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CME Review

The clinical relevance of filaggrin mutations
Effect on allergic disease

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INSTRUCTIONS

Credit can now be obtained, free for a limited time, by reading the review article and completing all activity components. Please note the instructions listed below:

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- Complete the pre-test.
- Read the article and reflect on all content as to how it may be applicable to your practice.
- Complete the post-test/evaluation and claim credit earned. At this time, physicians will have earned up to 1.0 *AMA PRA Category 1 Credit™*. Minimum passing score on the post-test is 70%.

Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the role of filaggrin in the maintenance of skin barrier function
- Discuss how filaggrin null mutations can augment the risk of developing allergic diseases

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

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Introduction

Allergic diseases, including atopic dermatitis (AD), have increased in prevalence and now affect approximately 20% of the world population.[1,2] AD (the most common form of eczema) is the most common chronic inflammatory skin disease in children and is characterized by dry, itchy skin and reduced skin barrier function.[2,3] Children with AD often develop other allergic diseases, including asthma and food allergy.[1] Within the first 7 years of life, approximately 70% of children with AD develop allergic rhinitis (AR) and asthma.[4] This is commonly referred to as the atopic march, a term that describes the tendency for infants to progress from AD to food allergy and then AR and asthma later (Fig 1).[2] Several studies define AD as the initial step of the atopic march, suggesting that an impaired skin barrier can contribute to allergic sensitization and increase the risk of allergic disease development.[5,6]

Filaggrin (FLG) is a key protein expressed in the skin and is largely involved in the maintenance of skin barrier function.[7] Loss-of-function or null mutations in the *FLG* gene can lead to impaired skin barrier function and represent the strongest genetic risk factor for developing AD.[8] Null mutations are changes in a gene that lead to the production of nonfunctional protein product.

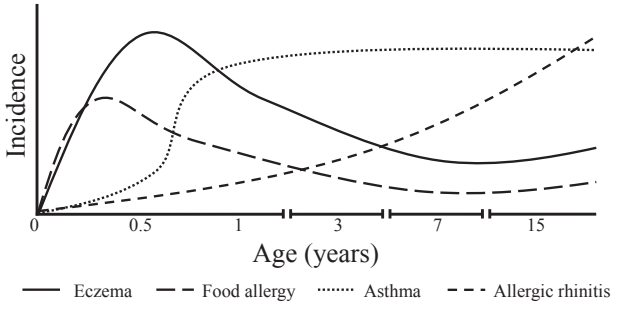

Figure 1. The atopic march is the tendency for infants with eczema and food allergy to develop asthma and allergic rhinitis in later life. Eczema commonly develops in young infants. With age, these infants often outgrow their eczema but are more likely to develop asthma and allergic rhinitis.

Several meta-analyses have highlighted the strong association between *FLG* null mutations and allergic diseases.[9,10] For example, in a population study, individuals with AD and *FLG* null mutations exhibited a greater risk of developing asthma than individuals with AD alone.[11] These studies suggest that FLG may be involved in the initial step and throughout the atopic march by augmenting the risk of developing allergic diseases. This review focuses on the effect of *FLG* null mutations on the skin and on the development of asthma, AR, and food allergies.

FLG in Healthy Epidermis

The stratum corneum (SC) is the outermost layer of the epidermis and acts as the primary barrier against chemicals and foreign pathogens. The brick-and-mortar model is often used to describe the cellular architecture of the SC. Protein-enriched corneocytes (the bricks) are surrounded by an organized extracellular network of hydrophobic lipids (the mortar).[7] Corneocytes are terminally differentiated keratinocytes that supply most of these hydrophobic lipids via lamellar body secretion, which include free fatty acids, cholesterol, and ceramides. These cells also contain natural moisturizing factors (NMFs), a group of metabolites and ions that serve to maintain adequate SC hydration and acidic pH of the SC.[7,12] Together, the corneocytes provide chemical and physical protection, whereas their extracellular lipid surroundings prevent the outward loss of water, otherwise known as transepidermal water loss (TEWL).[12]

FLG is a key structural protein primarily expressed in keratinocytes residing in the stratum granulosum and is involved in epidermal barrier function. Encoded on chromosome 1q21 of the epidermal differentiation complex, FLG is produced in keratohyalin granules within keratinocytes as 400-kDa profilaggrin polymers and is involved in corneocyte differentiation, and the maintenance of NMFs and SC pH. Once released from keratohyalin granules, profilaggrin polymers are rapidly dephosphorylated and proteolytically cleaved to form several FLG monomers (Fig 2).[12,13] These monomers trigger the aggregation of keratin filaments within the keratinocytes during their migration toward the SC.[13] Keratin filament aggregation promotes the collapse of the cytoskeleton, converting keratinocytes into the flattened corneocytes found in