Hereditary Disorders Presenting with Urticaria

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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