marrow aspiration revealed no hematologic abnormalities or malignancies. His thigh was examined with MRI to rule out dermatomyositis, but no remarkable changes were observed. Based on the observations that neither infectious nor malignant disorders were suspected, oral betamethasone (2 mg/day) was administered without a proper diagnosis at the age of 1 year. As expected, his skin eruptions and fever immediately disappeared, and the laboratory data became normal. However, these symptoms repeatedly recurred after tapering the medication, and oral betamethasone was administered intermittently at each flare-up. An analysis of his serum cytokine levels at 4 years of age revealed slightly high interleukin (IL)-6 (5.6 pg/ml; normal: <4.0 pg/ml), but his tumor necrosis factor-α, interferon-γ and IL-1β levels were normal.

Around the age of 5 years, his face gradually became angular and his fingers showed a mild deformity with swollen interphalangeal joints, which formed the characteristic appearance of long clubbed fingers (fig. 3a–c). On the suspicion of NNS, serial cranial CT scans were taken for the first time, and calcification of the basal ganglia, pons and white matter of the frontal lobe became apparent (fig. 3d). Furthermore, a genomic analysis of the patient and his parents was performed after informed consent was obtained according to the protocol approved by the ethics committee of Wakayama Medical University, and a c.602G>T mutation of the *PSMB8* gene causing the amino acid substitution of Gly201Val was homozygously detected in the patient, and heterozygously in his parents (fig. 3e). Since this mutation has been identified uniquely in NNS cases, his disease was finally confirmed as NNS. At the age of 6 years, methotrexate was further administered for the intractable skin rashes on his face. Notably, a severe worsening of laboratory findings was never experienced after the administration of oral corticosteroids, and methotrexate was effective against his skin lesions.

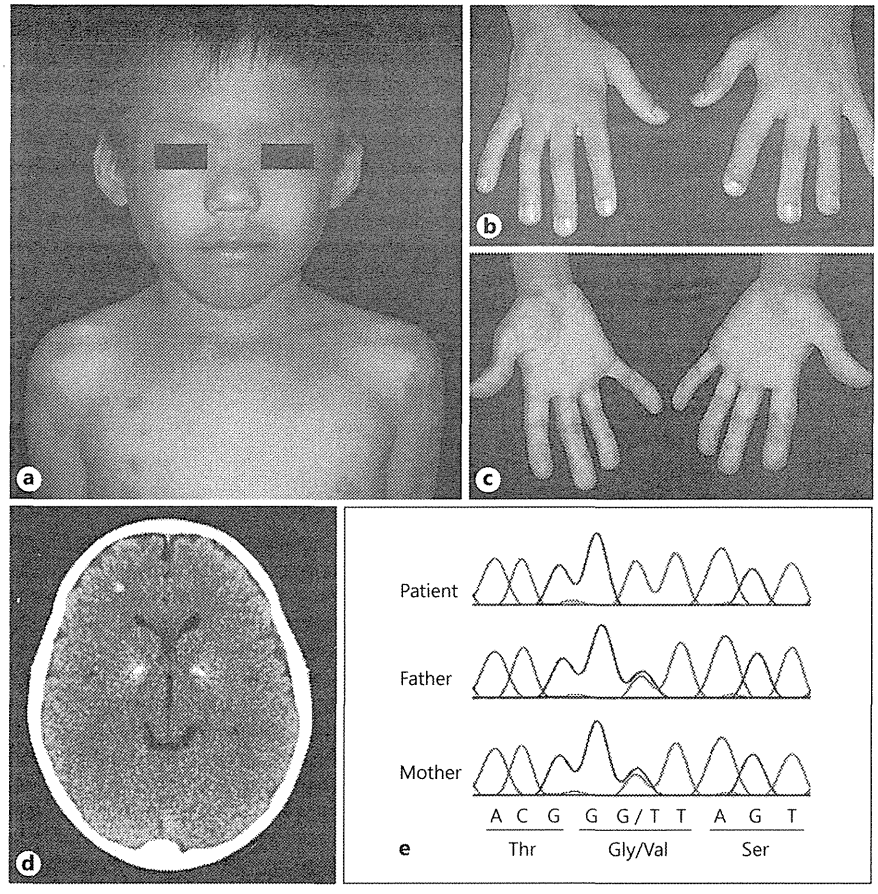

Fig. 3. Clinical photographs (**a–c**), cranial CT (**d**) and genomic analysis of the patient at 5 years of age (**e**). A thin angular face (**a**), long clubbed fingers with swollen interphalangeal joints (**b**, **c**) and calcification of the basal ganglia on cranial CT scans (**d**) were observed. **e** Electrophoretograms of the genomic sequence of the patient and his parents. A c.602G>T mutation causing an amino acid substitution of Gly201Val was found homozygously in this patient and heterozygously in both parents.

Discussion

NNS is a hereditary disorder that has its onset in infancy with pernio-like skin rashes, and is accompanied by remittent fever and nodular erythema-like skin eruptions [1]. Patients with NNS gradually develop a partial lipodystrophy, mainly in the face and upper extremities, and develop long clubbed fingers with contracture of the interphalangeal joints. There is no effective treatment to prevent the progression of this disease, and some patients die young. There have been more than 20 reports of NNS cases uniquely from Japan since the earliest reports by Nakajo [2] in 1939 and by Nishimura et al. [3] in 1950 as 'secondary hypertrophic osteoperiostosis with pernio' [4–6]. Due to the phenotypic similarities, NNS is considered to be a new member of the family of hereditary autoinflammatory disorders.

According to a review of all 28 reported cases with NNS, 8 features were selected for a tentative checklist of diagnostic criteria, and the detection of at least 5 features was defined to be sufficient for a clinical diagnosis of NNS (table 1) [1]. As 7 out of the 8 features were observed in our case, except for the autosomal recessive inheritance, our case can be clinically diagnosed as NNS. However, before the partial lipomuscular atrophy with characteristic long clubbed fingers became noticeable at 5 years of age, he had shown only 4 features (pernio-like rashes, nodular erythema-like eruptions, periodic fever and hepatosplenomegaly). Therefore, head CT scanning in search for basal ganglion calcification is a critical step for an early diagnosis of NNS. Furthermore, the establishment of a serum marker or simple examination

would be expected for an objective estimation of partial lipodystrophy. As a result of a national survey on NNS in Japan which had recently been performed using these criteria, 11 cases have been confirmed to be still alive, including our case. Notably, our patient is the only infant case who was born more than 20 years after the birth of the last NNS case [1].

Recently, Arima et al. [7] and Kitamura et al. [8] independently reported the identification of a homozygous c.602G>T mutation in the *PSMB8* gene encoding the immunoproteasome β5i subunit in NNS patients by homozygosity mapping. This mutation has been homozygously detected uniquely in all NNS cases investigated, including the present case. The resulting Gly201Val substitution causes the defective assembly of the immunoproteasome complex and severe defects in proteasome activities overall. Accordingly, detection of the *PSMB8* gene mutation is expected to confirm the diagnosis of NNS.

Although NNS has been assumed to be found exclusively in Japan, several cases of new syndromes presenting with similar clinical features and other *PSMB8* mutations have successively been reported from foreign countries [9–13]. Three cases were reported as JMP (joint contractures, muscular atrophy, microcytic anemia and panniculitis-induced lipodystrophy) syndrome harboring a homozygous mutation of c.224C>T in the *PSMB8* gene with a T75M amino acid transition, whereas another 8 cases were designated as CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) syndrome harboring a homozygous or heterozygous c.224C>T mutation, or a homozygous nonsense mutation of c.405C>A with a premature termination (C135X). In contrast to patients with JMP syndrome, who showed seizures without pernio-like rashes or recurrent fever, patients with CANDLE syndrome showed all 8 features of the list of criteria for a clinical diagnosis of NNS, and they looked quite similar to patients with this disease [9, 11–13]. Histologically, the massive infiltration of activated neutrophils into the dermis was reported to be highly characteristic of CANDLE syndrome, whereas such a feature was not observed in our case [11–13]. Actually, a palpable erythema on the chest showing inflammatory cell infiltration in the upper dermis without leukocytoclastic vasculitis was further analyzed immunohistochemically at 6 years of age, and the infiltrating cells were positive for myeloperoxidase but immunonegative for CD15, a marker of mature neutrophils (data not shown). Collectively, it appears that these related disorders with *PSMB8* mutations may be categorized as a novel class of hereditary autoinflammatory diseases, namely proteasome disability syndromes, and they might be subdivided by clinical, histologic and genetic features. To determine the precise genotype-phenotype correlations, the analysis of a greater number of cases would be required.

It took almost 5 years to make a proper diagnosis in our case. The clinical diagnostic criteria and genetic analysis were both useful, but they would not be routinely performed unless the disease was suspected. In order to determine the diagnosis of this disease and to start therapy before progression to lipomuscular atrophy or joint contracture, it is important to understand the variety of clinicopathological features.

Table 1. Tentative criteria for the clinical diagnosis of NNS

1	Autosomal recessive inheritance (parental consanguinity and/or familial occurrence)
2	Pernio-like purplish rashes on hands and feet (appearing in winter since infancy)
3	Haunting nodular erythema with infiltration and induration (sometimes circumscribed)
4	Repetitive spiking fever (periodic, not necessarily)
5	Long clubbed fingers and toes with joint contractures
6	Progressive partial lipomuscular atrophy and emaciation (marked in upper part of body)
7	Hepatosplenomegaly
8	Basal ganglion calcification

A clinical diagnosis of NNS can be made if at least 5 of the 8 features above are positive and other diseases are excluded.

Acknowledgments

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Disclosure Statement

The authors have no conflicts of interest to declare.

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LETTERS

NOTES & COMMENTS

Margins for standard excision of melanoma in situ

To the Editor: We would like to reply to the letter written by Horst et al[1] in response to our article entitled "Surgical margins for melanoma in situ." Our article showed the historically recommended 5-mm margin for excision of melanoma in situ to be inadequate, only clearing 86% of tumors. We recommended a 9-mm margin for standard excision of melanoma in situ to achieve a 99% clearance rate.[2] Horst et al[1] countered, "Why would I think it is appropriate in 86% of cases to take an extra 3 mm of normal-appearing skin, which in some cases will add to disfigurement or morbidity? This approach would defeat the entire purpose of microscopic margin control (eg, Mohs micrographic surgery)."

We agree Mohs micrographic surgery is the gold standard for margin control and tissue conservation. However, our recommendation was for the surgeon who chooses to treat melanoma in situ with standard excision (wide local excision), not Mohs micrographic surgery. This surgeon cannot simply use a 3-mm margin and then take more only if the pathology report shows margin involvement. Because less than 1% of the margin is examined with routine processing, positive margins are likely to be missed and unreported. Kimyai-Asadi at al[3] showed that only 19% of positive melanoma margins are detected with routine processing. Understanding the probability for missed tumor with lesser margins may prompt physicians to refer patients for Mohs micrographic surgery when 9-mm margins are not feasible.

Horst et al[1] also believe margins need to be correlated with the size of the lesion and the anatomic site, suggesting our large margin requirements were related to the larger mean size of our lesions. The data in our study did not support this. Clearance rates with 5-mm margins were low for all sizes, locations, and subtypes.[2,4]

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Monogenic early-onset sarcoidosis is no longer a variant of "idiopathic" sarcoidosis

To the Editor: We read with great interest the recent CME review on cutaneous sarcoidosis by Haimovic et al.[1] Table II of their article lists the symptoms of a "lichenoid" variant that the authors describe as "most frequently reported in young children who presented with eye and joint complications and no respiratory involvement."[1] This special type is also termed "early-onset sarcoidosis." Although the authors did not comment on this, it should be noted that early-onset sarcoidosis is caused by *NOD2* mutations and is considered to be the same disease as familial Blau syndrome, a hereditary autoinflammatory disease.[2]

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Reply to: Monogenic early-onset sarcoidosis is no longer a variant of "idiopathic" sarcoidosis

To the Editor: We thank Dr Kanazawa et al for their comments on our article "Sarcoidosis: a comprehensive review and update for the dermatologist."[1] We agree that our description of the lichenoid variant in Table II of our article may be seen in early-onset sarcoidosis (EOS). EOS typically occurs in children younger than 5 years of age; affects the skin, joints, and eyes; and, in contrast to adult-onset sarcoidosis, usually spares the lungs and lymph nodes.[2] Blau syndrome (autosomally inherited granulomatous eruption, arthritis/tenosynovitis, and uveitis) and EOS may share identical phenotypes.[2,3] Blau syndrome has been demonstrated to be a result of mutations in the NOD2 gene.[4] These mutations in NOD2 have also been shown to be present in some patients with EOS.[5-7] We agree that in young children with isolated granulomatous dermatitis or those who have eye or joint findings, Blau syndrome should be a diagnostic consideration.

We would like to clarify that although lichenoid sarcoidosis is more often seen in children,[8,9] it can affect individuals of all ages.[10,11]

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Research Letters

Periocular actinic keratosis, keratinocyte carcinomas, and eyeglasses use

To the Editor: Ultraviolet light exposure is a known risk factor for development of keratinocyte carcinomas (KCs). This study sought to determine the role of eyeglasses use on prevention of periocular KCs and actinic keratoses (AKs).

Questionnaires on use of occupational and leisure eyeglasses from birth to enrollment were distributed

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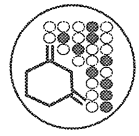

Journal of Genetic Disorders & Genetic Reports

Review Article

A SCITECHNOL JOURNAL

Comprehensive Review of Rare Hereditary Autoinflammatory Disorders

Nobuo Kanazawa[1*]

Abstract

Hereditary autoinflammatory syndromes are monogenic disorders with inborn errors of innate immunity, and include a variety of diseases in several clinical categories: 1) periodic fever syndromes such as familial Mediterranean fever (FMF), hyper IgD syndrome with periodic fever (HIDS), tumor necrosis factor receptor (TNFR)-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndromes (CAPS); 2) pyogenic pustular diseases such as pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, deficiency for interleukin-1 receptor antagonist (DIRA) and deficiency for interleukin-36 receptor antagonist (DITRA); 3) granulomatous diseases such as Blau syndrome (BS) and early-onset sarcoidosis (EOS); and 4) newly-defined disorders categorized as autoinflammation, lipodystrophy and dermatoses (ALDD) syndrome. By identifying the genetic abnormalities and subsequent analyses of the molecular mechanisms underlying these disorders, critical *in vivo* pathways in inflammatory processes have been clarified, and the disorders have been recategorized by their underlying dysregulated signaling pathways. The major and well-investigated disorders are inflammasomopathies with dysregulated *NLRP3* inflammasome activation, including CAPS with *NLRP3*, FMF with *MEFV*, PAPA syndrome with *PSTPIP1* and DIRA with *IL1RN* mutations. BS and EOS with *NOD2* mutations are caused by dysregulated *NOD2* signaling, analogous to the dysregulated *NLRP3* signaling in CAPS. In TRAPS with *TNFRSF1* mutations, the intracellular aggregation of abnormal TNFR1 protein seems to cause inflammation, similar to ALDD syndrome with *PSMB8* mutations, in which ubiquitinated and oxidated proteins accumulate intracellularly to cause inflammation. Since there still remain a number of cases with predicted but undefined hereditary autoinflammatory syndromes, it is expected that a number of new disorders with dysregulated critical inflammatory pathways will be discovered soon using new next-generation gene sequencing technology.

Historical Overview

The term "autoinflammatory" diseases has recently been defined as an antonym of "autoimmune" diseases, for a spectrum of inflammatory diseases with dysregulated innate immunity resulting in the hyperactivation of neutrophils and/or macrophages [1-3]. Historically, the presence of the prototypic familial Mediterranean fever (FMF; OMIM#249100) has been known since the Roman era, and hereditary cases with similar but different features have been reported as FMF-like syndromes. Periodic fever is the most characteristic common feature, whereas the duration and interval of the febrile attacks are variable and similar cases can be further distinguished by inheritance, ethnicity, other accompanying symptoms, the development of amyloidosis, and the effectiveness of colchicin [4]. In 1999, mutations in the *tumor necrosis factor receptor superfamily 1 (TNFRSF1)* gene encoding TNFR1 were identified to be responsible for autosomal dominant-type FMF-like syndrome or familial Hibernian fever, and the disease was re-designated as TNFR-associated periodic syndrome (TRAPS; OMIM#142680) [5]. Since TNF is one of the key players in inflammation and innate immunity, the term "autoinflammatory syndromes" has been designated for hereditary monogenic diseases with inborn errors of innate immunity. By 1997, mutations in the *Mediterranean fever (MEFV)* gene had been identified to be responsible for FMF, but the precise role of pyrin, a new molecule encoded by this gene, was not sufficiently clarified [6,7]. A pivotal role for pyrin in inflammation was determined after the identification of cryopyrin encoded by the gene *cold-induced autoinflammatory syndrome 1 (CIAS1, formally named NLRP3)*, whose mutations cause other periodic fever syndromes, familial cold-induced autoinflammatory syndrome (FCAS; OMIM#120100) and Muckle-Wells syndrome (MWS; OMIM#191900), and subsequently, chronic infantile neurological cutaneous and articular (CINCA) syndrome or neonatal onset multisystem inflammatory disease (NOMID; OMIM#607115) [8-10]. Identification of the pyrin domain shared by pyrin and cryopyrin and the definition of the inflammasome as a molecular platform to cleave pro-interleukin (IL)-1β have led to the finding that pyrin acts as a regulator of this molecular complex [11-14]. A number of disorders with inborn or acquired dysregulation of the inflammasome, including FMF, cryopyrin-associated periodic syndromes (CAPS) with *NLRP3* mutations and gout caused by uric acid crystals, are categorized as "inflammasomopathies". Because of the role of inflammasome-IL-1β signaling and the effectiveness of anti-IL-1 therapies in many autoinflammatory disorders, inflammasomopathies are now considered to be representative constituents of autoinflammatory disorders [1].

In 2000, *NOD2 (formally named NLRC2)* was reported as the first non-major histocompatibility (MHC) susceptibility gene for Crohn's disease simultaneously by two groups, a group working with linkage analysis and another one starting with molecular cloning [15,16]. Subsequently, other gain-of-function mutations in the same gene have been identified to be responsible for systemic granulomatosis, Blau syndrome (BS; OMIM#186580) and sporadic early-onset sarcoidosis (EOS; OMIM#609464) [17,18]. Notably, the *NOD2* mutations in these diseases were structurally and functionally homologous to the *NLRP3* mutations in CAPS [19]. *NOD2* (*NLRC2*) and cryopyrin (*NLRP3*) belong to the NOD-like receptor (NLR) family of molecules, and their dysregulation seems critical in autoinflammatory diseases [20].

Increased awareness and recognition of the expanding concept of autoinflammatory diseases has resulted in an increased number of patients that have been proven to harbor these disease-associated mutations. However, there still remain many cases potentially with an autoinflammatory disease, but without any mutation in known genes. In the case of CINCA syndrome, mosaicism of a *NLRP3*

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mutation was first identified in Japanese cases and subsequently in global "mutation-negative" cases, but a similar situation has not been reported in other diseases [21,22]. Instead, by hunting the genes responsible for rare inherited disorders concentrated in quite limited areas, several novel mutations have been successfully identified. Mutations in a distinct NLR family gene, *NLRP12*, were identified to be responsible for FCAS2 (OMIM#611762), which was first discovered in a small number of patients in Guadaloupe [23]. Identification of the responsible genes has defined distinct familial disorders with infantile pyogenic pustulosis mainly in Holland and Tunisia as deficiency for IL-1 receptor antagonist (DIRA; OMIM#612852) and deficiency for IL-36 receptor antagonist (DITRA; OMIM#614204), respectively [24,25]. Notably, the same *IL-36RN* mutations have subsequently been identified in sporadic cases with more common skin diseases, including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), acrodermatitis continua of Hallopeau (ACH), and acute generalized exanthematous pustulosis (AGEP) [26,27]. Finally, mutations of *PSMB8* encoding the β5i immunoproteasome (IP) subunit have been identified in the distinctive autoinflammation, lipodystrophy and dermatoses (ALDD) syndrome (OMIM#256040), including Nakajo-Nishimura syndrome (NNS) in Japan, joint contractures, muscular atrophy, microcytic anemia and panniculitis-associated lipodystrophy (JMP) syndrome in Portugal and Mexico and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome mainly in Spain and Israel [28-31]. The characteristic features of these diseases discussed in this review are summarized in Table 1.

The recently developed next-generation sequencer is now completely changing the world of gene hunting [32]. Actually, using whole genome/exome sequencing of each patient and his/her parents (the so-called trio), a number of novel mutations have been discovered in a short period, in contrast to the basic linkage analysis of a large family or homozygosity mapping of some small families, which need much more time. In the near future, so-called "mutation-negative" cases will be lost, even if the responsible mutation remains undefined.

Inflammasomopathies: CAPS, FMF, PAPA Syndrome, HIDS

Familial cold urticaria (FCU), which manifests as recurrent attacks of urticarial rash accompanied with pain, joint swelling, chills and fever after exposure to the cold, was first described in 1940 [33]. A related hereditary disease with recurrent episodes of urticarial rash without cold exposure and late-onset sensorineural deafness and renal amyloidosis was first described in 1962, and was termed urticaria-deafness-amyloidosis or MWS [34]. After linking both susceptibility genes for these diseases to chromosome 1q44, a new gene was identified to be responsible for both diseases in 2001 [8]. Since the identified gene is similar to pyrin, the *MEFV* gene product responsible for FMF, the molecule encoded by this gene has been designated as cryopyrin, which means "cold-induced fever" [35]. Moreover, based on the genetic and clinical similarities with FMF, the name of this disease was changed from FCU to FCAS, and its responsible gene has been designated *CIAS1*. In 2002, mutations in the same gene were detected in another rare hereditary disorder, CINCA syndrome, characterized by a neonatal-onset triad of skin rash, chronic meningitis and joint inflammation with recurrent fever [9,10]. Therefore, these 3 disorders sharing the same genetic origin form a sequential spectrum of CAPS [36].

Cryopyrin is composed of the N-terminal pyrin domain (PYD), a central nucleotide oligomerization domain (NOD) plus C-terminal leucine-rich repeats (LRR), and has formally been designated as *NLRP3*, one of the best characterized of the NLR family of molecules (Figure 1) [37]. When stimulated with various danger molecules such as bacterial RNA, imiquimod and uric acid crystals, *NLRP3* is oligomerized to form a pentamer and associates with procaspase-1 containing the caspase-recruitment domain (CARD), through an adaptor molecule apoptosis-associated speck-like protein with a CARD (ASC) consisting of both PYD and CARD. This *NLRP3*-ASC-procaspase-1 complex, formed through homophilic interaction of each domain (PYD-PYD and CARD-CARD), functions as a cytoplasmic platform activating caspases-1-mediated IL-1β/IL-18 secretion and has been designated as the *NLRP3* inflammasome [11]. In the case of CAPS, the stable oligomerization of *NLRP3* caused by missense mutations mainly located in NOD is considered to result in the constitutive activation of caspase-1 and subsequent IL-1β secretion (Figure 1). *NLRP3* activation in monocytes results in elevated levels of serum IL-1β, whereas its activation and IL-1β secretion by dermal mast cells are associated with vascular leakage and neutrophil recruitment in urticarial rash [38]. Clinically, anti-IL-1 therapies

Table 1: Summary of the diseases discussed in this review.

Category	Disease	Gene/protein	Phenotype	Treatment
Inflammasomopathies	CAPS	*NLRP3* (*CIAS1*)/cryopyrin	Urticarial rash, arthritis, fever, hearing loss/chronic meningitis, renal amyloidosis	Anti-IL-1β therapy (anakinra, rilonacept, canakinumab)
	FMF	*MEFV*/pyrin	Recurrent fever, painful peritonitis, pleuritis, renal amyloidosis, erysipelas-like rash	Colchicine, anti-IL-1β therapy
	PAPA syndrome	*PSTPIP1*/PSTPIP1	Recurrent destructive arthritis, fever, pyogenic gangrenosum, cystic acne	Corticosteroid, anti-TNFα therapy, anti-IL-1β therapy
	HIDS	*MVK*/mevalonate kinase	Recurrent fever, abdominal pain, diarrhea, arthritis, cervical lymphadenopathy, skin rash	Simvastatin, anti-IL-1β therapy
IL-1 family receptor antagonist deficiencies	DIRA	*IL1RN*/IL-1Ra	Sterile lytic bone lesions, pustulosis, fever	Anakinra
	DITRA	*IL36RN*/IL-36Ra	Generalized pustular psoriasis and related pustular diseases	Corticosteroid, anti-TNFα therapy
NOD2-associated granulomatous diseases	BS, EOS	*NLRC2*/NOD2	Maculopapular skin lesions, arthritis, uveitis	Corticosteroid, anti-TNFα therapy, thalidomide
Protein misfolding disease	TRAPS	*TNFRSF1*/TNFR1	Recurrent fever, arthralgia, myalgia, migratory rash, conjunctivitis, abdominal pain	Corticosteroid, anti-TNFα therapy, anti-IL-1β therapy
Proteasome disability syndromes	ALDD syndrome	*PSMB8*/β5i	Pernio-like rash, nodular erythema, periodic fever, lipomuscular atrophy, joint contractures	Corticosteroid, methotrexate, tocilizumab, JAK inhibitors

including the IL-1 receptor antagonist (IL-1Ra) anakinra, IL-1 Trap/rilonacept composed of extracellular IL-1R1 and accessory protein (AcP), and anti-IL-1β antibodies such as canakinumab, dramatically improved almost all symptoms of CAPS. These facts support a critical role for IL-1β in the development of CAPS [39-41]. Furthermore, the crucial role of *NLRP3* for IL-1β secretion has been revealed by analyses of knockout mice [42]. This *NLRP3*-ASC-caspase-1-IL-1β axis is considered to be the main pillar of autoinflammation.

FMF is the most common periodic fever syndrome known since the Roman era, and its clinical manifestations distinct from CAPS include the presence of painful peritonitis and/or pleuritis, and the effectiveness of colchicine. The skin rash in FMF is described as erysipelas-like, but the associated massive neutrophil infiltration in the dermis is similar to that observed in CAPS. The occasional development of amyloidosis is also common in both diseases. In 1997, the *MEFV* gene on chromosome 16 was identified as being responsible, and its encoding protein has been designated as pyrin, referring to the Greek word for fever, "pyrus" [6,7]. Pyrin is a multi-domain molecule containing B-Box, coiled-coil and B30.2/SPRY domains, as well as PYD. In most recessively-inherited FMF cases, homozygous loss-of-function mutations of pyrin were hypothesized to cause impairment of its immunoregulatory function to regulate *NLRP3* inflammasome activation through its PYD or B30.2/SPRY domain [12-14]. In particular, competitive inhibition of PYD-PYD interactions between *NLRP3* and ASC with the PYD of pyrin is comprehensive (Figure 1). Actually, pyrin-deficient mice showed a caspase-1-mediated hyperimmune phenotype, supporting the inhibitory role of pyrin on *NLRP3* inflammasome signaling [43]. On the other hand, some studies reported that pyrin activates inflammatory responses directly, and a recent analysis of dominantly-inherited FMF-causing gain-of-function pyrin mutation-knockin mice revealed the ASC-dependent but *NLRP3*-independent activation of inflammasomes in these mice [44,45]. Notably, anti-IL-1 therapies are reportedly effective against FMF, irrespective of its inheritance pattern [13,46].

Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome (OMIM#604416), which had previously been reported in 1975, has been defined as an autosomal dominantly-inherited pyogenic pustular disease in 1997 [47,48]. Early-onset pyogenic and corticosteroid-responsive but recurrent and destructive arthritis is remarkable, and the skin manifestations of pyoderma gangrenosum and severe cystic acne are often observed, especially from adolescence. By linkage analysis on two families, distinct missense mutations in the *proline-serine-threonine phosphatase-interacting protein 1 (PSTPIP1)* gene on chromosome 15 were identified in 2002 [49]. *PSTPIP1* is a molecule with multiple properties, including interactions with PEST-type protein tyrosine phosphatases such as protein tyrosine phosphatase non-receptor 12 (PTPN12) and PTPN18, binding to CD2, and interactions with Wiscott-Aldrich syndrome protein (WASP) for regulating cytoskeletal actin reorganization. More importantly, *PSTPIP1* can also bind to pyrin to inhibit its regulatory role, and thus the disease-associated mutations in its CC domain diminishes its binding with PTPNs and strengthens its interactions with pyrin, resulting in dysregulated activation of the *NLRP3* inflammasome (Figure 1) [50]. The phenotypic differences between PAPA syndrome and CAPS/FMF might be due to the multiple functions of PSTPIP1, but the precise explanation remains to be elucidated. A beneficial effect of IL-1Ra on PAPA syndrome has been reported [51]. Some alternative splice variants of the *PSTPIP1* gene have been specifically detected in intractable pyoderma gangrenosum patients, but their significance remains to be elucidated [52].

Hyper IgD syndrome with periodic fever (HIDS; OMIM#260920) is another classical periodic fever syndrome inherited recessively [53]. Typically, early-onset (usually under 1 year of age) recurrent attacks of fever with severe abdominal pain, diarrhea, arthritis, cervical lymphadenopathy and skin rash last 3 to 7 days, at 4 to 8 week intervals [4]. This disease is mostly seen in Northern Europe, especially in Dutch and French populations. A constantly high level of serum IgD is characteristic, but is neither specific nor causative for the attacks. Amyloidosis has only rarely been reported in association with HIDS. In 1999, the *mevalonate kinase (MVK)* gene on chromosome 12 was identified to be responsible for this disease [54,55]. MVK phosphorylates mevalonic acid as the essential step of the 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase-initiated isoprenoids/cholesterol biosynthesis cascade [56]. With a complete defect in MVK activity, mevalonic aciduria occurs with a much more severe phenotype, including the recurrent episodes seen in HIDS [57]. On the other hand, in HIDS patients, MVK activity is reduced but still present, and urinary mevalonate is apparent only during attacks [58]. Therefore, the designation mild mevalonate kinase deficiency, rather than HIDS, has been preferred in recent years. HIDS-type homozygous loss-of-function mutations are hypothesized to affect the stability and/or maturation of MVK, leading to a lack of isoprenoids, especially geranylgeranyl pyruvate, followed by IL-1β-mediated inflammation [59-61]. Furthermore, the beneficial effects of anti-IL-1 therapies, as well as the HMG-CoA reductase inhibitor simvastatin,

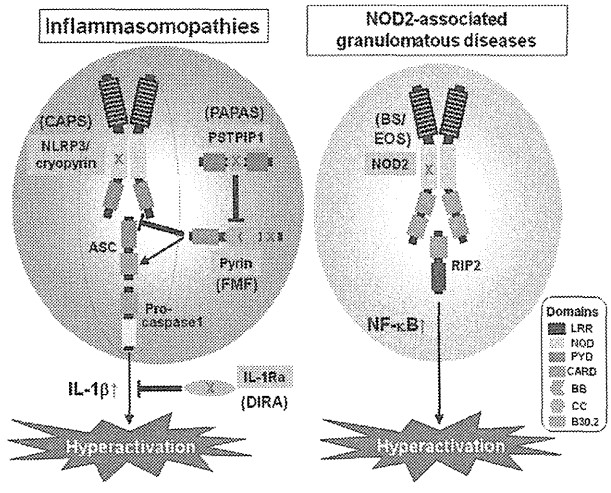

Figure 1: Signaling through NLR molecules in inflammasomopathies and *NOD2*-associated granulomatous diseases.
In CAPS, a heterozygous missense mutation mainly located in the NOD of *NLRP3*/cryopyrin causes its stable oligomerization, and the consequent formation of an inflammasome with ASC and pro-caspase-1 results in constitutive caspase-1 activation and subsequent IL-1β secretion. In FMF, a homozygous missense mutation mainly in the PYD or B30.2 domain of pyrin causes an impaired inhibitory effect on *NLRP3* inflammasome activation. In PAPAS, a heterozygous missense mutation in the CC domain of *PSTPIP1* causes dysregulated pyrin inhibition of the *NLRP3* inflammasome. In DIRA, a homozygous nonsense mutation in IL-IRa causes dysregulated IL-1 signaling. On the other hand, a heterozygous missense mutation located in the NOD of *NOD2* causes its stable oligomerization in BS/EOS, and through interaction with RIP2 induces constitutive NF-kB activation. The names of the diseases and the responsible molecules are indicated in parentheses and in gray squares, respectively.

have been reported [62,63]. Therefore, HIDS is also categorized as an inflammasomopathy, although the precise underlying mechanisms are still unclear [1].

IL-1 Family Receptor Antagonist Deficiencies: DIRA, DITRA

Hispanic patients showing sterile lytic bone lesions and cutaneous pustulosis with fever had already been reported in 1985 and 1993, and their similarities to chronic recurrent multifocal osteomyelitis has been pointed out [64,65]. In 2009, homozygous deletions of 2 base pairs causing premature termination or nonsense mutations in the IL1RN gene encoding IL-1Ra were identified in cases with neonatal-onset sterile multifocal osteomyelitis, periostosis and pustulosis, and the term DIRA has been denoted for this syndrome [24,66]. Clinically, fetal distress, pustular rash, mouth ulcers and painful joint swelling begin around birth and some patients die before 10 years of age due to visceral involvement. Febrile attacks are not apparent, in spite of the high serum C-reactive protein (CRP) levels. Although the effects of anti-rheumatic drugs and corticosteroids are limited, the administration of IL-1Ra gives a rapid response. Since IL-1Ra works as a natural competitive inhibitor of both IL-1α and IL-1β, the defective IL-1Ra causes hyperactivation of IL-1α as well as IL-1β signaling. Therefore, dysregulated IL-1α signaling in keratinocytes and the bone marrow should induce the characteristic phenotypes of DIRA. As compared with IL-1Ra-deficient mice, which gradually develop an autoimmune disease similar to rheumatoid arthritis, the role of IL-1Ra on autoinflammation in the early stages of human development, especially in the skin and bone marrow, should be noted [67].

IL-1Ra, formally called IL-1F3, is structurally similar to other IL-1 family molecules, and its gene is located on the IL-1 family locus [68,69]. Recently, IL-1 family cytokines have expanded to include 11 molecules by a homology search of sequence databases. Interestingly, in two cases with DIRA, a homozygous deletion of 175 kilobases in chromosome 2, which includes *IL 1F9, F6, F8, F5* and *F10*, as well as *IL 1RN*, in the order of the genomic localization, was identified [24,66]. With respect to nomenclature, IL-1F6, F8 and F9 have been changed to IL-36α, β and γ, respectively, whereas IL-1F5 has been renamed IL-36 receptor antagonist (IL-36Ra), which can block signaling with IL-36α, β and γ. Since such a large defect of the IL-1 family members seems to have only a limited effect on the clinical phenotype other than that of IL-1Ra, the effects of both agonistic (IL-36α, β and γ) and antagonistic (IL-36Ra) molecules might be balanced.

In 2011, homozygous mutations were identified in the *IL36RN* gene encoding IL-36Ra by homozygosity mapping of the genome of Tunisian cases with familial GPP, and by exome sequencing of the genome of sporadic European GPP cases [25,70]. IL-36Ra as well as IL-36α, β and γ are predominantly expressed in keratinocytes, and play a role in the induction and regulation of skin inflammation [71,72]. GPP-associated *IL36RN* mutations cause the defective expression and/or impaired antagonistic function of IL36Ra, leading to dysregulated skin inflammation. Recently, the identification of other homozygous and compound heterozygous *IL36RN* mutations has been reported in Japanese sporadic GPP cases and, therefore, a global and ethnicity-specific distribution of *IL36RN* mutations has been revealed [73,74]. Since it has been recently reported that the same mutations are detected in patients with GPP-related various pustular disorders, the phenotypes of DITRA cases have emerged to include GPP, PPP, ACH and AGEP [26,27]. Thus, defective IL-1 family receptor antagonists are crucial for the development of pyogenic pustular disorders in humans.

NOD2-Associated Granulomatous Diseases: BS, EOS

Sarcoidosis is a multi-organ inflammatory disease of unknown etiology, characterized by the histologic features of non-caseating epithelioid granulomas. It is already known that there is a rare but distinct type of sarcoidosis called EOS, characterized by onset in infancy and a triad of arthritis, uveitis and skin rash, without any apparent involvement of the lung and hilar lymph nodes [75]. In 1985, a large family showing EOS-like systemic granulomatosis was reported by Edward Blau and a new entity, named BS, was defined as a distinct disease from EOS by its autosomal dominant inheritance [76]. Histologically, it is hard to distinguish these diseases from sarcoidosis, but their clinical features are clearly different. The skin lesion most commonly shows scaly maculopapules with a tapioca-like appearance, and is described as a lichenoid-type, which is rarely observed in ordinary sarcoidosis [77]. Since the gene responsible for BS had been mapped close to the *inflammatory bowel disease 1 (IBD1)* locus on chromosome 16, mutations of the *NOD2* gene, which was identified for IBD1, were searched and novel heterozygous mutations were identified in familial BS cases, and subsequently in sporadic EOS cases, indicating the same etiology for these diseases [15-18,78]. The designation "pediatric granulomatous arthritis" was proposed to unify them for the international registry, but has not been widely accepted because of the systemic involvement of these diseases [79,80].

NOD2 is mainly expressed in the cytoplasm of monocytes and is essential for the recognition of muramyl dipeptide, which is the minimum and common immunocompetent module of both gram-negative and positive bacterial cell wall peptidoglycans [19,81]. *NOD2*, which contains CARD as an effector domain instead of the PYD in *NLRP3*, interacts with RIP2 (receptor-interacting protein 2) through CARD-CARD homophilic interactions and causes nuclear factor (NF)-κB activation, instead of IL-1β secretion as in the case of *NLRP3* (Figure 1). The most frequent BS/EOS-associated *NOD2* mutation R334W/Q, corresponds to the CAPS-associated *NLRP3* mutation R260W/Q. Although loss-of-function mutations in the C-terminal LRR of *NOD2* are reportedly associated with Crohn's disease in Caucasians but not in Eastern Asians, BS/EOS-related gain-of-function mutations in the central NOD of the same gene are detected in both ethnic groups. An analysis of 20 Japanese BS/EOS cases with *NOD2* mutations revealed genotype-phenotype correlations to some extent between the mutant *NOD2*-induced *in vitro* NF-κB activation and the disease severity, especially for ocular complications [82]. The clinical effect of the NF-κB inhibitor thalidomide, as well as its inhibitory effect on *ex vivo* giant cell formation of the patient's monocytes, further support the role of NF-κB activation in the pathogenesis of BS/EOS [83]. Moreover, histological analyses of the patients' skin specimens demonstrated emperipolesis of the lymphocytes within multinucleated giant cells as another aspect of gain-of-function *NOD2* mutations [84].

Protein Misfolding Disease: TRAPS

Although TRAPS was formerly called familial Hibernian fever ("Hibernia" is the ancient name of Ireland), its prevalence is not limited to a particular area. Clinically, this syndrome is characterized by recurrent episodes of fever, myalgia, rash, arthralgia, abdominal

pain and conjunctivitis that usually last longer than 5 days [4]. Amyloidosis leading to renal dysfunction develops in almost half of the affected families. The most common cutaneous manifestation is a centrifugal migratory and erythematous patch overlying the area with myalgia. Histologically, perivascular and interstitial infiltrates of mononuclear cells are apparent. Corticosteroids, but not colchicine, are reportedly effective for treatment of this disease. Although more than 100 mutations in the *TNFRSF1* gene have been reported, some of them have been identified not only in the affected cases, but also in unaffected relatives [85]. However, considering that this disease reportedly onsets at ages from 2 weeks to 53 years, unaffected mutation carriers may develop symptoms in the future. In some patients, a reduced level of serum soluble TNFR1, a putative negative-feedback regulator of TNF signaling, was observed, and therefore a defective shedding of the surface TNFR1 had been postulated to cause dysregulated TNF signaling [85]. However, the serum soluble TNFR level is not constantly reduced in all patients, and therefore another hypothesis was postulated in which the intracellular aggregation of misfolded TNFR1 causes a hyperimmune response independent of TNF signaling [86,87]. Analyses of disease-associated *TNFRSF1* mutation-knockin mice showed that heterozygous rather than homozygous mutant mice developed the inflammatory phenotype by a synergy of the intracellular aggregation of misfolded TNFR1 plus the surface expression of intact TNFR1 [88]. The effectiveness of IL-1Ra as well as the anti-TNF drug etanercept, a recombinant soluble TNFR1 fused to human IgG1, has been reported, suggesting the involvement of both TNF-dependent and independent inflammation in the pathogenesis of TRAPS [89,90].

Proteasome Disability Syndromes: ALDD Syndrome

NNS is a very rare autosomal recessive disease, originally reported in Japan by Nakajo in 1939 and Nishimura in 1950 as "secondary hypertrophic osteoperiostosis with pernio". This disease was soon recognized as a new entity uniquely reported from Japan, and has subsequently been reported as "a syndrome with nodular erythema, elongated and thickened fingers, and emaciation" or "hereditary lipomuscular atrophy with joint contracture, skin eruptions and hyper-γ-globulinemia" based on its common characteristic features [91,92]. NNS usually begins in early infancy with pernio-like rashes and develops periodic high fever, nodular erythema-like eruptions and myositis. Lipomuscular atrophy and joint contractures gradually progress, mainly in the upper body, to form the characteristic thin facial appearance and elongated clubbed fingers. Marked inflammatory changes include constantly elevated CRP levels and hyper-γ-globulinemia, hepatosplenomegaly, basal ganglia calcification and focal mononuclear cell infiltration with vasculopathy on histopathology. Although autoantibodies are negative at the onset, their titers increase as the disease progresses in some cases. Using homozygosity mapping, a G201V mutation of the *PSMB8* gene encoding the β5i IP subunit was identified to be responsible for NNS in 2011 [28,29]. This mutation not only impairs the β5i-induced chymotrypsin-like activity, but also inhibits proper IP assembly and all proteasome activities [28]. With the accumulation of ubiquitinated and oxidated proteins, p38-mitogen-activated protein kinase (MAPK) activation and IL-6 overproduction were shown to be involved in the autoinflammatory phenotype. It has also been reported that IP contributes to adipocyte differentiation, and the impaired β5i activity causes lipoatrophy *in vivo* [29]. Although NNS has been considered to be unique to Japan, similar cases have been reported overseas in 2010 by different designations [93,94]. Portuguese and Mexican familial cases were reported as JMP syndrome, and commonly showed sclerodermic skin with erythematous lesions, generalized or partial lipomuscular atrophy, joint contractures, a short stature, hepatosplenomegaly, hyper- γ-globulinemia and microcytic anemia. Although no cases showed fever, elevated erythrocyte sedimentation rates, basal ganglia calcification and seizures were noted in some patients [93]. In addition, Spanish, Hispanic, Caucasian and Jewish cases were reported as CANDLE syndrome, which was characterized by onset during the first year of life, recurrent fever, purpuric skin lesions, violaceous swollen eyelids, arthralgia, progressive lipodystrophy, anemia, delayed physical development, increased acute phase reactants and a characteristic histological feature with an atypical infiltration of mixed mononuclear cells and neutrophils [31,94-96]. A homozygous p.T75M mutation, which only impairs the β5i-responsible chymotrypsin-like activity, has been identified in all JMP and most CANDLE cases, whereas p.C135X predictably abolished IP formation in a Jewish case [30,31]. Interestingly, a marked elevation of interferon (IFN) γ-induced protein-10 (IP-10, formally called CXCL10) was commonly observed in the sera of NNS and CANDLE patients, and the IFN pathway was identified as the most dysregulated one by whole blood microarray analysis of the CANDLE patients. Furthermore, stronger phosphorylation of the signal transducers and activators of transcription (STAT)-1 in the CANDLE patients' monocytes was observed, and the therapeutic application of a Janus kinase (JAK) inhibitor, tofacitinib, was proposed [31]. Thus, NNS, JMP and CANDLE syndromes, showing similar but slightly different clinical features, are caused by distinct mutations of the *PSMB8* gene affecting slightly different inflammation pathways. To classify these diseases together, ALDD syndrome has recently been proposed in OMIM. It should be noted that they commonly indicate the significance of the ubiquitin-proteasome system in the regulation or homeostasis of inflammation, and establish a new category of autoinflammatory disorders as "proteasome disability syndromes".

Concluding Remarks

The identification of the genes responsible for rare hereditary autoinflammatory syndromes has given us important clues to find novel and critical *in vivo* inflammatory pathways. There still remain a number of undefined hereditary autoinflammatory syndromes with novel mutations, and further clinical and genetic studies are necessary to clarify the underlying pathophysiology. Clinicians should distinguish the disease as known or novel according to the clinical criteria, and if novel, should further define whether it can be caused by any known pathway by profiling the serum cytokines, immunohistochemistry of the lesional tissues, flow cytometry, DNA microarray and genomic analyses. If the results predict the presence of a novel disorder with a novel pathway, then whole exome/genome sequencing might be considered. Using such a strategy, novel diseases and novel pathways would be discovered, and thus novel therapies can be developed which target the disease origin specifically and effectively with minimal side effects.

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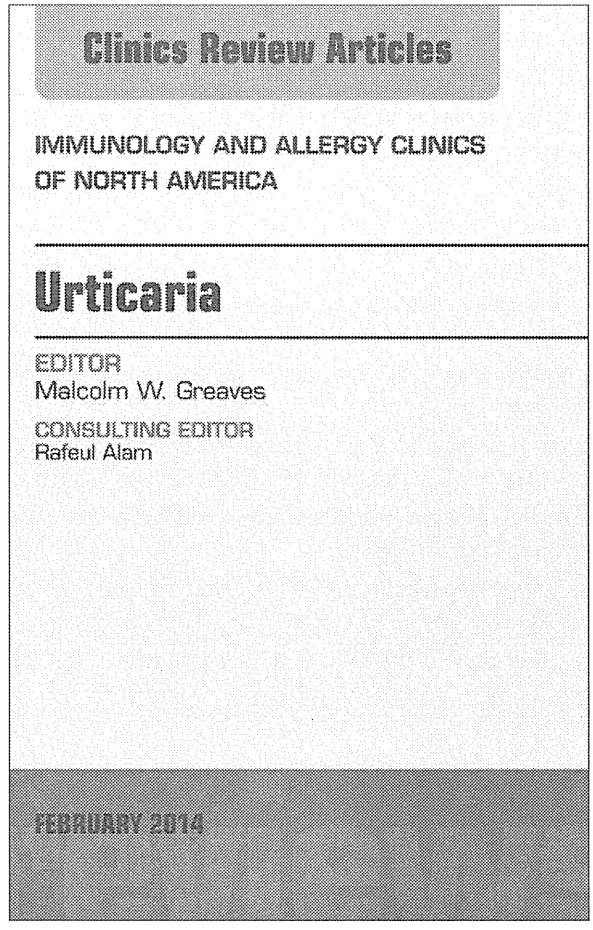

Hereditary Disorders Presenting with Urticaria

Nobuo Kanazawa, MD, PhD

KEYWORDS

• KIT • C1-inhibitor • Bradykinin • NLRP3 inflammasome • IL-1β • NLRP12 • PLCγ2 • Autoinflammatory syndrome

KEY POINTS

- Hereditary disorders presenting with urticaria are not common and may not be encountered by most physicians.
- Hereditary disorders presenting with urticaria can be easily missed or misdiagnosed without correct knowledge.
- With proper diagnosis and understanding of the genetic cause and consequent pathogenesis, disease-specific essential therapeutic regimens can be offered.
- Recent discovery of the genetic origins for rare cases with distinct hereditary cold urticaria encourages examination of more cases.
- With rapid progress in genetic analysis, further insights into undefined hereditary urticaria will emerge in the near future.
- The knowledge obtained is promising for the development of novel therapeutics.

INTRODUCTION

Hereditary diseases listed in the latest clinical guideline for urticaria include *KIT* mutations–induced urticaria pigmentosa (mastocytosis), *C1NH* mutations–induced hereditary angioedema (HAE), and *NLRP3* mutations–induced cryopyrin-associated periodic syndromes (CAPS).[1] Although acquired somatic mutations in the *KIT* gene have a central role in the pathogenesis of mastocytosis, some germline *KIT* mutations have been reported in rare familial cases of pediatric mastocytosis.[2] HAE is a potentially life-threatening disease, and a precise diagnosis is required for replacement therapy of complement component 1 inhibitor (C1-INH).[3] CAPS are the most studied hereditary autoinflammatory disorders with dysregulated inflammasome signaling,

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for which a precise diagnosis is also critical for early intervention with anti-interleukin (IL)-1β therapy.[4]

In recent years, distinct syndromes with urticarial skin lesions, termed familial cold-induced autoinflammatory syndrome 2 (FCAS2) and FCAS3, have been designated as NLRP12-associated periodic syndromes (NAPS12) and PLCG2-associated antibody deficiency and immune dysregulation (PLAID), respectively, by identification of their genetic origins.[5–7] Moreover, there still remain more than a few cases with genetically undefined hereditary urticaria. The diseases discussed in this article are summarized in Table 1.

MASTOCYTOSIS

Mastocytosis (also known as mast cell disease, OMIM #154800) is divided into cutaneous mastocytosis (CM) and systemic mastocytosis (SM).[2] CM includes urticaria pigmentosa (UP), mastocytoma of the skin, and diffuse CM. In contrast to CM confined to the skin, SM is defined by mast cell infiltration in at least one extracutaneous lesion with or without cutaneous involvement (Table 2). CM is more commonly observed in children, especially before 6 months of age, but also affects adults mainly in the third to fourth decade.[8] Whereas pediatric CM spontaneously regresses before puberty in most cases, UP in adults has a significant risk of progression to SM.[9] UP is the most common variant of CM, and is characterized by disseminated brown macules or papules.[10] Consistent with the histologic feature showing massive mast cell infiltration in the papillary dermis with epidermal hypermelanosis, scratching the lesions induces mast cell degranulation and causes local flare and wheal reaction. This phenomenon, called Darier's sign, is useful for the diagnosis of UP. Similarly, cutaneous symptoms such as urticarial rashes, edema, and pruritus can be triggered by mechanical and thermal stimuli. Mastocytoma of the skin usually presents a few brown or orange plaques or

Table 1
Hereditary diseases with urticaria

Designation		OMIM Number	Responsible Gene
Mastocytosis		#154800	*KIT*
Hereditary angioedema (HAE)	Types I and II	#106100	*CINH*
	Type III	#610618	*F12*
Cryopyrin-associated periodic syndrome (CAPS)	Familial cold-induced autoinflammatory syndrome (FCAS)	#120100	*NLRP3*
	Muckle-Wells syndrome (MWS)	#191900	
	Chronic infantile neurologic cutaneous articular (CINCA) syndrome	#607115	
NLRP12-associated periodic syndrome (NAPS12)		#611762	*NLRP12*
PLCG2-associated antibody deficiency and immune dysregulation (PLAID)		#614468	*PLCG2*
Aquagenic urticaria		191850	Unknown
Familial localized heat urticaria		191950	Unknown
Dermodistortive urticaria		125630	Unknown
Familial dermographism		125635	Unknown

Table 2
Classification of mastocytosis

Variant	Subvariant	Prognosis (Expected Median Survival)
Cutaneous mastocytosis (CM)	Urticaria pigmentosa (UP)	Good
	Mastocytoma of the skin	
	Diffuse CM	
Systemic mastocytosis (SM)	Indolent SM	Good (>16 y)
	SM with an associated clonal hematologic non–mast cell lineage disease (SM-AHNMD)	Poor (2 y)
	Aggressive SM	Poor (3.5 y)
	Mast cell leukemia	Very poor (2 mo)
	Mast cell sarcoma	Very poor
	Extracutaneous mastocytoma	Good

nodules, larger than 1 cm in diameter.[11] Diffuse CM is an extremely rare variant of CM, in which the skin undergoes generalized infiltration and may even cause erythroderma. Because of the dense infiltration of mast cells, bullous lesions can appear after stimuli or even spontaneously, more commonly in the latter 2 variants of CM.[12] Although evidence of systemic involvement (eg, bone marrow infiltration) is common, systemic symptoms are rare (indolent systemic mastocytosis).[13] Rarely, florid systemic symptoms (diarrhea, wheezing, syncope, and even anaphylaxis) may occur (aggressive systemic mastocytosis) after extensive release of mast cell mediators.

Functional mutations in the *KIT* gene have been detected from mast cells in the lesional skin, and rarely in the blood or bone marrow, indicating the somatic occurrence of these mutations.[14] KIT (CD117) is a receptor for stem cell factor (SCF), the essential growth factor for mast cells and melanocytes, and functions as a receptor tyrosine kinase. The most common activating *KIT* mutation, D816V, can be identified in mast cells from more than 90% of SM cases in adults. By contrast, the same mutation has been found in mast cells from only about one-third of pediatric CM patients.[15] The remaining 5% of adult SM cases and more than half of pediatric CM cases predictably show other *KIT* mutations.[16,17] It should be noted that the presence of the mutation in D816V does not alone induce malignant transformation of mast cells, and pediatric CM cases with this mutation reportedly fail to segregate with progressive or persistent disease.[18,19] Most strikingly, as predicted by an early report of an occurrence of mastocytosis in familial traits and monogenic twins, germline *KIT* mutations have been identified in some familial cases, indicating that mastocytosis can be a hereditary disease with a KIT mutation.[20,21]

HAE

HAE (OMIM #106100) is a rare autosomal dominant disorder with recurrent attacks of nonpitting tissue edema, as a result of increased vascular leakage in subcutaneous or submucosal tissue.[3] Although a description of this disease originates from the late nineteenth century, the underlying deficiency of C1-INH was identified in the 1960s.[22,23] The tissue edema is self-limited, with a longer duration than the wheals of chronic spontaneous urticaria. However, swelling of the extremities, face, and genitals often interferes with daily life, and laryngeal and upper airway swelling is potentially life-threatening and needs emergency control. Abdominal pain with nausea, vomiting, and diarrhea caused by intestinal edema may be misdiagnosed as acute

abdomen and treated surgically. Moreover, facial edema, especially affecting the eyelids or lips, can damage the patient's body image and impair the quality of life of patients and their families.[24]

HAE is classified into 3 types depending on the level and activity of C1-INH (Table 3). Type I, with low level and activity of CI-INH, accounts for approximately 85% of HAE cases. Type II, with normal or elevated CI-INH level and impaired functional activity, affects the remaining 15% or so. Both types are caused by heterozygous mutations in the *C1NH* (also called *SERPING1*) gene, possibly leading to haploinsufficiency of the C1-INH activity. More than 200 disease-related mutations, deletions, or insertions causing reduced production of the C1-INH protein are associated with type I HAE, whereas point mutations in the protease-binding region of the C1-INH protein are linked to type II HAE.[25] By contrast, type III HAE (OMIM #610618), with normal level and activity of C1-INH, is rare but restricted to females.[26] In 2006, a unique heterozygous missense mutation in the *F12* gene was identified in 4 families with a founder effect.[27,28] This gain-of-function mutation has been shown to increase the activity of factor XII (also called Hageman factor), which is involved in the generation of kinins and is regulated by estrogens.

C1-INH is a plasma protein belonging to a family of serine protease inhibitors (serpins) and plays a regulatory role in multiple steps of the complement, contact, and coagulation systems (Fig. 1). The effect of C1-INH deficiency in the complement system has a diagnostic value, because a low serum C4 level is highly suggestive of C1-INH deficiency. By contrast, the role of C1-INH in the contact system is more important for the pathogenesis of HAE. In the case of C1-INH deficiency, activation of this system is exaggerated by hyperactivation of factor XII and prekallikrein, leading to overproduction of bradykinin, a potent vasodilator and inducer of vasopermeability. In fact an increased plasma bradykinin level has been revealed in HAE patients, especially during attacks.[29]

Appropriate management of HAE requires urgent therapy, and short-term and long-term prophylaxis.[30] For acute attacks neither corticosteroid nor epinephrine is effective, and plasma-derived pasteurized C1-INH is most widely administered. Fresh frozen plasma is still used in cases of emergency, but should be used carefully because of a risk of worsening the attack. Recently, a kallikrein inhibitor (ecallantide) and a selective bradykinin B2 receptor antagonist (icatibant) have been approved in Europe and the United States for the treatment of acute attacks. For short-term prophylaxis before dental manipulation or surgery, danazol has been used and, recently, nanofiltered C1-INH has been used for adult and adolescent cases. The same regimens have been used for long-term prophylaxis.

CAPS

Familial cold urticaria (FCU), showing recurrent attacks of urticarial rashes after general exposure to the cold, was first described in 1940.[31] Arthralgia, myalgia, chills, and fever accompanied attacks. A related hereditary disease with recurrent episodes of urticarial

Table 3
Classification of HAE

	C4 Level	C1-INH Level	C1-INH Activity
Type I	Low	Low	Low
Type II	Low	Normal or elevated	Low
Type III	Normal	Normal	Normal

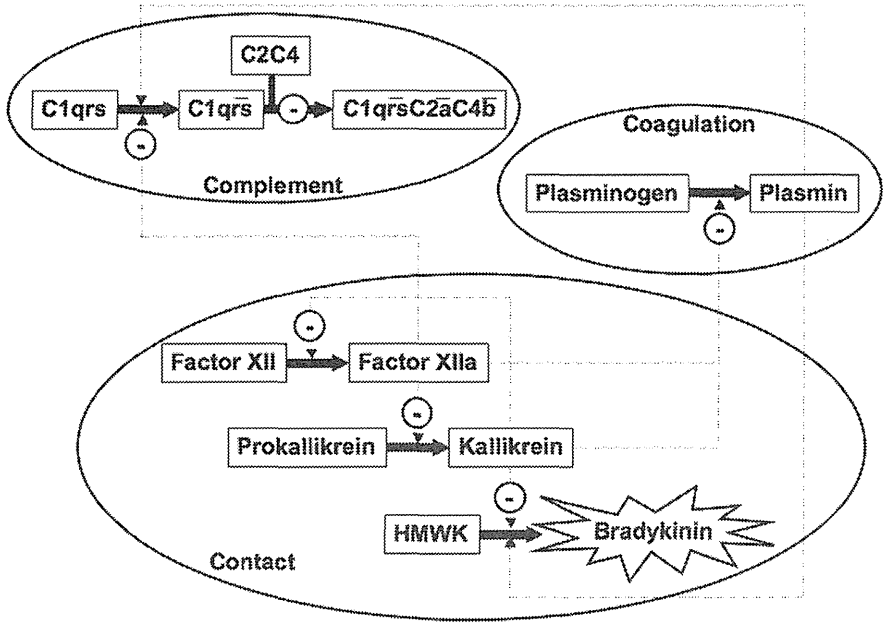

Fig. 1. The regulatory role of C1-INH in the complement, contact, and coagulation systems. Action points of CI-INH are indicated by dashes within circles. HMWK, high molecular weight kininogen.

rash with accompanying symptoms without cold exposure was first described in 1962.[32] Development of late-onset sensorineural deafness and renal amyloidosis was possible, and the disease was called urticaria-deafness-amyloidosis or Muckle-Wells syndrome (MWS; OMIM #191900). In 2001, a new gene in chromosome 1q44 was identified as being responsible for both diseases.[33] The identified gene product has been designated as cryopyrin, which means "cold-induced fever," because of its similarity to pyrin, the *MEFV* gene product responsible for familial Mediterranean fever.[34] Moreover, based on the genetic and clinical similarities to hereditary periodic fever syndromes, the name of the disease has been changed from FCU to familial cold-induced autoinflammatory syndrome (FCAS; OMIM #120100). In 2002, mutations in the same gene were further detected in more severe hereditary disorder, chronic infantile neurologic cutaneous and articular (CINCA) syndrome (OMIM #607115), characterized by a neonatal-onset triad of rash, chronic meningitis, and joint inflammation with recurrent fever.[35,36] Thus these 3 disorders sharing the same genetic origin are defined as forming a sequential spectrum of CAPS.[37] Although CAPS patients may show absence for *NLRP3* mutations, especially in the case of the severe variant, somatic mosaicism of the *NLRP3* mutation has globally been identified in some of these cases.[38]

Cryopyrin is composed of the N-terminal pyrin domain (PYD), central nucleotide oligomerization domain (NOD), and C-terminal leucine-rich repeats (LRR). This molecule is one of the most characterized NOD-like receptor (NLR) family molecules, and has formally been designated as NLRP3.[39] When stimulated with various danger signals, NLRP3 forms a pentamer and associates with procaspase-1 containing the caspase-recruitment domain (CARD), through an adaptor molecule, "apoptosis-associated speck-like protein with a CARD (ASC)," consisting of both PYD and CARD. This NLRP3–ASC–procaspase-1 complex, formed through homophilic interaction of each domain (PYD-PYD and CARD-CARD), has been designated as the NLRP3 inflammasome.[40] This complex works as a cytoplasmic platform activating caspases-1–mediated IL-1β/IL-18 secretion. In the case of CAPS, missense mutations in NLRP3 cause constitutive formation of the inflammasome complex and subsequent IL-1β secretion

(Fig. 2). NLRP3 activation in monocytes results in elevated serum IL-1β level, while its activation and IL-1β secretion by dermal mast cells are associated with vascular leakage and neutrophil recruitment in the urticarial rash.[41]

Anti–IL-1 therapies, including recombinant IL-1 receptor antagonist (IL-1Ra) known as anakinra, rilonacept, composed of extracellular IL-1RI and accessory protein (AcP), and anti–IL-1β antibodies such as canakinumab, dramatically improve almost all symptoms of CAPS, indicating the critical role played by IL-1β in the development of CAPS.[42–44]

NAPS12

Two unrelated families with an autosomal dominantly inherited periodic fever syndrome were reported from Guadeloupe in 2008.[5] In one family, twin sons and their father were affected. The sons showed episodic fever, arthralgia, and myalgia induced by generalized cold exposure since the first days of life. Urticaria was also observed twice in each patient. Headache and lower limb pain occurred during and between episodes, and both patients had bilateral sensorineural hearing loss. Their father had also experienced occasional attacks during childhood and still showed episodes of fever and urticaria triggered by physical activities, without hearing loss. An affected daughter in the second family developed cold-induced episodic fever with abdominal pain, vomiting, arthralgia, buccal aphthous ulcers, and lymphadenopathy since the

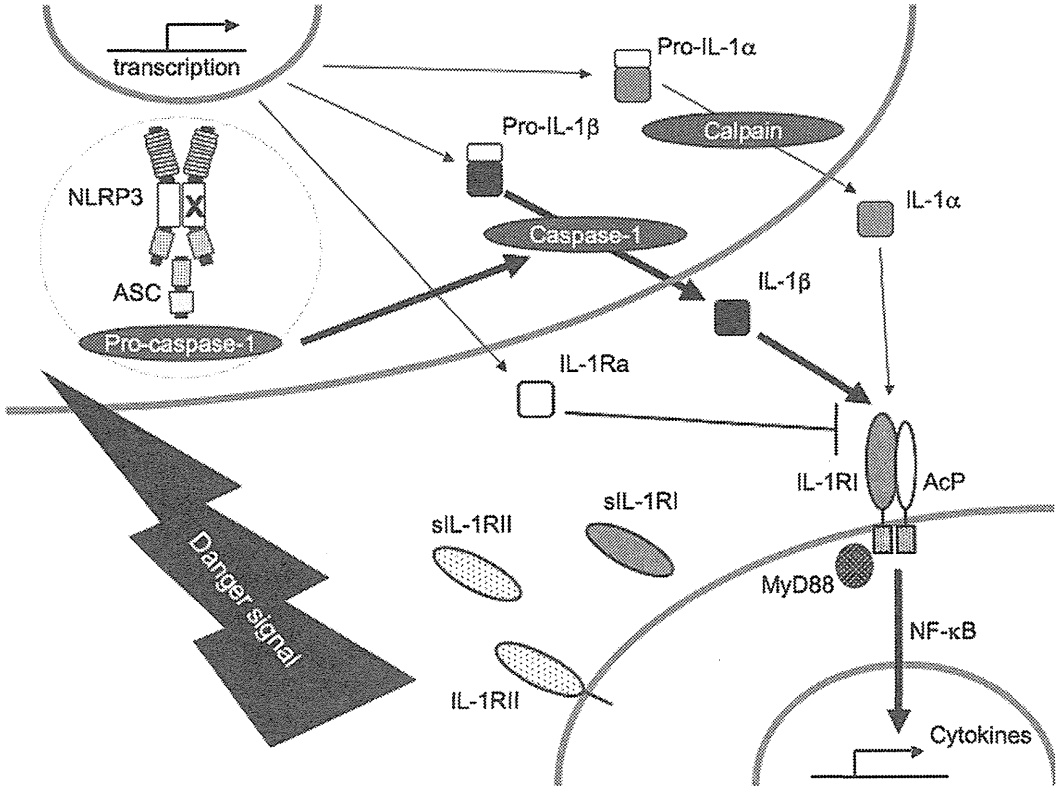

Fig. 2. Molecular pathogenesis of CAPS. In CAPS, a heterozygous *NLRP3* mutation (indicated by X in dimerized molecules) causes constitutive activation of the inflammasome complex (surrounded by a broken-lined circle), leading to cleavage of preformed pro-IL-1β with activated caspase-1 and secretion of mature IL-1β to cause sustained inflammation. On danger, only one signal to induce transcription of pro-IL-1β mRNA is enough for secretion of mature IL-1β. The decoy receptor IL-1RII, soluble (s) IL-1RI and sIL-1RII, as well as IL-1Ra, are all negative regulators of IL-1 signaling.