



CME Review

The clinical relevance of filaggrin mutations Effect on allergic disease

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- 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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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.

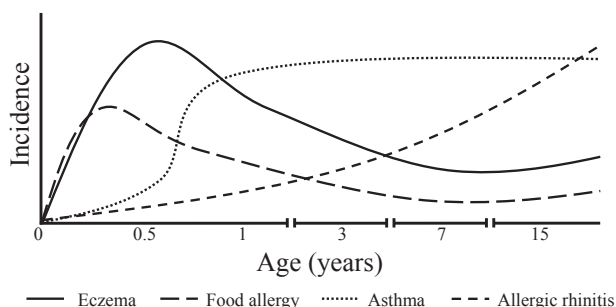


Figure 1. The atopic march is the tendency for infants with eczema and food allergy to develop asthma and allergic rhinitis in later life. Eczema commonly develops in young infants. With age, these infants often outgrow their eczema but are more likely to develop asthma and allergic rhinitis.

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

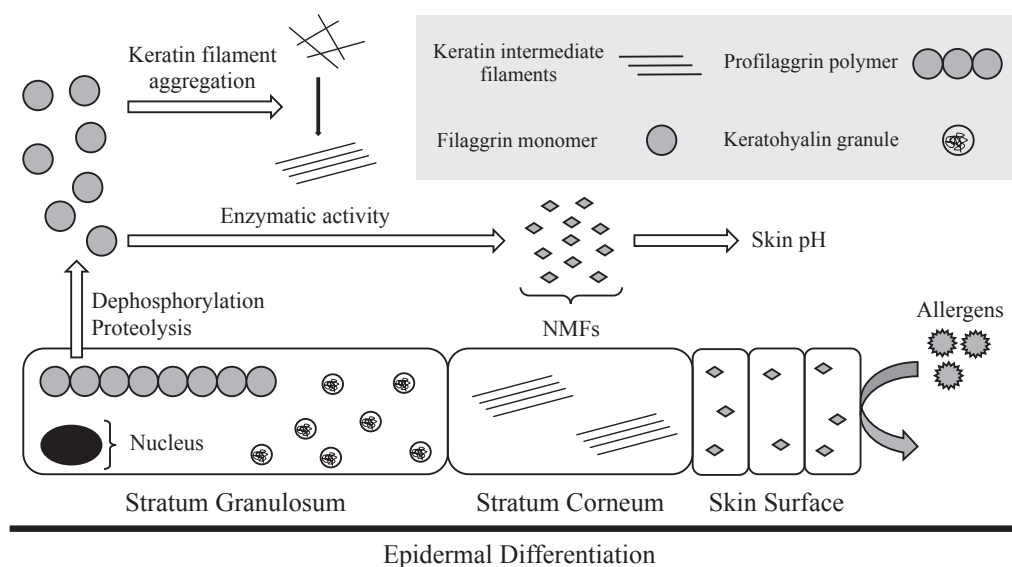


Figure 2. Processing of profilaggrin and functions of filaggrin in the skin. Profilaggrin polymers are produced and stored in keratohyalin granules within keratinocytes. Once released, profilaggrin polymers are rapidly dephosphorylated and proteolytically cleaved to form FLG monomers. These monomers promote the aggregation of keratin filaments and the collapse of the cytoskeleton. This collapse is critical to the formation of corneocytes from keratinocytes in the stratum corneum. FLG monomers are also degraded into free amino acids (ie, histidine and glutamine). These amino acids are further converted into their respective amino acid derivatives (histidine into transurocanic acid; glutamine into pyrrolidone 5-carboxylic acid), which are called natural moisturizing factors (NMFs) and help maintain skin pH and prevent water loss. FLG deficiency can lead to a loss of FLG monomers, impairing corneocytes formation and reducing the levels of NMFs in the skin. These changes lead to increased water loss, dry skin, and reduced skin barrier function, which can enhance the penetration of allergen through the skin.

the SC.^{7,13} After cytoskeletal collapse, the FLG monomers are deaminated and further degraded by several proteases into key amino acids, including histidine and glutamine (Fig 2). Histidine is converted into transurocanic acid, whereas glutamine is converted into pyrrolidone 5-carboxylic acid. Both are major components of the NMFs and help maintain proper skin pH and water retention within the SC.⁷

Effect of FLG Deficiency on the Epidermis

Null mutations in the *FLG* gene produce truncated profilaggrin polymers that cannot be processed into functional FLG monomers.^{14,15} The loss of FLG monomers can have profound structural and functional changes on the epidermal barrier (Fig 2). Keratin filament aggregation becomes disrupted, leading to cytoskeletal disorganization and abnormal keratinocyte morphologic features. This impairs both cargo loading into lamellar bodies and lamellar body secretion, resulting in reduced quantities and organization of hydrophobic lipids in the SC.^{16,17} Tight junction (TJ) formation is also impaired in FLG-deficient epidermis because of the reduced expression of the TJ proteins ZO-1 and occludin.¹⁶ TJs are intercellular junctions found between adjacent epithelial cells that play a critical role in the maintenance of the epithelial barrier. Impaired formation of these junctions can result in increased water loss and reduced integrity of the epidermal barrier. The reduction in FLG metabolites (eg, histidine and glutamine) due to the loss of FLG monomers can reduce the levels of NMFs in the SC. This increases TEWL and skin pH and decreases skin hydration in individuals with *FLG* null mutations, leading to a dry skin phenotype.¹⁸ The increase in the normally acidic pH of the SC can also lead to the degradation of lipid-generating enzymes (such as acidic sphingomyelinase, an enzyme required for ceramide production), further reducing the extracellular lipid content.¹⁹ Overall, *FLG* null mutations lead to a disrupted skin barrier phenotype characterized by reduced barrier integrity and reduced skin hydration due to increased water loss.

This skin barrier phenotype can be seen in animal and human studies that involve FLG deficiency caused by null mutations. The flaky tail (*ft/ft*) mouse is an animal model used frequently to investigate the effect of FLG deficiency on the epidermis. These mice exhibit a spontaneous autosomal recessive mutation on chromosome 3 of the murine epidermal differentiation complex, leading to truncated profilaggrin that cannot be proteolytically processed into FLG monomers. As a result, *ft/ft* mice have dry and scaly skin accompanied by increased TEWL, acting as a good animal model to study ichthyosis vulgaris in humans.²⁰ Ichthyosis vulgaris is the most common disorder of skin keratinization caused by *FLG* null mutations in humans.²¹ These mutations can lead to the loss of the stratum granulosum and reduced or total absence of epidermal keratohyalin granules and FLG protein in the skin. Individuals with ichthyosis vulgaris often present with dry and flaky skin, palmer hyperlinearity (exaggerated skin markings on the palms), and a strong association with atopic disorders.^{13,22} The integrity and permeability of the epidermal barrier are also impaired in these individuals.¹⁶

The reduced integrity of the epidermal barrier caused by *FLG* null mutations can also enhance the penetration of environmental allergens through the skin and facilitate systemic allergic sensitization. Several animal studies that used FLG-deficient mice observed increased skin penetration of irritants and ovalbumin (a model protein antigen), followed by skin inflammation in these mice compared with the control group. Systemic allergic sensitization to ovalbumin was also only elicited in FLG-deficient mice as measured by a significant increase in ovalbumin specific IgE and IgG1 antibodies after epicutaneous ovalbumin exposure.^{23,24} This finding suggests that the risk of allergic sensitization can be modified in individuals with a disrupted skin barrier. In a broader context, individuals with *FLG* null mutations may progress more quickly along the atopic march because of their disrupted skin barrier. This disruption can enhance allergen penetration through the skin, facilitating allergic sensitization and augmenting the risk of developing allergic diseases in these individuals.

FLG Null Mutations in Atopic Dermatitis and Eczema

AD is a chronic inflammatory skin disorder characterized by dry and itchy skin, enhanced TEWL, and increased permeability to environmental antigens. The main therapy used to treat AD includes the use of moisturizing creams to help maintain skin hydration and restore epidermal barrier function, emphasizing the reduced skin barrier integrity seen in these individuals.²⁵ Similar to ichthyosis vulgaris, *FLG* null mutations represent the strongest genetic risk factor for developing AD.⁸ This strong association, initially found in an Irish cohort with dermatologist-diagnosed AD, has been widely replicated in Scottish, Danish, and German cohorts using several study methods. These methods included case-control, prospective birth cohort, and family-based studies.^{26,27} The association between *FLG* null mutations and AD has also been confirmed in several meta-analyses, yielding an overall odds ratio (OR) of 3.12 to 4.78.^{9,10} In addition to the development of AD, *FLG* null mutations are associated with disease severity. Two separate prospective cohort studies followed up children up until 7 years of age with visits every 6 months and found that children with *FLG* null mutations had an earlier onset of AD, had more widespread dermatitis, and were approximately 50% less likely to have symptom-free skin during a 6-month period compared with children without mutations.^{28,29} This finding suggests that of those with AD, *FLG* null mutation carriers are likely to have a more impaired skin barrier compared with those without mutations.

Having a defective skin barrier due to *FLG* null mutations may not only predispose carriers to AD (initial step of the atopic march) but also enhance their risk of developing subsequent allergic diseases, making these individuals progress more quickly along the march. A meta-analysis that investigated the association between *FLG* null mutations and the risk of developing allergic diseases found that in individuals with AD, the overall OR for developing asthma or AR ranged from 2.30 to 2.78 and 2.46 to 2.84, respectively.⁹ This finding suggests that the odds of developing asthma or AR are at least 2 times greater in individuals with AD and *FLG* null mutations than in individuals with AD alone. These studies highlight both *FLG* null mutations and skin barrier integrity as predisposing factors to all points along the atopic march. Early interventions (such as moisturizing creams) aimed at restoring skin barrier function may be used to potentially lower the risk of AD and perhaps allergy development, slowing the progression from AD to asthma and AR. In a recent randomized clinical trial that investigated the efficacy of emollients in reducing AD incidence in high-risk neonates, daily full-body emollient therapy (which included oil, ointment, or cream/gel) was significantly associated with reduced AD development at 6 months of age. Only 22% of infants treated with emollients developed AD at 6 months of age compared with the 43% observed in untreated infants, corresponding to a relative risk reduction of 0.50 (relative risk, 0.50; 95% confidence interval [CI], 0.28–0.90; $P = .02$).³⁰ These findings highlight the daily use of emollients as a novel approach for preventing the development of AD in high-risk neonates and may perhaps lower the risk of allergic diseases by decreasing the permeability of the skin to environmental allergens.

FLG Null Mutations in Asthma and Allergic Rhinitis

Asthma

Asthma is a chronic airway inflammatory disorder, with allergic asthma representing most cases of persistent adult asthma that originated in early childhood. It is a complex disease with asthma susceptibility largely influenced by genetics.³¹ In an early study that investigated the association between *FLG* null mutations and AD, *FLG* null mutations were significantly associated with asthma development in Scottish children with physician-diagnosed

asthma, yielding an OR of 1.8 (95% CI, 1.3–2.5; $P = .0002$). However, this association pertained to only children with previous AD, which reported a larger OR of 3.3 (95% CI, 2.0–5.6; $P = 4 \times 10^{-6}$). In children without preexisting AD, *FLG* null mutations were not significantly associated with asthma.²⁶ These observations have been replicated in several large cross-sectional and prospective cohort studies using well-established cohorts of mothers and children. As in the Scottish cohort, the association between *FLG* null mutations and asthma development was restricted only to children with previous AD.^{11,26,32–35} Of note, a large cross-sectional study obtained contrasting results. In the Epidemiology of Allergic Diseases in Poland (ECAP) cohort, *FLG* null mutations were significantly associated with asthma in the presence and absence of AD, reporting an overall asthma risk of 1.70 (95% CI, 1.07–2.69; $P = .024$). This association remained significant in patients with (OR, 3.61; 95% CI, 1.05–12.38; $P = .029$) and without (OR, 2.02; 95% CI, 1.07–3.81; $P = .027$) previous AD.³⁶ These differences may have been due to inappropriate patient or parent recall of previously resolved cases of AD, falsely classifying patients with previous AD as without AD. Other genetic and environmental factors specific to the ECAP cohort could have also accounted for the observed differences.³⁶

Although asthma primarily affects the lower airways, *FLG* is not expressed in the bronchial epithelium.³⁷ This finding suggests that the increased risk of asthma associated with *FLG* null mutations in those with AD may be due to the impaired skin barrier, facilitating allergic sensitization in these individuals.

Allergic Rhinitis

AR is a nasal inflammatory disorder that involves IgE-mediated inflammation of the nasal mucosa. Symptoms are triggered after reexposure to the offending allergen and include sneezing, rhinorrhea, congestion, and nasal pruritus.³⁸ The association between *FLG* null mutations and AR has been previously reported.⁹ However, the association between the two remains unclear because several cross-sectional and population-based studies yielded varying observations. In the German International Study of Asthma and Allergies in Childhood, phase II (ISAAC II) cohort, *FLG* null mutations were significantly associated with AR, reporting an OR of 2.64 (95% CI, 1.76–3.96; $P = 2.5 \times 10^{-6}$).³³ This finding was replicated in the Polish ECAP cohort, with a resulting OR of 1.43 (95% CI, 1.01–2.04; $P = .046$) for AR and 1.69 (95% CI, 1.12–2.54; $P = .011$) for persistent AR (defined as symptoms presenting for >4 days a week and for >4 consecutive weeks).³⁶ Although lower than the OR reported in the ISAAC II cohort, these associations remained significant. Contrasting these results, studies using other large birth cohorts have yielded opposite findings. In one study, children were recruited from the Prevention and Incidence of Asthma and Mite Allergy cohort and followed up until 8 years of age. The overall AR risks associated with *FLG* null mutations for children aged 3 to 5 years and 6 to 8 years were 1.4 (95% CI, 0.6–3.3; $P = .39$) and 2.3 (95% CI, 0.9–6.0; $P = .10$), respectively. Although these values are above 1.0, they were not statistically significant.³⁵ Another study observed similar findings in a population cohort in Northwest England, yielding a smaller value of 1.2 (95% CI, 0.7–2.0; $P = .66$) that did not reach statistical significance.³⁹ These contradictory results regarding the association between *FLG* null mutations and AR may in part be attributed to the specific criteria used for AR classification. In the ISAAC II and ECAP cohorts, AR classification was defined as per the International Global Initiative for Asthma guidelines or a physician's diagnosis of hay fever together with a positive skin prick test result against at least 1 of the tested allergens.^{33,36} The latter 2 cohorts instead classified AR based on parental reports to questions such as, "Has your child ever had hay fever?".^{35,39} The use of parental reports over standardized guidelines and physician

diagnoses may have led to recall or overreporting bias. Notably, a recent Japanese study observed a significant association between *FLG* null mutations and AR, yielding an OR of 2.0 (95% CI, 1.03–3.94; $P < .05$), agreeing with the findings from the ISAAC II and ECAP cohorts. However, it was unclear whether this association was due to preexisting AD.⁴⁰

The study of AD on the association between *FLG* null mutations and AR has also led to mixed results. A study involving the German Multicenter Allergy Study cohort observed a significant association between *FLG* null mutations and AR. However, like asthma, this association was limited only to children with previous AD.³² This finding is contrasted by the results from both the ISAAC II and ECAP cohorts, which found that AR risk was significantly associated with *FLG* null mutations independent of AD status.^{33,36} Taking these results together, it is clear that the association between *FLG* null mutations and the risk of AR is complex. Additional research may be helpful in further elucidating this association.

Overall, results from several large cohort studies suggest that *FLG* null mutations may be a significant predisposing factor for asthma and AR in individuals with preexisting AD.

This finding further emphasizes the integrity of the skin barrier as an important factor in determining whether an individual will progress through the atopic march.

***FLG* Null Mutations in Food Allergy and Sensitization**

Food Allergy

The disrupted skin barrier in individuals with AD is thought to be a predisposing factor for epicutaneous sensitization to food proteins and food allergy development. Topical application of protein antigen can lead to systemic allergic sensitization (as measured by specific IgE and IgG1 antibodies) and anaphylaxis after oral allergen challenge in mice if preceded by tape stripping of the skin.^{41,42} Tape stripping disrupts the SC and leads to skin barrier impairment and local inflammation. Allergic sensitization also developed in *fl/fl* mice after topical application of ovalbumin.²³ Tape stripping was not required to elicit this sensitization, suggesting that skin barrier impairment due to *FLG* deficiency can enhance epicutaneous sensitization to food proteins and perhaps food allergy development. The association between *FLG* null mutations and food allergy has only recently been investigated. From the Avon Longitudinal Study of Parents and Children cohort and several pediatric allergy clinics, a significant association between *FLG* null mutations and peanut allergy was observed in a mixed cohort of English, Irish, and Dutch patients with peanut allergy, reporting an overall OR of 5.3 (95% CI, 2.8–10.2; $P = 3.0 \times 10^{-6}$).⁴³ True clinical reactivity to peanut was defined as a positive oral food challenge test result to peanut. This association remained significant even after controlling for coexisting AD and was replicated in a separate Canadian peanut allergy cohort, yielding an overall OR of 1.9 (95% CI, 1.4–2.6; $P = 5.4 \times 10^{-5}$).⁴³ Although lower than the OR reported in the mixed cohort, this may have been due to the use of population controls whose peanut allergy status were unknown. These observations were further strengthened in a separate Canadian pediatric cohort in which the significant association between *FLG* null mutations and peanut allergy persisted despite asthma status and varying peanut allergy diagnostic criteria.⁴⁴ Both studies support the notion that *FLG* null mutations may be a strong independent risk factor for peanut allergy.

The association between early-life environmental peanut exposure (EPE) and peanut allergy development in the context of *FLG* null mutations was also recently assessed in the Manchester Asthma and Allergy Study cohort. Children were followed up from birth until 11 years of age, and EPE was defined as the amount of peanut protein in household dust collected at 36 weeks' gestation.

Children with *FLG* null mutations exhibited a greater than 6-fold increase in the odds of peanut sensitization and a greater than 3-fold increase in the odds of peanut allergy development to increasing peanut dust levels compared with children without *FLG* null mutations. The interaction between *FLG* null mutations and early-life EPE remained significant even after adjusting for infantile AD and preceding egg sensitization and was absent in children without mutations.⁴⁵ A separate cross-sectional study further extended these findings to a high-risk atopic cohort. After adjusting for known risk factors for allergy development, the risk of peanut sensitization and peanut allergy associated with EPE was strongly augmented in children with concurrent AD. Moreover, the odds of peanut sensitization associated with EPE was further increased in children with AD (OR, 1.97; 95% CI, 1.26–3.09; $P < .01$) and severe AD (OR, 2.41; 95% CI, 1.30–4.47; $P < .01$).⁴⁶ Contrasting the previous study results, an interaction between *FLG* null mutations and EPE was not present, and no association was found between *FLG* null mutations and peanut sensitization or peanut allergy. This finding may have been in part due to the extensive preexisting history of AD seen in these children, resulting in an already impaired skin barrier.⁴⁶ Overall, the studies that investigated the association between *FLG* null mutations and peanut allergy thus far support the notion that peanut sensitization can occur through a disrupted skin barrier, potentially leading to peanut allergy development.

A significant association between *FLG* null mutations and other food allergies has also been documented.⁴⁷ In a recent study that investigated the association between *FLG* null mutations and food allergy, children with *FLG* null mutations were more likely to be reactive to at least one food (including milk, eggs, soy, and different types of tree nuts) compared with children without mutations, yielding an OR of 4.9 (95% CI, 1.6–14.7; $P = .005$).⁴⁸ When *FLG* null mutations were included in a predictive multivariate model for clinical reactivity to foods, the model generated high positive predictive and sensitivity values, supporting the potential role of *FLG* as a genetic marker of food allergy.⁴⁸

Food Sensitization

Recent studies investigating the association between *FLG* null mutations and food sensitization report mixed results. In a cross-sectional study that involved 1-year-old infants, *FLG* null mutations were significantly associated with food sensitization even after adjusting for AD, reporting an OR of 3.0 (95% CI, 1.0–8.7; $P = .043$).⁴⁹ Similar findings were seen in the Manchester Asthma and Allergy Study cohort, in which children with *FLG* null mutations had an increased odds of peanut sensitization associated with EPE. This association also remained significant after adjusting for infantile AD.⁴⁵ In contrast with these results, a study that investigated the longitudinal and temporal association among AD, *FLG* null mutations, food sensitization, and food allergy found that *FLG* null mutations were not directly associated with food sensitization in children at 1, 2, 4, 10, or 18 years of age. However, a significant indirect effect of *FLG* null mutations was observed at 4, 10, and 18 years of age through AD.⁵⁰ This finding suggests that *FLG* null mutations were significantly associated with food sensitization only with concurrent AD in children 4, 10, and 18 years of age. Another large cross-sectional study found *FLG* null mutations to be significantly associated with sensitization to milk and horse only in adults with concomitant AD. These mutations were not associated with food or aeroallergen sensitization in adults without AD.⁵¹ In this adult cohort, it was also apparent that food sensitization was largely dependent on AD status than *FLG* null mutations. These studies reveal the complex association between *FLG* null mutations and allergic sensitization. They support the notion that skin barrier impairment attributable to these mutations alone may not be

sufficient to elicit sensitization and may also depend on preexisting skin disorders (ie, AD) and other factors, such as age.

In the context of both food allergy and allergic sensitization, it is clear that the skin barrier plays an important role in their pathogenesis. Although the association between *FLG* null mutations and both food allergy and allergic sensitization is not as clear, these studies consistently find that AD can increase the risk of developing sensitization and subsequent allergy. Early introduction of interventions aimed to maintain skin barrier function in individuals with prior skin conditions (ie, AD) may potentially reduce the risk of developing allergies to food and aeroallergens.

Conclusion

FLG is a key structural protein expressed in the skin. It is largely involved in the maintenance of skin barrier function and aids in physical protection against irritants and environmental allergens. Null mutations in the *FLG* gene can reduce the structural and functional integrity of the skin, facilitating the entry of irritants and allergens through the skin barrier.

The atopic march describes the tendency for infants and children to progress from AD to asthma, AR, and food allergies in later life. Children with *FLG* null mutations may progress more quickly and/or completely along the march because of an impaired skin barrier. This impairment can enhance allergic sensitization and augment the risk of developing allergic diseases. *FLG* null mutations are a predisposing factor to several points along the atopic march. Additional studies are required to examine whether providing early interventions targeted to restoring skin barrier function (ie, moisturizing creams) in those with preexisting skin conditions (ie, AD) may alter the progression toward subsequent development of other allergic diseases.

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