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SUPPLEMENT ARTICLE

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# Primary atopic disorders and chronic skin disease

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## Abstract

Primary atopic disorders (PADs) are monogenic diseases characterized by allergy or atopy-related symptoms as fundamental features. In patients with PADs, primary immune deficiency and immune dysregulation symptoms are usually coexist. Chronic skin disease, manifesting with erythroderma, severe atopic dermatitis or eczema, and urticaria, is one of the main features observed in PADs, such as hyper-IgE syndromes, Omenn syndrome, Wiskott-Aldrich syndrome, IPEX-linked syndrome, skin barrier disorders, as well as some autoinflammatory diseases. The recognition of PADs in the context of an allergic phenotype is crucial to ensure prompt diagnosis and appropriate treatment. This article provides an overview of the main PADs with skin involvement.

**KEYWORDS**
allergy, IgE, inborn errors of immunity, primary atopic disorders, skin

Bianca Laura Cinicola and Stefania Corrente contributed equally to work.

## 1 | INTRODUCTION

Primary atopic disorders (PADs) are monogenic diseases characterized by allergy or atopy-related symptoms as fundamental features. Different pathways are involved in the pathogenesis of these genetic disorders and are responsible for the generation of an atopic environment, possibly associated with marked IgE elevation.[1] In patients with PADs, the coexistence of a primary immune deficiency or immune dysregulation disorder is often observed. Indeed, several inborn errors of immunity (IEI) can manifest with a broad spectrum of phenotypes ranging from immunodeficiency to allergy, autoimmunity, and autoinflammation. Furthermore, chronic skin disease is frequently present in these conditions. This article summarizes different PADs with chronic skin involvement as a prominent feature (Table S1 in the online repository).

**Key Message**

The recognition of primary atopic disorders (PADs) in the context of an allergic phenotype is crucial to ensure prompt diagnosis and appropriate treatment of these rare diseases.

### 1.1 | Hyper-IgE Syndromes (HIES)

The prototype of HIES is the STAT3-HIES, caused by autosomal dominant (AD) loss-of-function (LOF) mutations in Signal Transducer and Activator of Transcription 3 (STAT3). Patients have elevated serum IgE, eosinophilia, newborn rash, eczema, recurrent bacterial sinopulmonary infections, pneumatoceles, chronic mucocutaneous candidiasis, connective tissue, and vascular abnormalities.[2] A similar phenotype was identified in patients with autosomal recessive (AR) or AD mutations in the STAT3 pathway, which includes a novel AR form of HIES due to biallelic mutations in Zinc Finger Protein 341 (ZNF341) or to hypomorphic mutations of the Interleukin 6 Signal Transducer (IL6ST) gene. Recently, AD mutations in IL6ST have been described as the second genetic etiology of STAT3-HIES.[3]

Patients with ERBIN deficiency, due to LOF mutation in ERBB2IP, present with similar allergic and connective tissue phenotypes of STAT3-HIES, T-regulatory cell proliferation, and Th2 polarization.[4]

AR hypomorphic mutation in phosphoglucomutase 3 (PMG3) causes a HIES disease characterized by severe combined immune deficiency (CID) with severe atopy, skeletal dysplasia, autoimmunity, and neurological features.[5]

Dedicator of Cytokinesis 8 (DOCK8) deficiency is an AR-HIES, characterized by severe eczema, increased susceptibility to opportunistic infections, in particular, viral infections, autoimmunity, neurological manifestations, cerebral vascular malformations, and increased risk for malignancies.[3]

## 2 | OTHER MONOGENIC IEIS WITH ATOPIC PHENOTYPES

Other monogenic diseases distinct from the classical forms of HIES may be associated with eczematous skin lesions, erythroderma, and hyper-IgE.

Omenn Syndrome (OS) is a rare condition associated with multiple genetic abnormalities such as severe combined immune deficiencies and is caused by marked Th2-skewing and inflammation. It is characterized by severe eczema and erythroderma, eosinophilia, hyper-IgE, marked lymphoproliferation, and organomegaly.[1] An Omenn-like presentation can also occur in children with an atypical complete DiGeorge syndrome, caused by a hemizygous 22q11 deletion or TBX1mutation who also develop severe eczema and erythroderma.[3]

Immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome is caused by mutations in the FOXP3 gene, which is relevant for the generation of regulatory T cells. Patients may present with eczema, hyper-IgE, eosinophilia, immediate hypersensitivity, diarrhea, severe infections, and endocrinopathies. Recently several IPEX-like syndromes have been described, including CD25 deficiency, STAT5 deficiency, and Itchy E3 Ubiquitin Protein Ligase deficiency.[3]

Wiskott Aldrich syndrome (WAS) is an X-linked immunodeficiency caused by mutations in the WAS gene and characterized by micro-thrombocytopenia, severe eczema, and recurrent infections. Patients have a clinical phenotype ranging from autoimmunity to atopy and autoinflammation.[3] Immune dysregulation and, especially defective Treg cell function may be responsible for the atopic phenotype.[6]

Atopic diathesis is also described in the platelet abnormalities with eosinophilia and immune-mediated inflammatory disease (PLTEID). It is caused by biallelic mutations of the actin-related protein 2/3 complex subunit 1B (ARPC1B) gene, leading to a WAS-like phenotype characterized by systemic inflammation and lymphoproliferation immunodeficiency with severe infections, eczema, and early-onset vasculitis.[3]

CBM-opathies are IEI characterized by a wide range of manifestations, from combined immunodeficiency (CID) to early-onset severe atopic dermatitis. They are caused by germline mutations in genes encoding for caspase recruitment domain (CARD) proteins–B-cell CLL/lymphoma 10 (BCL10)–MALT1 paracaspase (MALT1) [CBM] complexes.

Hypomorphic dominant-negative mutations in CARD11 may result in recurrent respiratory and cutaneous infections associated with an atopic phenotype and elevated IgE levels.

MALT1-LOF mutations result in CID with variable expressivity of atopic dermatitis and other signs of loss-of-tolerance, such as inflammatory bowel disease.

A numerical or functional defect in Tregs or inadequate activation of mTORC1, a key metabolic regulator of T-helper differentiation,

has been suggested as a potential underlying mechanism of the atopic disease.

CARD14 is a pro-inflammatory signaling molecule expressed in different cells of the skin. Dominant GOF mutations in the CARD14 gene are associated with psoriasis, while dominant LOF mutations fail to normally activate NF-κB or upregulate CARD14 and AMP expression, leading to severe atopic dermatitis and skin infections.[7]

Phospholipase C gamma 2–(PLCγ2), associated with antibody deficiency and immune dysregulation (PLAID), is a monogenic disorder affecting mast cell function, caused by heterozygous genetic deletions autoinhibitory domain of PLCγ2. In patients with PLAID, evaporative cooling leads to degranulation of mast cells, cold urticaria, and skin rash development. Other manifestations may include atopy, granulomatous dermatitis, hypogammaglobulinemia, recurrent sinopulmonary infection, enterocolitis, cellulitis, and autoimmunity.[1]

## 3 | CHRONIC SKIN BARRIER DISORDERS

Mutations in genes encoding for key structures involved in skin barrier function lead to severe atopic disease. Biallelic LOF mutations in FLG, encoding for Filaggrin, cause a severe form of eczematous dermatitis, ichthyosis vulgaris, and hyper-IgE, while heterozygous LOF variants are responsible for atopic dermatitis.[1]

Mutations in multiple subunits of the desmosome, such as corneodesmosin (CDSN), desmoplakin (DSP), and desmoglein-1 (DSG1), lead to erythrodermic skin diseases. Biallelic LOF mutations in CDSN result in peeling skin syndrome type B, characterized by pruritic spontaneous exfoliation, diffuse ichthyosiform erythroderma, and hyper-IgE and allergic manifestations.[4]

AD mutations in DSP and AR LOF mutations DSG1 result in severe dermatitis, multiple allergies, and marked metabolic wasting syndrome (SAM).[4]

AR LOF mutations in SPINK5, which encodes for the lymphoepithelial Kazal-type-related inhibitor (LEKTI), lead to Comel-Netherton syndrome. Patients present with excessive desquamation, severe ichthyosis, erythroderma, trichorrhexis *invaginatum* (bamboo hair), hyper-IgE, atopy, and recurrent infections.[3]

## 4 | AUTOINFLAMMATORY DISEASES

Chronic skin disease resembling an allergic phenotype is also observed in autoinflammatory disorders. Familial Mediterranean fever (FMF) is a multisystemic disease caused by homozygous or compound heterozygous mutations in the MEFV gene, characterized by periodic fever, polyserositis, and skin rash.

Some studies showed a decreased prevalence of allergic disease in patients with FMF.[8] On the contrary, another study observed that 95.3% of the patients with FMF had an atopic manifestation. Atopic dermatitis was the main cutaneous finding, with a severe form in half of the cases.[9]

Cryopyrin-associated periodic syndrome (CAPS) is a multisystem disease caused by GOF mutations in the NLRP3 gene. It manifests with fever, fatigue, and multiorgan damage, including sensorineural hearing loss, urticaria-like skin rash, nephritis, vision loss, skeletal deformities, and cognitive disability. Recently Schwartz et al. analyzed different monogenic AID and found that CAPS was associated with eczema, urticaria, and increased Type 2 responses, linked to eosinophilia and Th2 expansion.[10] According to the authors, manifestations of allergy in CAPS could be supported by the role of NLRP3 in promoting Th2 immunity.[10] The effects of mutations in genes related to autoinflammation on allergic inflammation need to be further investigated.

In conclusion, recognizing PADs in the context of an allergic phenotype is crucial to ensure prompt diagnosis and appropriate treatment of these rare diseases.

### CONFLICT OF INTEREST

Authors declared that they have no conflict of interests.

### AUTHOR CONTRIBUTIONS

**Bianca Laura Cinicola**: Writing-original draft (equal). **Stefania Corrente, Riccardo Castagnoli, Vassilios Lougaris, Giuliana Giardino, Lucia Leonardi, Stefano Volpi, Francesco La Torre, Silvia Federici, Annarosa Soresina, and Caterina Cancrini**: Writing-original draft (equal). **Gian Luigi Marseglia**: Supervision (lead); Writing-review & editing (equal). **Fabio Cardinale**: Conceptualization (equal); Supervision (lead); Writing-review & editing (equal).

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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