstpip2* gene, which encodes a protein with similar structure to PSTPIP1. In the first murine model, the phenotype is limited to inflammatory bone lesions in tails and hindfeet; some mice also develop inflammation of ear cartilage and overlying skin. The second murine model has a more severe phenotype with bone and significant skin lesions and necrosis of the ears and digits. The two models suggest that factors other than the *pstpip2* mutations can modify disease expression. In humans, preliminary screening for mutations in *PSTPIP2* and *LPIN2* in sporadic forms of CRMO has been negative.

*Pathogenesis*

Despite the association of PSTPIP2 and LIPIN2 with clinical phenotypes of CRMO in mice and men, their roles in inflammation remain unresolved. Pstpip2 is ubiquitously expressed and plays a role in cytoskeletal reorganization [65•]. PAPA syndrome is caused by mutations in the structurally related PSTPIP1, which suggests that PSTPIP1 and PSTPIP2 may affect similar immunologic pathways. Investigations of the role of these molecules will likely reveal important pathways in bone inflammation and provide additional candidate genes for genetic screening.

*Treatment*

Antibiotics are not effective, but NSAIDs, corticosteroids, interferon α or γ, azithromycin, bisphosphonates, and TNF inhibitors have been reported to be helpful in individual patients [66].

## "Common Principles" in the Pathogenesis of Autoinflammatory Diseases

The mammalian immune system has evolved to protect the host against microbial infections and cellular waste that accumulates when cells are damaged or die. Two types of immune defense systems have emerged. Recognition of exogenous and endogenous "danger" by the innate immune system is mediated through pattern recognition receptors, which are germline coded; they bind invariant microbial molecules such as microbial cell wall components. Recognition of danger by the adaptive or acquired immune system is mediated by receptors on T and B cells that undergo somatic mutation, leading to fine tuning of the receptor specificity in response to antigen contact. This mechanism allows the development

of a highly diverse receptor repertoire, and enables the development of immunologic memory [67•].

*NALP3* or *NLRP3* (the gene causing CAPS) and its structurally related cousin *NOD2* (the gene involved in PGA and Crohn's disease) are members of the newly discovered NOD-like receptors that have structural homology with plant resistance proteins, which play a role in host-parasite interaction. This family consists of 14 NALP and five NOD receptors [68•]. NLRs have been shown to form active multimolecular complexes called inflammasomes that, in the case of the most often studied NALP3 inflammasome, result in increased caspase-1–mediated IL-1β processing and secretion. Whether the inflammasome is activated through direct interaction of a trigger with the LRR domain, or whether NLRs function as "guards" that interact with host proteins targeted by microbial or stress signals [69], is a topic of active research.

The unraveling of the central role of the NLR inflammasomes in immune recognition and autoinflammatory disease has been paralleled by successful clinical investigations exploring the role of blocking IL-1. Mutations of several genes that may modulate the IL-1β–producing inflammasome—such as pyrin (protein mutated in FMF), PSTPIP1 (protein mutated in PAPA), and likely PSTPIP2 (protein mutated in mouse CRMO)—have provided the conceptual framework to use IL-1 blockade in other autoinflammatory diseases and point to a central role of IL-1β regulation in their pathogenesis.

Although considerable insight has been gained into the regulatory function of pyrin on the inflammasome, the role of pyrin mutations in the B30.2 domain (or SPRY domain, a protein domain recently shown to target retroviruses and prevent their replication [70•]) on altered sensing of danger signals has yet to be explored.

Other systemic inflammatory diseases with presumed more complex modes of inheritance, such as systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, and Behçet's disease, have been added to the group of autoinflammatory diseases. The recent discovery that gout is caused by increased activation of the NALP3 inflammasome by uric acid crystals has illustrated the role of the NALP3 inflammasome in a common disease. Evidence is emerging that the innate immune system may play a role in other common rheumatic diseases (rheumatoid arthritis, dermatomyositis, and systemic lupus erythematosus).

## Conclusions

Unraveling the genetics of the monogenic autoinflammatory diseases resulted in the discovery of a new class of intracellular microbial sensors, fueling intense research in the mechanisms of microbial and danger recognition and the innate immune pathways that are consequently triggered. Molecules mutated in several monogenic autoinflammatory syndromes are pivotal components or regulators of the NALP3 or NOD2 inflammasomes. Studies of the NALP3 inflammasome provide a model that links microbial triggers to caspase-mediated IL-1β production and secretion. The dissection of the molecular pathways of inflammasome activation in the laboratory was paralleled by clinical trials confirming the central role of IL-1β activation in several autoinflammatory syndromes. Research in microbial and danger recognition by the inflammasomes may finally provide molecular mechanisms answering the quest for a role of infection and stress in explaining disease flares not only in the autoinflammatory diseases, but also in the more common rheumatic diseases. This research may allow us to explore the manipulation of microbial recognition and the associated signaling pathways as therapeutic strategies in rheumatic diseases.

## Acknowledgment

Dr. Goldbach-Mansky's research is supported by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.

## Disclosures

No potential conflicts of interest relevant to this article were reported.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. **A candidate gene for familial Mediterranean fever. The French FMF Consortium.** *Nat Genet* 1997, **17:**25–31.
2. The International FMF Consortium: **Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever.** *Cell* 1997, **90:**797–807.
3. 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:**133–144.
4. Drenth JP, van der Meer JW: **Hereditary periodic fever.** *N Engl J Med* 2001, **345:**1748–1757.
5. 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:**175–177.
6. 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:**3340–3348.
7. 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.

8. Hoffman HM, Mueller JL, Broide DH, et al.: **Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle-Wells syndrome.** *Nat Genet* 2001, **29:**301–305.
9. Wise CA, Gillum 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:**961–969.
10. Miceli-Richard C, Lesage S, Rybojad M, et al.: **CARD15 mutations in Blau syndrome.** *Nat Genet* 2001, **29:**19–20.
11.• Kanazawa N, Okafuji I, Kambe N, et al.: **Early-onset sarcoidosis and CARD15 mutations with constitutive nuclear factor-kappaB activation: common genetic etiology with Blau syndrome.** *Blood* 2005, **105:**1195–1197.

First paper to connect the spontaneous and familial forms of pediatric granulomatous arthritis; demonstrates upregulated NF-κB responses in patients with mutation-positive disease.

12.• 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 anaemia (Majeed syndrome).** *J Med Genet* 2005, **42:**551–557.

Original report describing homozygous mutation in *LIPIN2* as a cause for a severe infantile form of chronic recurrent multifocal osteomyelitis called Majeed syndrome.

13. Lidar M, Livneh A: **Familial Mediterranean fever: clinical, molecular and management advancements.** *Neth J Med* 2007, **65:**318–324.
14.• 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:**1706–1712.

Cross-sectional review of patients with FMF from 14 countries demonstrated country of origin as the key risk factor for development of amyloid nephropathy.

15. 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:**1149–1155.
16. **Infevers: an online database for autoinflammatory mutations.** Available at http://fmf.igh.cnrs.fr/ISSAID/infevers/. Accessed February 2008.
17. Tchernitchko DO, Gerard-Blanluet M, Legendre M, et al.: **Intrafamilial segregation analysis of the p.E148Q MEFV allele in familial Mediterranean fever.** *Ann Rheum Dis* 2006, **65:**1154–1157.
18. Chae JJ, Komarow HD, Cheng J, et al.: **Targeted disruption of pyrin, the FMF protein, causes heightened sensitivity to endotoxin and a defect in macrophage apoptosis.** *Mol Cell* 2003, **11:**591–604.
19. Martinon F, Burns K, Tschopp J: **The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-beta.** *Mol Cell* 2002, **10:**417–426.
20.• Chae JJ, Wood G, Masters SL, et al.: **The B30.2 domain of pyrin, the familial Mediterranean fever protein, interacts directly with caspase-1 to modulate IL-1beta production.** *Proc Natl Acad Sci U S A* 2006, **103:**9982–9987.

Demonstrates the interaction of the pyrin B30.2 domain with caspase-1, independent of ASC adaptor protein. Pyrin mutations decrease the binding to caspase-1 at this site.

21.• Yu JW, Fernandes-Alnemri T, Datta P, et al.: **Pyrin activates the ASC pyroptosome in response to engagement by autoinflammatory PSTPIP1 mutants.** *Mol Cell* 2007, **28:**214–227.

Pyrin, a receptor for PSTPIP1, is activated via ligation by PSTPIP1 and is necessary for the assembly of the pyrin inflammasome. The authors suggest an in vitro model demonstrating a proinflammatory role of pyrin.

22. Bhat A, Naguwa SM, Gershwin ME: **Genetics and new treatment modalities for familial Mediterranean fever.** *Ann N Y Acad Sci* 2007, **1110:**201–208.
23. Williamson LM, Hull D, Mehta R, et al.: **Familial Hibernian fever.** *Q J Med* 1982, **51:**469–480.
24. Hull KM, Shoham N, Chae JJ, et al.: **The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations.** *Curr Opin Rheumatol* 2003, **15:**61–69.
25.• 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:**1320–1327.

Reports that mutated TNF receptor in patients with TRAPS is misfolded and retained in the endoplasmic reticulum. The authors propose that the proinflammatory response seen in these patients may be related to intracellular accumulation of misfolded TNFR1.

26. Drewe E, Huggins ML, Morgan AG, et al.: **Treatment of renal amyloidosis with etanercept in tumour necrosis factor receptor-associated periodic syndrome.** *Rheumatology (Oxford)* 2004, **43:**1405–1408.
27. Simon A, Bodar EJ, van der Hilst JC, et al.: **Beneficial response to interleukin 1 receptor antagonist in traps.** *Am J Med* 2004, **117:**208–210.
28. Kile RL, Rusk HA: **A case of cold urticaria with unusual family history.** *JAMA* 1940, **114:**1067–1068.
29. Muckle TJ, Wells M: **Urticaria, deafness, and amyloidosis: a new heredo-familial syndrome.** *Q J Med* 1962, **31:**235–248.
30. Muckle TJ: **The 'Muckle-Wells' syndrome.** *Br J Dermatol* 1979, **100:**87–92.
31. Ansell MB, Bywaters EG, Elderkin FM: **Familial arthropathy with rash, uveitis and mental retardation.** *Proc R Soc Med* 1975, **68:**584–585.
32. Prieur AM, Griscelli C: **Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation.** *J Pediatr* 1981, **99:**79–83.
33. Hill SC, Namde M, Dwyer A, et al.: **Arthropathy of neonatal onset multisystem inflammatory disease (NOMID/CINCA).** *Pediatr Radiol* 2007, **37:**145–152.
34.• 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:**1273–1285.

Comprehensive description of genetic spectrum of CAPS.

35.• Goldbach-Mansky R, Dailey NJ, Canna SW, et al.: **Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition.** *N Engl J Med* 2006, **355:**581–592.

Largest clinical trial in 18 patients with NOMID that demonstrates effectiveness of IL-1 blockade, supporting a pivotal role in the pathogenesis of this disorder. Demonstrates role of MRI in following inflammatory CNS lesions.

36. 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.
37. Neven B, Callebaut I, Prieur AM, et al.: **Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU.** *Blood* 2004, **103:**2809–2815.
38. Hoffman HM, Gregory SG, Mueller JL, et al.: **Fine structure mapping of CIAS1: identification of an ancestral haplotype and a common FCAS mutation, L353P.** *Hum Genet* 2003, **112:**209–216.
39. Saito M, Nishikomori R, Kambe N, et al.: **Disease-associated CIAS1 mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients.** *Blood* 2008, **111:**2132–2141.
40. Jesus AA, Silva CA, Segundo GR, et al.: **Phenotype-genotype analysis of cryopyrin-associated periodic syndromes (CAPS): description of a rare non-exon 3 and a novel CIAS1 missense mutation.** *J Clin Immunol* 2007, **28:**134–138.

41. Medzhitov R, Janeway CA Jr: **Decoding the patterns of self and nonself by the innate immune system.** *Science* 2002, **296:**298–300.

42.• McDermott MF, Tschopp J: **From inflammasomes to fevers, crystals and hypertension: how basic research explains inflammatory diseases.** *Trends Mol Med* 2007, **13:**381–388.
Reviews components of known inflammasomes and their role in monogenic autoinflammatory diseases and in more common diseases.

43. O'Connor W Jr, Harton JA, Zhu X, et al.: **Cutting edge: CIAS1/cryopyrin/PYPAF1/NALP3/CATERPILLER 1.1 is an inducible inflammatory mediator with NF-kappa B suppressive properties.** *J Immunol* 2003, **171:**6329–6333.

44. Wang L, Manji GA, Grenier JM, et al.: **PYPAF7, a novel PYRIN-containing Apaf1-like protein that regulates activation of NF-kappa B and caspase-1-dependent cytokine processing.** *J Biol Chem* 2002, **277:**29874–29880.

45.• Caroli F, Pontillo A, D'Osualdo A, et al.: **Clinical and genetic characterization of Italian patients affected by CINCA syndrome.** *Rheumatology (Oxford)* 2007, **46:**473–478.
Descriptive series of 12 patients with NOMID, a subset of whom were treated with anakinra with good response.

46. Hawkins PN, Lachmann HJ, Aganna E, McDermott MF: **Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra.** *Arthritis Rheum* 2004, **50:**607–612.

47. 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:**1779–1785.

48.• Hoffman HM, Throne ML, Amar NJ, et al.: **Efficacy and safety of rilonacept (IL-1 trap) in cryopyrin-associated periodic fever syndromes (CAPS): results from two sequential placebo-controlled studies.** *Arthritis Rheum,* in press.
Randomized placebo-controlled trial in 47 patients with FCAS and MWS that led to approval of rilonacept, the first drug approved for an orphan disease indication in the autoinflammatory disease group.

49. Goldbach-Mansky R, Shroff S, Wilson M, et al.: **A pilot study to evaluate the safety and efficacy of the long-acting IL-1 inhibitor, rilonacept (IL-1 Trap) in patients with familial cold autoinflammatory syndrome (FCAS).** *Arthritis Rheum,* in press.

50. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD): **Online Mendelian Inheritance in Man, OMIM.** Accessed February 8, 2008. Available at http://www.ncbi.nlm.nih.gov/omim.

51. McTaggart SJ: **Isoprenylated proteins.** *Cell Mol Life Sci* 2006, **63:**255–267.

52.• Simon A, van der Meer JW: **Pathogenesis of familial periodic fever syndromes or hereditary autoinflammatory syndromes.** *Am J Physiol Regul Integr Comp Physiol* 2007, **292:**R86–R98.
Comprehensive review of current theories of pathophysiology and role of inflammasomes in familial periodic fever syndromes.

53. Frenkel J, Rijkers GT, Mandey SH, et al.: **Lack of isoprenoid products raises ex vivo interleukin-1beta secretion in hyperimmunoglobulinemia D and periodic fever syndrome.** *Arthritis Rheum* 2002, **46:**2794–2803.

54. 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:**476–483.

55. Bodar EJ, van der Hilst JC, Drenth JP, et al.: **Effect of etanercept and anakinra on inflammatory attacks in the hyper-IgD syndrome: introducing a vaccination provocation model.** *Neth J Med* 2005, **63:**260–264.

56. Demirkaya E, Caglar MK, Waterham HR, et al.: **A patient with hyper-IgD syndrome responding to anti-TNF treatment.** *Clin Rheumatol* 2007, **26:**1757–1759.

57. 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:**2645–2651.

58. Lindor NM, Arsenault TM, Solomon H, et al.: **A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome.** *Mayo Clin Proc* 1997, **72:**611–615.

59. 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 U S A* 2003, **100:**13501–13506.

60. Cortis E, De Benedetti F, Insalaco A, et al.: **Abnormal production of tumor necrosis factor (TNF)-alpha and clinical efficacy of the TNF inhibitor etanercept in a patient with PAPA syndrome** [corrected]**.** *J Pediatr* 2004, **145:**851–855.

61.• Rose CD, Wouters CH, Meiorin S, et al.: **Pediatric granulomatous arthritis: an international registry.** *Arthritis Rheum* 2006, **54:**3337–3344.
Clinical summary of international registry describing the clinical spectrum of Blau syndrome and early-onset sarcoidosis; suggests using *pediatric granulomatous arthritis* as unifying term.

62. Blau EB: **Familial granulomatous arthritis, iritis, and rash.** *J Pediatr* 1985, **107:**689–693.

63. Becker ML, Rose CD: **Blau syndrome and related genetic disorders causing childhood arthritis.** *Curr Rheumatol Rep* 2005, **7:**427–433.

64.• Arostegui 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:**3805–3813.
Describes clinical characteristics, genetics, and response to treatment of 12 patients with PGA. Reports improvement after treatment with anakinra in one patient.

65.• Ferguson PJ, El Shanti HI: **Autoinflammatory bone disorders.** *Curr Opin Rheumatol* 2007, **19:**492–498.
Excellent review of clinical features and current understanding of the genetics and pathophysiology of CRMO and Majeed syndrome.

66. El Shanti HI, Ferguson PJ: **Chronic recurrent multifocal osteomyelitis: a concise review and genetic update.** *Clin Orthop Relat Res* 2007, **462:**11–19.

67.• Medzhitov R: **Recognition of microorganisms and activation of the immune response.** *Nature* 2007, **449:**819–826.
Excellent overview of current pathophysiologic pathways that activate innate and adaptive immune systems by microbial stimuli.

68.• Ye Z, Ting JP: **NLR, the nucleotide-binding domain leucine-rich repeat containing gene family.** *Curr Opin Immunol* 2008, **20:**3–9.
Comprehensive description of the family of NLR receptors, a new group of intracellular microbial sensors.

69. Schneider DS: **Plant immunity and film noir: what gumshoe detectives can teach us about plant-pathogen interactions.** *Cell* 2002, **109:**537–540.

70.• James LC, Keeble AH, Khan Z, et al.: **Structural basis for PRYSPRY-mediated tripartite motif (TRIM) protein function.** *Proc Natl Acad Sci U S A* 2007, **104:**6200–6205.
Paper modeling the three-dimensional structure of the SPRY domain, a conserved binding interface belonging to the TRIM family of recently recognized retroviral sensors.