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**Commentary**

# Defining intrinsic vs. extrinsic atopic dermatitis

**Chante Karimkhani BA[1], Jonathan I. Silverberg MD PhD MPH[2], Robert P Dellavalle MD PhD MSPH[3,4,5]**

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**[1] Columbia University College of Physicians and Surgeons; [2] Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL; [3] Department of Dermatology, University of Colorado Anschutz Medical Campus; [4] Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus; [5] Department of Dermatology, Denver Veterans Administration Hospital**

**Correspondence:**

Robert P. Dellavalle MD PhD MSPH
Chief, Dermatology Service
Department of Veteran Affairs Medical Center
1055 Clermont Street, Box 165
Denver, CO 80220
Tel: (303) 399-8020, ext. 2475
Fax: (303) 393-4686
Email: robert.dellavalle@ucdenver.edu

## Abstract

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin condition characterized by eczematous lesions, i.e. ill-demarcated erythematous patches and plaques. AD is commonly associated with elevated immunoglobulin E (IgE) and atopic disorders, such as asthma, hay fever, and food allergies. Rackemann and Mallory were some of the first to distinguish between asthma based on the presence ("extrinsic") or absence ("intrinsic") of allergy. This distinction has subsequently been applied to AD based on the presence ("extrinsic") or absence ("intrinsic") of increased IgE and atopic disease. Although the distinction between intrinsic and extrinsic AD is widely used, it remains controversial.

**Keywords: atopic dermatitis, eczema, asthma, allergy, fillagrin**

## Extrinsic vs. intrinsic AD

In 1941, Rackemann and Mallory made a distinction between asthma based on the presence ("extrinsic") or absence ("intrinsic") of allergy [1]. This distinction has subsequently been applied to AD based on the presence ("extrinsic") or absence ("intrinsic") of increased IgE and atopic disease. The association of AD with rhinitis and asthma in the US pediatric population was explored in a large, cross-sectional study of 79,667 children using the National Survey of Children's Health (NSCH) [2]. A history of AD within the past 12 months was associated with increased risk for ever having asthma (25.1% vs. 12.3%, $p<0.0001$), allergic rhinitis (34.3% vs 14.3%, $p<0.0001$), and food allergies (15.1% vs 3.6%, $p<0.0001$). Of all patients with physician-diagnosed AD, 19.0% experienced asthma within the past 12 months, 34.1% experienced hay fever within the past 12 months, and 14.1% experienced food allergies within the past 12 months.

## Phenotype of extrinsic vs. intrinsic AD

Although both forms of dermatitis cause characteristic eczematous skin lesions of the flexures, neck, and hands with associated pruritus and xerosis, there are important differences. By definition, extrinsic AD is associated with increased total serum IgE levels and the myriad of atopic comorbities. Distinct phenotypes have been associated with the non-IgE intrinsic AD subtype [3]. In particular, females appear at increased risk for intrinsic AD. Adults are less likely to harbor the intrinsic phenotype than children. Finally, intrinsic AD is associated with later onset and reduced disease severity compared to its extrinsic counterpart [3].

## The fillagrin hypothesis

The traditional model of AD as a primary immune reaction has been supplemented by recent discoveries of the disease as an epidermal barrier defect. In particular, abnormalities in a key protein of the epidermis, fillagrin (FLG), have been shown to increase skin permeability, thus allowing environmental allergens to stimulate a TH2 immune response [4]. The fillagrin hypothesis is especially important in our definition of AD with allergic disease. FLG is one of 30 genes located in the epidermal differentiation complex (EDC) on chromosome 1q21. Epidermal cell regeneration consists of cell migration from the inner basal layer to the outer stratum corneum of the epidermis. The stratum corneum functions to prevent water loss and prevent allergens, microbes, and irritants from penetrating the skin. End-products of fillagrin are found in the remaining cytoplasm of the squamous cells [4]. Mutations in FLG, denoted as FLG null mutations, result in a protracted profillagrin protein leading to the absence of FLG in the stratum corneum [4]. FLG null mutations are found in approximately 15% of children with AD, compared to 7% of non-affected children (hazard ratio = 2.23, p = 0.0002). Furthermore, AD children with the FLG null mutation experienced particular anatomical disease localizations, especially on the dorsal hands and cheeks [5]. These findings have been further demonstrated in large-population investigations such as the Avon Longitudinal Study of Parents and Children (ALSPAC) and the International Study of Asthma and Allergies in Childhood (ISAAC) II studies [6,7]. These results demonstrate that fillagrin-induced skin barrier defects may be a herald for the development of allergic sensitization and a pathogenetically distinct entity of atopic dermatitis with asthma [8].

Subsequent large-population investigations into the FLG mutation have further demonstrated a genetic susceptibility that helps to define the AD plus allergy phenotype as a distinct entity. In the ALSPAC study, overall asthma risk with FLG mutations was 1.80 (95% CI, 1.34-2.41; p=.00019) whereas in the ISAAC II study, overall asthma risk was 1.79 (95% CI, 1.19-2.68; p=.0048) [6,7]. For both studies, FLG mutations had no association with asthma if patients did not have AD. These large, population-wide studies provide evidence that AD and asthma occur together. However, it is unknown whether there is an advantage to define patients with AD and allergic disease separately from patients suffering from either disorder alone. In other words, do patients with AD and asthma have a worse disease prognosis?

## The atopic march

As demonstrated by FLG mutations, a large contribution to the pathogenesis of AD is impaired barrier function. The model of the atopic march helps to explain disease development and progression [9]. Genetic mutations in key components of the epidermal barrier lead to trans-epidermal water loss. This altered integrity of barrier function allows for transcutaneous sensitization with potential allergens. Sensitization is the necessary first step for the development of allergic disease. The association between AD, skin barrier impairment, and food sensitization was elegantly demonstrated in a prospective study of 619 infants [10]. The presence of AD conferred a significantly increased risk for food sensitization (OR=6.18, 95% CI 2.94-12.98, p<0.001). In addition, increasing AD severity was associated with increased food sensitization [10].

## AD and the severity of allergic disease

The NSCH study demonstrated that history of AD was associated with more severe atopic disease [2]. A diagnosis of AD within the past year was associated with an 8.9% prevalence of severe asthma in the past year, compared to 4.3% severe asthma in those with no AD (p<0.0001). Similar findings were found for severe allergic rhinitis (6.6% vs 3.1%, p<0.0001) and severe food allergy (26.3% vs 16.4%, p<0.0001). In the 2013 PEER longitudinal cohort study of 2104 children, 76.3% of children with AD and asthma reported one or more episodes of wheezing at study enrollment, which increased to 88.7% at 3-year follow-up [11]. A diagnosis of asthma at enrollment decreased the likelihood of being rash-free during any 6-month interval by 40%. In addition, patients with increased frequency of wheezing were 33-43% less likely to be rash free (p<0.01) and more likely to use topical medications for their AD control than AD patients without asthma [11]. Children with AD that developed asthma in pre-school were more likely to have persistent asthma with frequent wheezing into school-age.

Another study of the natural history of AD found that the prevalence of wheeze was significantly increased in children with early AD accompanied by scratching, compared to children with no AD or AD without scratching [12]. The combination of early AD

and early asthma wheezing, which was observed in over one third of children with early AD, resulted in significantly reduced lung function (BHR) at age 7 compared to no early AD or no early wheezing. In fact, the combination of early AD and early wheezing conferred 3 times the risk of wheezing at age 7 than children with no early AD (adjusted OR=2.84) [12]. Sensitization patterns were also tested in participants, including serum total IgE and specific IgE to food and inhalant allergens. Patients with the combination of early AD, early wheezing, and less prevalent sensitization types at 2 years had 9 times the risk of wheezing at age 7 (adjusted OR=9.13). Since the majority of children with early AD and wheezing at 7 years already had wheezing in their early childhood, study investigators concluded that there was stronger evidence for concurrent co-manifestation of the two disorders over the traditional, progressive "atopic march" hypothesis [12].

Finally, the severity of AD is positively correlated with the prevalence and severity of allergic disease [2]. Severe AD, compared to mild-moderate disease, was associated with a 1.5-fold greater prevalence of ever asthma ($p=0.002$), 1.7-fold greater prevalence of asthma in the past year ($p=0.0003$), and 6.6-fold increased prevalence of severe asthma ($p<0.0001$). Severe AD was also associated with a 6.3-fold increased prevalence of allergic rhinitis ($p<0.0001$), but not allergic rhinitis in the past year ($p=0.26$). Finally, severe AD, compared to mild-moderate AD, was associated with a 1.9-fold increased prevalence of food allergies in the past year ($0<0.0001$) and 2.0-fold increased prevalence of severe food allergy ($p<0.0001$).

## Utility for a separate epidemiological definition

There is a paucity of studies exploring the inclusion of allergic disease in the epidemiological definition of AD and determining whether this has any impact on specificity. Given the pathophysiological and phenotypic association, we speculate that there is utility in a separate epidemiological definition of AD with allergic disease. This is certainly an area for future study. Research presented here provides an introduction to AD and its pathogenetic models, evidence of fillagrin as a specific link between AD and allergic disease, and evidence for AD with asthma as a prognostic severity indicator compared to either disease alone. The remaining 85% of AD patients lacking FLG null mutations may also benefit from this genotype to phenotype understanding, as other candidate genes may contribute to the progression and treatment of AD.

Patients with co-manifestation of AD and asthma, particularly from the pediatric population in which most studies have been performed, experience greater morbidity from both diseases than patients with either disease alone. Perhaps the establishment of AD with allergic disease as a distinct diagnostic etiology could allow providers the opportunity to make better prognostic decisions for disease treatment. Patients with the combined AD-asthma phenotype have increased risk of wheezing and increased risk of being rash-free. Thus, they may benefit from more aggressive management of their dermatitis and respiratory symptoms. Perhaps the near future will reveal a direct mechanistic connection between AD and allergic disease, helping to decrease the increased morbidity of the combined atopic phenotype.

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