

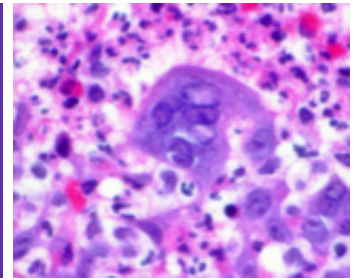


eLITERATURE REVIEW

eMedicalDermatology Review

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December 2008: VOLUME 1, NUMBER 11

Atopic Dermatitis - A Disease Caused by a Barrier Defect?



In this Issue...

Although atopic dermatitis (AD) is a common and often chronic condition, its treatment remains a frustration to both clinicians and patients alike. Much of our understanding of the disease has focused on characterization of the inflammation observed within lesions. From this work, we have recognized the importance of allergen-reactive T-helper cells that release the cytokines interleukin (IL)-4, and IL-13, or the so-called Th2 cells. These cytokines are responsible for the eosinophilia and elevated immunoglobulin (Ig)E levels observed in the circulation and tissues of individuals with AD. Recent studies have begun to better characterize the cutaneous barrier defects observed in this disease. Several stratum corneum proteins have been implicated (eg, filaggrin, loricrin, and involucrin), as well as proteases and antiproteases that may be important in posttranslational modifications of these proteins.

In this issue, we review the evidence that patients with AD have a barrier defect that is apparent in both their lesional and nonlesional (ie, clinically normal-appearing) skin; examine the data suggesting that several of these epidermal proteins are AD candidate genes; and discuss how this notion of defective skin barrier function might affect the susceptibility of individuals with AD to allergens, irritants, and pollutants.

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■ **GENETIC DEFECTS IN STRATUM CORNEUM GENES (SPINK5, KLK7, AND FLG) AND RISK FOR ATOPIC DERMATITIS**

■ **BARRIER DEFECTS IN NONLESIONAL SKIN OF PATIENTS WITH ATOPIC DERMATITIS**

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Guest Faculty Disclosures

Dr. Beck has served as a consultant for Merck, Glyco-mimetics, Anacor, Novartis and CombinatorRx, and is an investigator for Lucid, Anacor and Centocor.

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Dr. Rabizadeh has disclosed no relationships with commercial supporters.

Unlabeled/Unapproved Uses

The authors have indicated that there will be no reference to unlabeled or unapproved uses of drugs or products in this presentation.

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LEARNING OBJECTIVES

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

- Explain how both inherited and acquired defects in filaggrin and other stratum corneum proteins may impact barrier function in patients with atopic dermatitis (AD)
- Describe the clinical observations that support the notion that individuals with AD have a barrier defect
- Identify 3 different genes linked to AD and explain the strength of the association of each with the disease

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COMMENTARY

Atopic dermatitis (AD) is a chronic pruritic eczematous dermatitis that affects up to 20% of children in the United States. The majority of persons with AD exhibit hypersensitivity, as defined by allergen-specific immunoglobulin (Ig)E to numerous environmental allergens that collectively result in elevated total serum IgE levels. This group is also at greatest risk for developing other atopic diseases and are thought to have the greatest epidermal barrier defect.¹ Much of this barrier function resides within the cells that comprise the outer layer of the epidermis, called the stratum corneum (SC). The SC has been likened to a brick wall, consisting of terminally differentiated keratinocytes or corneocytes (bricks), which are surrounded by a matrix of specialized lipids (mortar). AD barrier dysfunction was first suspected as having a genetic basis when genome-wide studies identified linkage to the epidermal differentiation complex (EDC) on chromosome 1q21 (ATOD2).² In a landmark paper by Palmer and colleagues published in 2006, two null mutations in an EDC gene - namely, filaggrin (*FLG*) - were identified and shown to be strongly linked to the phenotype of AD and asthma-associated AD, whereas no associations were observed with psoriasis, another inflammatory skin disease with EDC (1q21-PSORS4) linkage.³ As addressed in this newsletter, Sandilands and associates demonstrated the robustness of these findings by confirming this association in several primarily European populations.

The articles by Nemoto-Hasebe and coworkers and Jakasa and colleagues, reviewed in this issue, help to validate the AD barrier defect theory. Kim and associates and Weidinger et al. highlight the fact that additional epithelial genes may play a role in this barrier abnormality. Howell and colleagues demonstrate that some of these barrier proteins are regulated on a genetic as well as on an environmental basis.

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2. Cookson WO, Ubhi B, Lawrence R, et al. [Genetic linkage of childhood atopic dermatitis to psoriasis susceptibility loci](#). *Nat Genet.* 2001;27(4):372-373.
3. Palmer CNA, Irvine AD, Terron-Kwiatowski, et al. [Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis](#). *J Am Acad Dermatol.* 2006;38(4):441-446.

FILAGGRIN MUTATIONS ASSOCIATED WITH ATOPIC DERMATITIS AND ICHTHYOSIS VULGARIS

Sandilands A, Terron-Kwiatowski A, Hull PR, et al. **Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema**. *Nat Genet.* 2007;39: 650-654.

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Filament aggregation protein (filaggrin) is a critical protein thought to play an important role in the barrier function of the stratum corneum. Two publications in 2006 identified 2 relatively common filaggrin (*FLG*) null mutations strongly associated with AD or with the most common genetic ichthyotic disorder, ichthyosis vulgaris (IV), in Northern European populations.^{1, 2} Since that time, these results have been replicated in multiple European AD populations, and different *FLG* mutations have been found among Asian AD populations. The goal of Sandilands' 2007 study was to comprehensively evaluate additional ethnic populations (Dutch, Austrian, and Irish) with IV and/or AD for both known and unique mutations in *FLG*. The large, repetitive *FLG* exon 3 was targeted for sequencing using a combination of long-range polymerase chain reaction (PCR) and numerous primer pairs, because of significant base polymorphism in the 10 to 12 full-tandem *FLG* repeats located within this exon.

This approach identified 3 novel but rare null mutations, several nonsense or frameshift mutations, as well as confirmed the 2 originally described null mutations (R501X and 2282del4). Five of these *FLG* mutations were observed even in a population of Irish controls (n=736), with a combined minor allele frequency (MAF) of 0.039. The MAF is the frequency of the less common (eg, *FLG* null mutations) allele in a polymorphic locus and can range from 0 to 0.5. In contrast, Irish children with dermatologist-diagnosed moderate to severe AD had a significant increase in their combined MAF to 0.287. Analysis of the combined allele frequency between Irish controls and AD cohorts yielded a chi-squared (χ^2) test with a P value of 2.12×10^{-51} . In general, the more 3' mutations were not a significant as those observed for the mutations in exon 1 (eg. R501X and 2282del4).

In summary, this study has highlighted the importance of gene sequencing in identifying both common and rare *FLG* gene variants, many of which might not have been identified by single nucleotide polymorphisms. This investigation brings the number of known *FLG* mutations associated with AD to 15. An unanswered question is why the frequency of some of the null mutations is so high, even among control (ie, clinically unaffected) populations. The authors speculate that these mutations may have developed because they provide an evolutionary advantage to the host, allowing for a "natural vaccination" to microbial antigens through a leaky epithelium. It is important to note that little is known about the role that these *FLG* mutations play in populations of African descent and in European Americans. Interestingly, a recent publication reports the complete lack of association between the 2 most common null mutations (R501X and 2282del4) in an Italian AD population, providing additional support for the polymorphic nature of this gene among different racial and ethnic groups.³

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REDUCED FILAGGRIN EXPRESSION CAN BE AN ACQUIRED DEFECT

Howell MD, Kim BE, Gao P, et al. **Cytokine modulation of atopic dermatitis filaggrin skin expression.** *J Allergy Clin Immunol.* 2007;120(1):150-155.

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This 2007 report by Howell et al evaluated filaggrin expression in lesional and nonlesional skin of patients with mild to moderate AD with and without one of the filaggrin mutations (2282del4) originally described by Palmer and colleagues.¹ A total of 30 US patients with AD and 39 healthy controls were screened for the 2 *FLG* null mutations (R501X and 2282del4). The effect of Th2 cytokines (IL-4 and IL-13) on filaggrin expression in human primary keratinocytes was determined using real-time PCR and immuno-dotblot.

Although the sample size was small, the R501X mutation was not identified among any of the AD or control subjects in this US population. Of the 17 European Caucasian subjects with AD only 3 had the 2282del4 null mutation, compared with 2 of 27 healthy European Caucasian controls, which is consistent with other published frequency data from Northern European populations. The epithelial immunoreactivity of filaggrin was decreased in lesional as well as nonlesional AD skin ($P < 0.05$) vs healthy controls, even among individuals with AD who did not have one of the 2 common *FLG* mutations. Filaggrin expression was further decreased in the nonlesional skin of 3 patients with AD heterozygous for the 2282del4 mutation and was even further decreased in their lesional skin, suggesting that the inflammation present in lesional skin can also affect filaggrin expression. To clarify whether inflammation affects filaggrin expression, the authors studied primary human keratinocytes. When these keratinocytes were cultured in the presence of IL-4 and IL-13, a significant reduction in filaggrin expression was observed at the mRNA and protein levels, compared with that observed with the media alone ($P < 0.001$).

Prior to this publication, filaggrin was considered a purely heritable defect. At the time, it was unclear whether these mutations - detected in up to 50% of European patients with AD - could explain the nearly universal observation of barrier disruption characteristic of AD subjects. This paper may explain why nearly 100% of patients with AD appear to have a barrier defect, but at best only 50% of these individuals can be heterozygous for one of the *FLG* mutations. The authors demonstrated that even in patients without *FLG* mutations, overexpression of Th2 cytokines characteristically present in AD skin lesions (lesional more than) can significantly reduce filaggrin epithelial expression. Importantly, the AD subjects who were heterozygous for one of the *FLG* mutations (2282del4) had even greater reductions in filaggrin immunoreactivity in their lesional vs nonlesional skin, which is likely due to the greater expression of Th2 cytokines in these skin lesions. Although the authors studied a very small number of African Americans ($n=11$ cases; $n=12$ controls) and European Americans ($n=27$ cases; $n=17$ controls), they noted a remarkably lower allele frequency of the 2282del4 mutation among European Americans (8.8% in cases vs 3.7% in controls) than has been observed among Northern European populations. Even more remarkable is the complete absence of R501X in European Americans and the fact that both mutations were not observed in any of the African American subjects (cases or controls). As has been suggested earlier, it may be that each population has its own unique *FLG* mutations or that barrier genes other than *FLG* will be more relevant for AD susceptibility in these populations.

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TH2 CYTOKINE MODULATION OF OTHER STRATUM CORNEUM PROTEINS

Kim BE, Leung DY, Boguniewicz M, Howell MD. **Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6.** *Clin Immunol.* 2008;126 (3):332-337.

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Loricrin (LOR) and involucrin (IVL) are important proteins for the structural integrity of the stratum corneum (SC) and are markers of epidermal differentiation. The aim of this study was to evaluate the mRNA and protein expression of LOR and IVL in both lesional and nonlesional skin of patients with AD vs healthy controls. To further understand the effect of LOR and IVL in the skin of individuals with AD, primary human keratinocytes were evaluated in the presence and absence of the Th2 cytokines typically overexpressed in AD skin - namely IL-4 and IL-13. The transcription factor called *signal transducer, and activator of transcription* (STAT)-6, is critical for the production of Th2 cytokines. The authors used a STAT-6 transgenic (or overexpressing) mouse model and compared it with the wild-type mouse control to evaluate the effect of IL-4 and IL-13 overproduction on cutaneous expression of LOR and IVL.

Subjects included 14 patients with moderate to severe AD (20% to 60% skin involvement) and 13 healthy controls. Patients who had received systemic corticosteroids or cyclosporine were excluded, and enrolled patients could not have received either topical corticosteroids or calcineurin inhibitors within 1 week of study initiation. Healthy skin, and both acute (<3 days old) AD lesional and AD nonlesional skin, was obtained. Real-time PCR was used to examine mRNA expression, and protein expression was evaluated by immunohistochemistry. The authors found that both LOR and IVL were decreased in involved ($P<0.001$) and uninvolved ($P<0.001$) AD skin compared with healthy controls. Th2 cytokines (IL-4 and IL-13) inhibited LOR and IVL mRNA and protein expression in primary human keratinocytes ($P<0.001$ for all comparisons). Skin biopsies from STAT-6 transgenic mice demonstrated reduced immunoreactivity for both LOR ($P<0.037$) and IVL ($P<0.034$), providing confirmation that Th2 cytokines inhibit the production of these barrier proteins.

Similar to filaggrin, LOR and IVL are proteins that are cross-linked with keratin and help flatten or compact the corneocyte, ultimately causing it to form the impervious "brick" structure that is required in order to have an effective SC. This is the first study to demonstrate that Th2 cytokines inhibit the production of these key SC proteins. Is it possible that any disease characterized by Th2 inflammation, such as alopecia areata or bullous pemphigoid, would also have reduced expression of these key SC proteins (ie, filaggrin, LOR, and IVL) and therefore produce a defective skin barrier? The effect of Th2 cytokines on key SC proteins may help to explain the observation that greater transepidermal water loss (TEWL), a physiologic measure of barrier function, is correlated with disease severity.

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TRANSEPIDERMAL WATER LOSS (TEWL) IS NOT HIGHER AMONG ATOPIC DERMATITIS PATIENTS WITH FILAGGRIN MUTATIONS VS THOSE WITHOUT SUCH MUTATIONS

Nemoto-Hasebe I, Akiyama M, Nomura T, Sandilands A, McLean WI, Shimizu H.
Clinical severity correlates with impaired barrier in filaggrin-related eczema.
J Invest Dermatol. 2008 Sep 25. [Epub ahead of print]

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The authors of this study investigated various indicators of skin barrier function, such as SC hydration, TEWL, and SC thickness, and the relationship of each to common *FLG* mutations in a cohort of Japanese patients. The 4 *FLG* mutations that were screened in this study had been previously identified in a published study of Japanese patients with ichthyosis vulgaris (IV) and AD conducted by the same authors.¹ A total of 24 patients with AD (3 with concomitant IV), 3 patients with IV without concomitant AD who had *FLG* mutations, and 12 control subjects were enrolled. Of the 24 patients with AD, 12 had an *FLG* mutation. AD disease severity was evaluated using the objective score of AD (OSCORAD) tool. SC hydration was measured using a corneometer as a function of both low-frequency corneal susceptance and conductance. SC thickness was measured using a corneometer as a function of low-frequency corneal susceptance and high-frequency admittance. SC thickness was also confirmed by immunohistochemistry. TEWL, which was assessed with an evaporimeter, was the difference between the humidity of incoming and outgoing air passing over the target skin area. All evaluations were performed on 3 anatomical sites-flexor aspect of forearm, extensor aspect of forearm, and back.

The average SC hydration in AD patients with one of the *FLG* mutations was significantly reduced ($P<0.01$) compared with normal controls. The average SC hydration in the filaggrin-related AD group was lower than in the non-filaggrin-related AD group, but this difference was not statistically significant. The average SC thickness in the $>FLG$ group was significantly increased compared with both non-filaggrin-related-AD ($P<0.05$) and normal controls ($P<0.01$). The average TEWL in patients with non-filaggrin-related AD was significantly higher than in those with filaggrin-mutated AD ($P<0.05$) and normal controls ($P<0.01$). No significant difference in OSCORAD score was reported between both AD groups (ie, those with and those without *FLG* mutations). However, a negative correlation between OSCORAD score and average SC hydration in filaggrin-mutated patients with AD ($P<0.05$) was observed. Similarly, the investigators also found a positive correlation between OSCORAD score and TEWL ($P<0.005$) and OSCORAD score and SC thickness ($P<0.05$) in patients with filaggrin-related AD. In patients with non-filaggrin-mutated AD, however, no association was reported between OSCORAD score and any of the 3 aforementioned variables (ie, SC hydration, TEWL, and SC thickness).

This is the first study to evaluate various measures of epidermal barrier integrity in AD patients with and without a *FLG* mutation. Although the sample size was fairly small, with 12 individuals in each group (*FLG*-associated and non-*FLG*-associated), the authors were still able to observe interesting and somewhat unexpected differences between the 2 AD groups, and between the AD groups and the controls. For all 3 parameters measured, differences were noted between either AD group and the controls, with the same trends observed for both the AD groups.

In summary, this study suggests that in AD skin, the TEWL is increased, and the SC is less hydrated and thicker. What is surprising is that TEWL measurements were higher, indicating greater barrier defect in AD subjects who did not have 1 of the 4 common *FLG* mutations observed in the Japanese population, compared with those AD subjects with a *FLG* mutations. The interpretation of this finding is either that *FLG* mutations are not responsible for the observation that patients with AD have increased TEWL or that there are other *FLG* mutations not yet accounted for in this population. It is also plausible that



mutations in other genes that impact the skin barrier could have as their effect reduced filaggrin expression. It will be interesting to see if this finding is confirmed in larger studies, and in other racial and ethnic groups. It would be beneficial to broaden the barrier assays in future studies of this type to include those that provide some measure of the barrier integrity from the outside-in, as they may provide results quite different from those with TEWL, which is measuring inside-out permeability.

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GENETIC DEFECTS IN STRATUM CORNEUM GENES (*SPINK5*, *KLK7*, AND *FLG*) AND RISK FOR ATOPIC DERMATITIS

Weidinger S, Baurecht H, Wagenpfeil S, et al. **Analysis of the individual and aggregate genetic contributions of previously identified serine peptidase inhibitor Kazal type 5 (*SPINK5*), kallikrein-related peptidase 7 (*KLK7*), and filaggrin (*FLG*) polymorphisms to eczema risk.** *J Allergy Clin Immunol.* 2008;122(3):560-568.

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The investigators of this study evaluated the contribution of *FLG* and 2 other candidate genes that have been linked to AD but have been less robustly validated. The variants analyzed were the serine peptidase inhibitor Kazal type 5 (*SPINK5*) polymorphism rs2303067 (Glu420Lys),¹ a 3' untranslated region (UTR) AACCC insertion in the serine protease kallikrein-related peptidase 7 (*KLK7*) gene,² and the 2 most common *FLG* mutations - R501X and 2282del4. The *KLK7* gene encodes for the protease stratum corneum chymotryptic enzyme (SCCE), which has been hypothesized to play a role in the post-translational processing of filaggrin. The *SPINK5* gene, defective in Netherton syndrome, encodes for the serine protease inhibitor lymphoepithelial Kazal-type inhibitor (LEKTI), which is thought to regulate SCCE activity.

This sizable study evaluated patients from several different cohorts, including a German family-based eczema and case-control cohort, an English/Irish eczema cohort, and the population-based Avon Longitudinal Study of Parents and Children (ALSPAC), as well as corresponding healthy control groups. Single nucleotide polymorphism (SNP) evaluation was performed for *FLG*, *SPINK5*, and *KLK7* in all cohorts except for the ALSPAC study. *KLK7* SNP evaluation was not performed in the ALSPAC study, as recurrent negative associations with *KLK7* were observed in the eczema cohorts. In both the family-based and case-control cohorts, *FLG* polymorphisms were consistently associated with AD, with an odds ratio (OR) of 3.36 (95% confidence interval [CI], 2.97 to 3.79; $P=1.3 \times 10^{-84}$). In the family-based German study, the *SPINK5* maternally inherited rs2303067 allele appeared to have a weak association with AD, with an OR of 1.25 (95% CI, 1.04 to 1.50; $P=0.018$). The *KLK7* mutation was not associated with AD in any cohort.

This paper provides further confirmation that the 2 common loss-of-function *FLG* mutations are significantly associated with AD in 3 Northern European populations. By comparison, the SNP analyzed at the *SPINK5* locus is much more weakly associated with AD (only in the German family-based cohort and the pooled cohorts), and appears to play a role only when it is maternally inherited. By contrast, the *KLK7* 3'UTR insertion had no association with AD in the German and English/Irish cohorts. The real objective of this study was to examine whether those genes (*FLG*, *SPINK5*, and *KLK7*) necessary for effective cornification interact or demonstrate any evidence of gene-gene interactions (ie. epistasis) or synergy. In other words, is the risk for AD significantly enhanced if a person has mutant alleles for 2 of these genes compared with either gene alone? The low allele

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frequencies for the *SPINK5* and *KLK7* mutations hinder the ability to detect such interactions, but from their statistical discussion, it appears that the authors do not consider this a major factor. They observe no evidence of epistasis with these 3 genes. It is possible that epistasis might be more likely if one compared SC genes with those genes key to the function of tight junctions. It is important to acknowledge the massive undertaking that a study of this size involves, with total populations exceeding 13,000 cases and controls. Pooling cohorts obtained using different entry or diagnostic criteria is always problematic. In these studies, the only group in whom the diagnosis of AD is particularly suspect is the ALSPAC cohort, in whom AD is defined by "reports of flexural dermatitis at 2 time points between 6 and 42 months of age."

1. Kato A, Fukai K, Oiso N, Hosomi N, Murakami T, Ishii M. [Association of *SPINK5* gene polymorphisms with atopic dermatitis in the Japanese population.](#) *Br J Dermatol.* 2003;148(4):665-669.
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BARRIER DEFECTS IN NONLESIONAL SKIN OF PATIENTS WITH ATOPIC DERMATITIS

Jakasa I, Verberk MM, Esposito M, Bos JD, Kezic S. **Altered penetration of polyethylene glycols into uninvolved skin of atopic dermatitis patients.** *J Invest Dermatol.* 2007;127(1):129-134.

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When this paper was published in 2007, the evidence that the lesional skin of patients with AD had a barrier defect was quite solid, but the notion that nonlesional skin was also dysfunctional was still controversial. In this study, the authors used a clinically useful *in vivo* marker of barrier function, TEWL, to evaluate whether uninvolved skin in patients with AD had a diminished barrier. A total of 20 patients with mild AD and 20 healthy controls were recruited, all of whom were >18 years of age and Caucasian. Of the patients with AD, 12 were considered active (ie. with pruritic lesions) and 8 were inactive (ie. no lesions for >3 months). A hydrophilic polymer called polyethylene glycol (PEG) of different molecular weights (150 to 590 Da) was applied to the uninvolved skin in both groups for 6 hours using Finn Chambers. After removal of the Finn Chamber patch, SC was harvested using a tape stripping method. The concentration of PEGs in each tape strip was measured by gas chromatography and normalized to total protein. To estimate penetration, the researchers applied Fick's second law of diffusion, which enabled them to calculate a diffusion coefficient and permeability coefficient for each PEG size.

SC thickness did not differ significantly between the AD and control groups after PEG exposure. TEWL measurements were higher in AD skin before tape stripping compared with controls ($P<0.05$) and did not differ significantly after tape stripping. The diffusion coefficient for all PEGs (except PEG-150) was twice as high in patients with AD compared with control subjects ($P<0.0001$). Additionally, the diffusion coefficient of PEGs decreased equally in both controls and AD patients with increasing molecular weight. Patients with active AD had significantly higher diffusion coefficients in their nonlesional skin than did control subjects ($P<0.05$). No significant difference in the diffusion coefficient between active and inactive AD patients was reported. The partition coefficient in patients with AD was half that of control subjects for all PEGs except PEG-150 ($P<0.0001$). However, the partition coefficients of active vs inactive AD did not differ significantly.

The increased diffusion coefficient in clinically inactive AD skin supports the hypothesis that even nonlesional skin has a barrier defect. This abnormality suggests that in the same period of time, more chemicals will penetrate the skin in patients with AD compared with controls. This may result in greater tissue reactivity, as the various mechanisms available to neutralize the irritant or immunologic reactions to such substances may be

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overwhelmed in AD patients. This barrier abnormality may explain, at least in part, why these patients are more likely to develop irritant contact dermatitis and allergen sensitization. It may also explain why certain topical anti-inflammatory agents (ie. tacrolimus and pimecrolimus) work better in individuals with AD than in those with psoriasis. Whether persons with AD may be at risk for greater penetration of pollutants and nanoparticles present in more and more over-the-counter medications, such as sunscreens, awaits further study.

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This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Credit Designations — [back to top](#)

Physicians

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*TM. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses

This 1.0 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hours.

Post-Test — [back to top](#)

To take the post-test for eMedicalDermatology Review you will need to visit [The Johns Hopkins University School of Medicine's CME website](#) or [The Institute for Johns Hopkins Nursing](#). If you have already registered for another Hopkins CME program at these sites, simply enter the requested information when prompted. Otherwise, complete the registration form to begin the testing process. A passing grade of 70% or higher on the post test/evaluation is required to receive CME/CNE credit.

Statement of Responsibility — [back to top](#)

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CME/CNE activity.

Intended Audience — [back to top](#)

This activity has been developed for the Dermatologist, PharmD, Nurses, Dermasurgeon, Dermatopathologist, Pediatric Dermatologist, Immunodermatologist, and Wound Care Specialist.

Learning Objectives — [back to top](#)

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

- Explain how both inherited and acquired defects in filaggrin and other stratum corneum proteins may impact barrier function in patients with atopic dermatitis (AD)
- Describe the clinical observations that support the notion that individuals with AD have a barrier defect
- Identify 3 different genes linked to AD and explain the association of each with the disease

COMPLETE THE POST-TEST

Step 1.

Click on the appropriate link below. This will take you to the post-test.

Step 2.

If you have participated in a Johns Hopkins on-line course, login. Otherwise, please register.

Step 3.

Complete the post-test and course evaluation.

Step 4.

Print out your certificate.

PHYSICIAN
POST-TEST

NURSE
POST-TEST

Internet CME/CNE Policy — [back to top](#)

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Faculty Disclosure — [back to top](#)

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- **Bernard A. Cohen, MD** has indicated a past and current financial relationship with Novartis, Pharmaceuticals, Astellas Pharma Inc., Medicis and Connetics. He served on the Speaker's Bureau for Novartis, Pharmaceuticals, Astellas Pharma Inc., and Medicis. He has also received grants for studies from Novartis, Pharmaceuticals and Astellas Pharma Inc. and received support for a fellowship program from Connetics.
- **Susan Matra Rabizadeh, MD, MBA** has disclosed no relationships with commercial supporters.
- **Mark Lebwohl, MD** has disclosed that he has received grants for clinical research and educational activities from, has served as an advisor, consultant and speaker to, and has served as an investigator for Abbott, Amgen, Astellas, Centocor, Genentech and Novartis.
- **Elizabeth Sloand, PhD, CRNP** has disclosed no relationships with commercial supporters.

Guest Authors Disclosures

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