

Hereditary Disorders Presenting with Urticaria

Nobuo Kanazawa, MD, PhD

KEYWORDS

- KIT • C1-inhibitor • Bradykinin • NLRP3 inflammasome • IL-1 β • NLRP12 • PLC γ 2
- 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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Department of Dermatology, Wakayama Medical University, 811-1 Kimiidera, Wakayama 641-0012, Japan

E-mail address: nkanazaw@wakayama-med.ac.jp

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for which a precise diagnosis is also critical for early intervention with anti-interleukin (IL)-1 β 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	<i>KIT</i>
Hereditary angioedema (HAE)	Types I and II	#106100	<i>C1NH</i>
	Type III	#610618	<i>F12</i>
Cryopyrin-associated periodic syndrome (CAPS)	Familial cold-induced autoinflammatory syndrome (FCAS)	#120100	<i>NLRP3</i>
	Muckle-Wells syndrome (MWS)	#191900	
	Chronic infantile neurologic cutaneous articular (CINCA) syndrome	#607115	
NLRP12-associated periodic syndrome (NAPS12)		#611762	<i>NLRP12</i>
PLCG2-associated antibody deficiency and immune dysregulation (PLAID)		#614468	<i>PLCG2</i>
Aquagenic urticaria		191850	Unknown
Familial localized heat urticaria		191950	Unknown
Dermodistortive urticaria		125630	Unknown
Familial dermatographism		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 C1-INH, accounts for approximately 85% of HAE cases. Type II, with normal or elevated C1-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

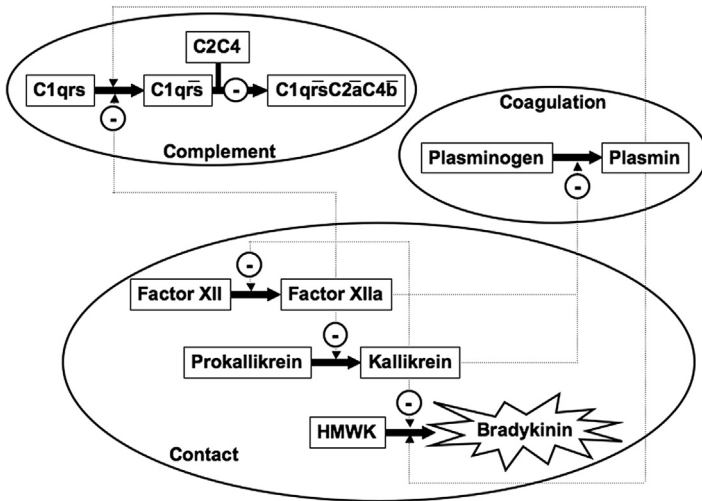


Fig. 1. The regulatory role of C1-INH in the complement, contact, and coagulation systems. Action points of CI-INH are indicated by dashes within circles. HMWK, high molecular weight kininogen.

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-1 β /IL-18 secretion. In the case of CAPS, missense mutations in NLRP3 cause constitutive formation of the inflammasome complex and subsequent IL-1 β secretion

(Fig. 2). NLRP3 activation in monocytes results in elevated serum IL-1 β level, while its activation and IL-1 β 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-1 β antibodies such as canakinumab, dramatically improve almost all symptoms of CAPS, indicating the critical role played by IL-1 β 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

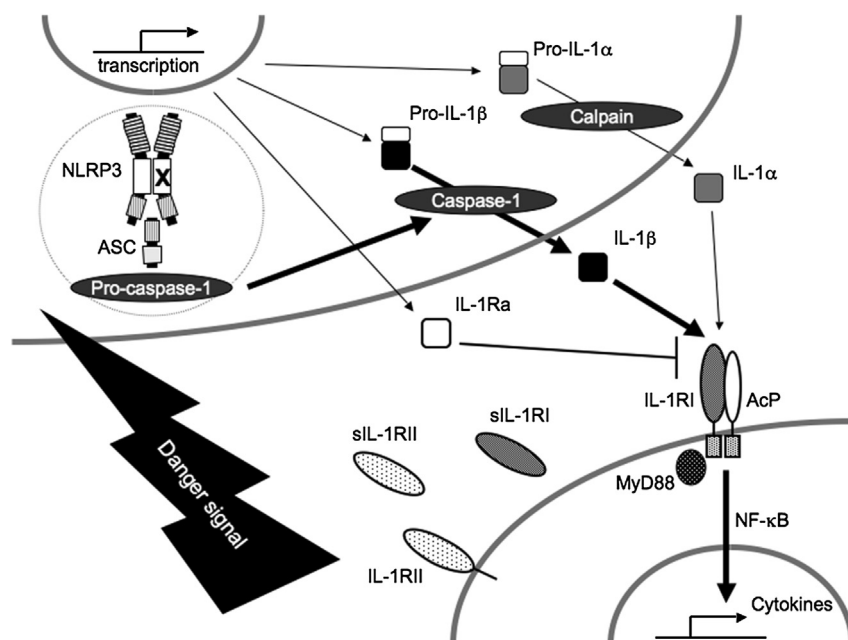


Fig. 2. Molecular pathogenesis of CAPS. In CAPS, a heterozygous *NLRP3* mutation (indicated by X in dimerized molecules) causes constitutive activation of the inflammasome complex (surrounded by a broken-lined circle), leading to cleavage of preformed pro-IL-1 β with activated caspase-1 and secretion of mature IL-1 β to cause sustained inflammation. On danger, only one signal to induce transcription of pro-IL-1 β mRNA is enough for secretion of mature IL-1 β . 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.

first year of life. Her affected father also had attacks with fever and abdominal pain between the ages of 5 and 12 years.

Because of the similarity of their symptoms to CAPS, their disease was designated as FCAS2 (OMIM #611762). Through an extensive search for mutations in NLR family molecules, heterozygous nonsense or insertion mutations in the *NLRP12* gene have been identified in each family.⁵ A base-pair insertion within the donor splice site of intron 3 activates a cryptic donor splice site, resulting in a frame shift and a premature termination. As *NLRP12* has been shown to be a negative regulator of nuclear factor (NF)- κ B signaling and such an inhibitory effect was actually impaired by these mutations, their heterozygosity seems to cause haploinsufficiency in patients.⁴⁵

PLAID

Three unrelated families with autosomal dominantly inherited atypical cold urticaria were first reported in 2009.⁴⁶ As a characteristic feature, water evaporation seems to be the most effective stimulus, which is occasionally induced by tears flowing down the cheeks or warm water on the skin exposed to room temperature. Accordingly, the patients show a negative cold-stimulation test using ice cubes, whereas urticarial rashes appear after direct contact of ice to the skin followed by rewarming to room temperature. Outdoor cold air also induces urticarial rash over unprotected areas. All patients experienced pruritus and erythema, whereas angioedema was experienced by less than half of the cases. Reactions are local rather than generalized, are not accompanied by systemic complications, and usually resolve within 30 minutes. Of note, ingestion of cold foods or beverages caused oropharyngeal swelling in some cases. Most patients develop the symptoms before 6 months of age and sustain them for life, although their severity usually improves after 30 years of age. The disease has been designated as familial atypical cold urticaria (FACU) or FCAS3 (OMIM #614468), which is clearly distinguished from FCAS by the absence of systemic involvement.

In 2012, immunologic abnormalities were added to their clinical features. These abnormalities include recurrent infections associated with low immunoglobulin (Ig)A and IgM, and high IgE levels in the serum, decreased circulating B cells and natural killer (NK) cells, and development of autoantibodies or autoimmune diseases and granulomatous skin lesions.⁶ Through linkage analysis, 3 different heterozygous deletions in the *PLCG2* gene have been identified as responsible, and the disease has been designated as PLAID. Phospholipase C (PLC) family enzymes hydrolyze membranous phospholipids and generate diacylglycerols and inositol triphosphate to activate calcium influx. Among them, $PLC\gamma 2$ is expressed in B, NK, and mast cells, and involves signaling through various receptor tyrosine kinases. All 3 deletions are included in the C-terminal Src-homology-2 (SH2) domain with an autoinhibitory role, and lack of this domain has been shown to increase the phospholipase activity of $PLC\gamma 2$. The downstream functions of the immune cells, however, were mostly decreased, probably as a result of chronic signaling. By contrast, mast cells with mutant *PLCG2* showed spontaneous degranulation at 20°C, probably responsible for cold urticaria.⁶

Almost simultaneously, familial cases showing recurrent blistering skin lesions with inflammatory lesions of the joints, eyes, and gastrointestinal tract were reported.⁷ Their skin lesions resembled epidermolysis bullosa in infancy, but progressed to erythematous plaques with vesiculopustules, which worsened with heat and sun exposure. These patients also showed mild deficiency of humoral immunity causing recurrent sinopulmonary infections, without circulating autoantibodies. Through whole exome sequencing, a heterozygous gain-of-function missense mutation in the *PLCG2*

Table 4
Hereditary diseases with cold-induced urticaria

		Episodic Symptoms	Sustained/Progressive Symptoms
CAPS	FCAS	Urticarial rash, arthralgia, myalgia, chills, fever, swelling of the extremities	Renal amyloidosis
	MWS	Urticarial rash, arthralgia, chills, fever	Sensorineural deafness, renal amyloidosis
	CINCA	Fever	Rash, arthritis, chronic meningitis, visual defect, deafness, growth retardation, renal amyloidosis
NAPS12 (FCAS2)		Fever, arthralgia, myalgia, urticaria, abdominal pain, aphthous ulcers, lymphadenopathy	Sensorineural deafness
PLAID (FCAS3)		Urticaria induced by evaporative cooling, sinopulmonary infections	Serum low immunoglobulin (Ig)M and IgA levels, high IgE levels, decreased B and NK cells, granulomata, antinuclear antibodies

gene has been identified as being responsible.⁷ Despite some distinctive clinical and genetic features, the diseases in this family and the families with PLAID possibly form a distinct type of hereditary autoinflammatory syndrome with immunodeficiency. The clinical features of hereditary diseases with cold-induced urticaria are summarized in [Table 4](#).

OTHER GENETICALLY UNDEFINED HEREDITARY URTICARIA

On searching the OMIM database, several disorders with distinct OMIM numbers remain to be genetically defined. Aquagenic urticaria (OMIM 191850) is characterized by urticaria induced by contact with water but not by heat or cold, and its familial occurrence was reported in 1979.⁴⁷ Familial cases with delayed heat urticaria were reported as familial localized heat urticaria (OMIM 191950),⁴⁸ in which the lesions were limited to the areas of contact with heat and were completely inhibited by local lidocaine pretreatment. Another 2 forms of familial physical urticaria, dermodistortive urticaria (OMIM 125630) and familial dermatographism (OMIM 125635), are also registered.^{49,50} The former is induced by repetitive vibratory or stretching stimulation, whereas the latter is defined by wheal formation on the skin after a single stroke with moderate pressure.

SUMMARY

Hereditary disorders presenting with urticaria are not common and may not be encountered by most physicians. However, without the correct knowledge they can be easily missed or misdiagnosed. 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 of rare cases with distinct hereditary cold urticaria encourages the examination of more cases. As technology in genetic analysis progresses rapidly, further insights into undefined hereditary urticaria will emerge in the near future. The knowledge obtained promises to lead to the development of novel therapeutics.

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